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Literature Review

Articles That May Change Your Practice: Prehospital Antibiotics

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Sepsis is the result of the body's dysregulated immune response to an infection, which can rapidly lead to multiorgan failure and death. Mortality can be as high as 35% and is highly dependent on the time interval between the onset of symptoms and treatment. The evidence suggests that early diagnosis of sepsis and early administration of intravenous antibiotics, as part of a bundle of care, can reduce morbidity and mortality from sepsis. The recognition of sepsis in the prehospital and transport setting before the patient's arrival in the hospital can speed up diagnostics and treatment upon arrival. Given that up to 50% of patients with sepsis arrive in the emergency department (ED) by ambulance, prehospital personnel have an opportunity to provide time-sensitive therapies in transport. The same holds true for patients with severe sepsis and septic shock who undergo interfacility transport from smaller hospitals to specialized centers of excellence.

Unlike the substantial contributions to improving care for patients with other time-dependent illnesses, such as trauma, stroke, and acute myocardial infarction, the evidence to support the use of prehospital antibiotics is not well established. Transport personnel have the opportunity to ensure patients receive appropriate bundles of care for sepsis, including intravenous antibiotics, and potentially impact patient outcome in this patient population. The emerging evidence regarding prehospital antibiotics in patients with sepsis is examined, with particular attention on the impact of their use before arrival at the hospital.

Hunter CL, Silverstri S, Stone A, et al. Prehospital sepsis alert notification decreases time to initiation of CMS sepsis core measures. *Am J Emerg Med.* 2019;37:114-117.

The key to effective care in the ED often depends on the notification of an incoming patient with a specific diagnosis for whom time-sensitive interventions impact morbidity and mortality. Hospital EDs routinely receive notification of an incoming patient with conditions such as multisystem traumatic injuries, cardiac arrest, ST-segment elevation myocardial infarction, or suspected acute stroke. This early notification allows the ED to mobilize the resources necessary to provide care to these patients with delay.

The authors of this study sought to determine if prehospital identification of sepsis and notification of the ED would improve core sepsis measures and improve patient outcomes. The retrospective cohort study included patients who were identified as "sepsis alerts" in the ED. The authors compared times from ED registration to fluid resuscitation, blood cultures and serum lactate draws, antibiotic administration, and mortality between patients who had prearrival notification versus those who did not. Of the 272 "sepsis alert" patients seen, the ED received a prearrival notification from prehospital personnel in 162 cases. The prehospital sepsis alert group had significantly lower times to intravenous fluid administration on arrival (6 vs. 41 minutes, $P < 0.001$), blood cultures drawn (12 vs. 34 minutes, $P = 0.003$), lactate levels drawn (12 vs. 34 minutes, $P = 0.003$),

and administration of antibiotics (33 vs. 61 minutes, $P = 0.004$). There was no difference in mortality (11% vs. 14%, $P = 0.565$) between the 2 groups. The authors concluded that although prearrival notification did not improve mortality, it decreased the time to specific interventions shown to improve outcomes in sepsis.

Alam N, Oskam E, Stassen PM, et al. Prehospital antibiotics in the ambulance for sepsis: a multicenter, open label, randomized trial. *Lancet Respir Med.* 2018;6:40-50.

Prehospital personnel are able to recognize sepsis, but studies identifying the impact of this recognition and the resultant timely treatment of patients with sepsis remain ill-defined. The authors of this study performed a prospective, randomized controlled open-label trial in 10 large regional ambulance services in the Netherlands to quantify the effects of early antibiotic administration to patients with sepsis. The study compared early antibiotics in the ambulance with usual care. Patients randomized to the intervention arm received open-label ceftriaxone 2 g intravenously in addition to usual care. The primary outcome was all-cause mortality at 28 days with analysis by intention to treat.

The study randomized 2,698 patients over 2 years, with 2,672 included in the final analysis (1,535 in the intervention group and 1,137 in the usual care group). The intervention group received antibiotics a median of 26 minutes (interquartile range, 16–34 minutes) before ED arrival, whereas in the usual care group the median time

to antibiotics was 70 minutes (IQR, 36–128 minutes). At day 28, 120 (8%) patients in the intervention group had died compared with 93 (8%) in the usual care group (relative risk = 0.95; 95% confidence interval, 0.74–1.24). When analyzing based on the severity of illness, prehospital personnel were able to correctly identify patients with sepsis and improve timeliness to antibiotics, regardless of severity. However, antibiotic administration did not improve survival, regardless of the severity of illness. There were 7 mild allergic reactions, none of which could be attributed to ceftriaxone.

The authors also assessed the effect of training on prehospital personnel's ability to recognize sepsis by examining the usual care group's time to antibiotic administration after ED arrival before and after training. The median time to antibiotic administration in the usual care group after training was 70 minutes compared with 93 minutes before training. This supported the belief that appropriate training improved early recognition and care in this patient population as a whole.

These 2 recently published studies reflect the ability of prehospital personnel to correctly identify patients with sepsis and provide either prearrival ED notification or prearrival interventions aimed at decreasing time to care. However, the theoretical advantage of decreasing times to antibiotic administration does not translate into a clear mortality benefit. It remains unclear whether antibiotics alone or a bundle of care that includes antibiotics and other therapies is key to outcomes in septic patients. In addition, the cost-effectiveness and impact on mortality and morbidity of obtaining blood cultures and administering intravenous antibiotics in the prehospital setting for patients with sepsis is not well understood. A feasibility study to answer this question is underway.¹

Until such a time as the true benefit is known, there is some evidence to guide prehospital management of sepsis, including antibiotic administration. First, prehospital personnel can identify patients with sepsis. Second, prearrival ED notification by prehospital and transport personnel improves

timeliness to care. Third, prehospital antibiotic administration has not yet been shown to improve mortality. Finally, although it may seem intuitively beneficial, there are no definitive studies to address the efficacy or benefit of timely antibiotic administration in the setting of an open or clearly contaminated wound, such as an open fracture. Despite the paucity of evidence, prehospital antibiotic administration is considered safe, does not require significant additional time in transit, and can provide a more timely delivery of a therapy that may have a potential downstream impact on patient care.

Reference

1. Moore C, Bulder J, Morgan M, et al. Prehospital recognition and antibiotics for 999 patients with sepsis: protocol for a feasibility study. *Pilot Feasibility Stud.* 2018;4:64.

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