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ABSTRACT

Objective: To compare the 30-day mortality rate of suspected sepsis patients who received prehospital (Emergency Medical Services- EMS) antibiotic administration in an ambulance as compared to antibiotic administration in the hospital. **Design:** Systematic literature review. **Methods:** Research was conducted in PubMed and Google Scholar with the search terms: sepsis, antibiotics, prehospital, EMS, ambulance. The 3 articles selected were chosen after removing articles not from a randomized control trial, no antibiotic administration, and not a free article. **Results:** From our meta-analysis of the three studies, we concluded that providing antibiotics before arriving at the hospital for patients with suspected septic infections. The Alam et al study demonstrated that there was no reduction in mortality when comparing prehospital administration of intravenous antibiotics to those who received their antibiotics in-hospital. Jones et al also showed no improvement in mortality rates in the treatment group but did find a statistically significant reduction in the 3-month readmission rate among the treatment group. In the third study, Chamberlain concluded that prehospital administration of intravenous antibiotics does in fact reduce 28-day mortality but correlating mortality with mean intensive-care unit (ICU) length of stay. **Conclusion:** 30-day mortality is not improved with early antibiotic administration in septic patients.

INTRO

Sepsis is a prevalent condition with a disconsolate prognosis. Typically a result of infection, sepsis is the body's overwhelming response to the life-threatening inflammation that can result in widespread dysregulation, multiple organ damage or failure, and even death.[1] When the body cannot defeat the infection locally there is a systemic inflammatory reaction. At the cellular level, the mass inflammation recruits neutrophils and macrophages to attack the bacteria. In turn this mass influx causes tissue damage, vascular injury, and organ injury. Repeated attacks cause the body to enter a hypercoagulable state and disseminated intravascular coagulopathy can occur.[2] Sepsis can progress to severe sepsis when there are signs of organ dysfunction. The final step is septic shock, when the patient's body is no longer able to maintain its blood pressure and provide sufficient oxygen for the body to function.[3] Unfortunately, sepsis is rather common- affecting 1.7 million Americans a year, of which 270,000 will die.[4] Sepsis is diagnosed by having at least 2 out of 4 systemic inflammatory response syndrome (SIRS) criteria. The SIRS criteria consists of the patient having a temperature >38°C or <36°C, heart rate >90/min, respiratory rate >20/min or Paco2 <32 mm Hg (4.3 kPa), and a white blood cell count >12 000/mm3 or <4000/mm3 or >10% immature bands.[1] A newer criteria for sepsis, the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) scoring system has recently replaced SIRS due to sepsis not always being caused by infection (Table 1).[5] However, since the SOFA score uses laboratory data that is unobtainable in the prehospital setting and we are dealing with infections, SIRS is the criteria used for this article.

It is imperative to quickly identify and treat sepsis, given the longer one waits to treat it, the higher the mortality they incur. In a study by Pelton et al, each additional hour waiting to begin administering antibiotics to be started was associated with 10% increased odds of 1 year mortality.[6] Mortality was highest waiting over 3 hours for treatment, but no difference was made in mortality between antibiotic administration greater than or less than 1 hour.[6] Another study done by Seymour et al showed that more rapid completion of the 3 hour nursing bundle and administration of antibiotics improved mortality rates from sepsis.[7] Due to its high mortality rate, there has been a recent push to apply hospital sepsis guidelines to the emergency medical field. Using the speculation that quicker administration time of antibiotics improves mortality rate, in theory giving antibiotics in route will then improve mortality rates. In this meta-analysis we aim to investigate the effectiveness of pre-hospitalization recognition of sepsis with subsequent administration of intravenous antibiotics and its effects on improving mortality as compared to the emergency department setting.

	Score				
	0	1	2	3	4
Respiratory system					
PaO_2/FiO_2 (mmHg)	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Hepatic system					
Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular system					
	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dose)[a]	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1[a]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[a]
Coagulation					
Platelets $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Central nervous system					
Glasgow coma scale	15	13–14	10–12	6–9	<6
Renal system					
Creatinine (mg/dL)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
Urine output (mL/d)				<500	<200

Notes: [a]All catecholamine doses represent μg/kg/min. Organ dysfunction is identified as an increase in the SOFA score of ≥2 points. In patients with not known preexisting organ dysfunction, the baseline SOFA score is assumed to be zero. *Intensive Care Med*. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. 22(7), 1996, 707–710, Vincent JL, Moreno R, Takala J, et al. With permission of Springer.[17]
Abbreviations: PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure.

Table 1. *SOFA Criteria*[8]

METHODS

A PubMed and Google Scholar database search was conducted in September 2021 using the search terms: sepsis, antibiotics, prehospital, EMS, ambulance. The search yielded 71 results with Google Scholar and 14 from PubMed. The 14 articles from PubMed were already found in the Google Scholar search and were subsequently removed from the total article count leaving 57 records to be screened. 23 records were excluded once a filter was applied to only show randomized control trials. 34 records were then examined, with the removal of 31 records for the following reasons: there was no antibiotic administration prehospital, it was not a free full-text article, or the study was not a randomized control trial. This left 3 randomized control trials comparing the effects of prehospital antibiotic administration and emergency department administration of antibiotics to septic patients (Figure 1).

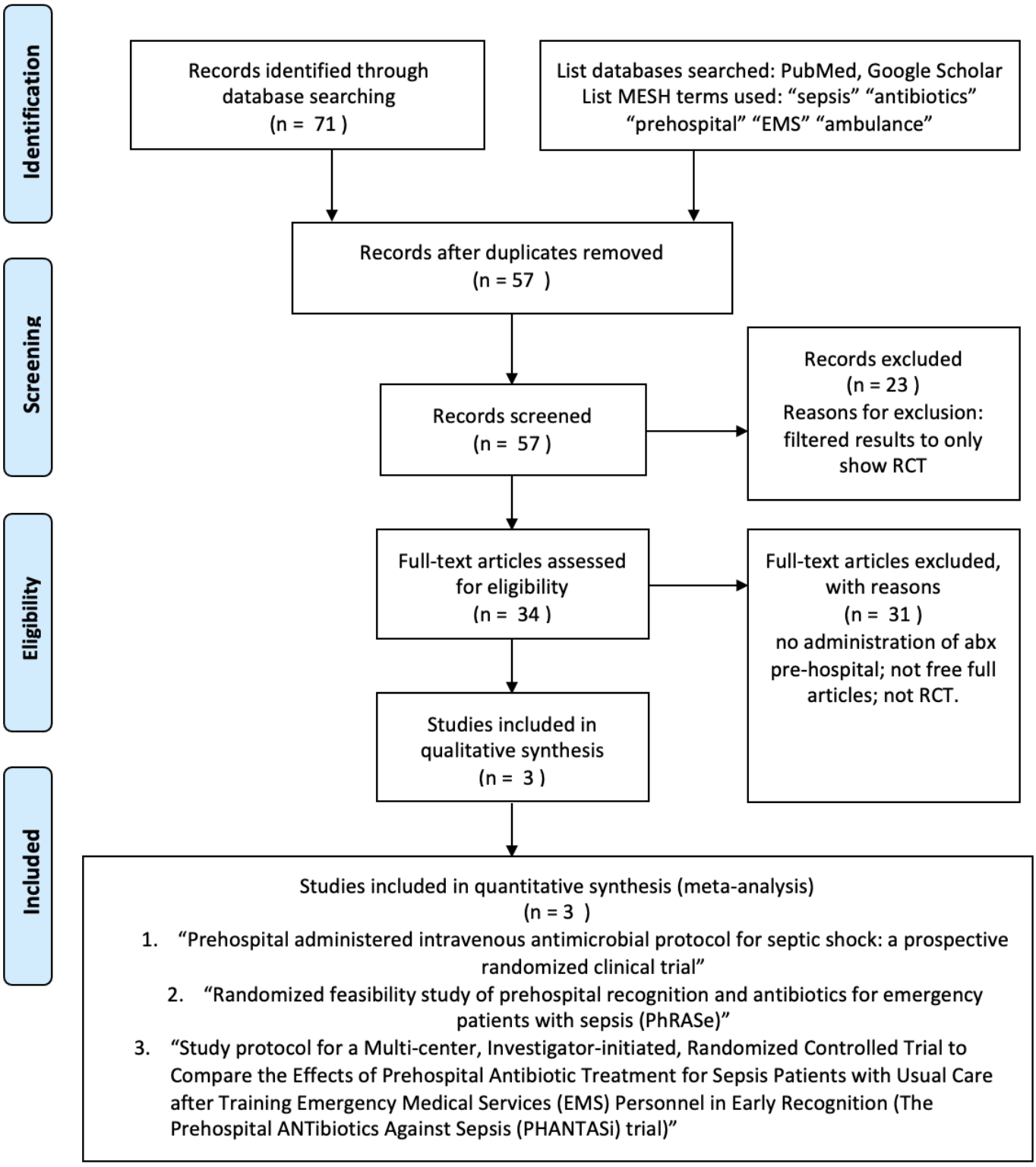

Figure 1. *PRISMA diagram for article selection.*

RESULTS

Study 1: *Study protocol for a Multi-centre, Investigator-initiated, Randomized Controlled Trial to Compare the Effects of Prehospital Antibiotic Treatment for Sepsis Patients with Usual Care after Training Emergency Medical Services (EMS) Personnel in Early Recognition (– The Prehospital ANTibiotics Against Sepsis (PHANTASi) trial*[9]

Objective

To compare 28-day mortality, length of hospital stay, and admission to intensive care units for early administration of antibiotics to suspected sepsis patients pre hospital as compared to the usual treatment.

Study Design

The study was a multicenter open label randomized controlled trial conducted in all settings: prehospital, emergency departments and in patient centers in the Netherlands for a total of 2698 patients between June 30, 2014, and June 26, 2016. included all patients over 18 years old with a suspected infection and a temperature above 38° C and below 36° C. Participants also had to meet either an abnormal pulse above 90 beats per minute or an abnormal respiratory rate above 20 breaths per minute. Patients who had a known severe allergy to ceftriaxone or other beta lactams, were pregnant, and patients with a suspected prosthetic joint infection were excluded.

Emergency medical services (EMS) personnel were trained in recognizing sepsis and then patients were block randomized with blocks of 4 in a non-blinded study. The control group received the usual care and the intervention group received 2000 mg Ceftriaxone IV after one blood culture was obtained. The study had 80% power and determined this by reviewing the data in live time. If the 28-day mortality was under 40% for standard care and under 34% for pre-hospital antibiotic administration, then 2144 patients were required to participate.

Data was analyzed for 28-day mortality between prehospital administration and those receiving standard care. Secondary measurements were for proportion of patients with adverse events, proportion of patients being transferred to higher care, and proportion of patients receiving antibiotics unnecessarily. Hospital stay length, door to needle time and response time was also measured

Study Results

Of the 2698 total patients participating in the study, 1548 were assigned to the intervention group and 1150 were assigned to the usual care group. 2672 total patients were used for intention to treat analysis. At the 28-day mark, 120 (8%) of the intervention group and 93 (8%) of the control group patients had died. There was an increase in mortality for more severe sepsis but no difference from the 2 different treatment groups. No significant difference was found in 90-day mortality, length of stay, or ICU vs. regular hospital admission rates. In 90 days, 178 (12%) of the intervention participants and 132 (12%) of the usual care participants had died (p=0.87). ICU admissions included 155 (10%) patients of the intervention group and 98 (9%) of the usual treatment group with the median length of stay being 6 days. The median time to treatment of antibiotics was 26 minutes from emergency department arrival. The 28 day re-admission rate was statistically significant in the intervention group with 102 patients (7%) as compared to 119 (10%) (p=0.0004). The treatment group received their antibiotics 26 minutes before arrival to the emergency department.

Study Critique

Overall, this study was well conducted. It was a randomized control trial that actively responded to potential barriers skewing results. The results were extensive and displayed with all information needed for the reader to confirm the numbers were calculated correctly.

One study critique is that there was an issue with randomization and more patients ended up in the intervention group than was supposed to happen. This was likely due to EMS personnel treating

preemptively and would open randomization envelopes until they found one with instructions to treat. The over randomization did not affect the outcome. Another critique is that this study was based in the Netherlands which has a different healthcare system than the United States so these results may not be transferable to the healthcare system in America. Another critique is the antibiotic given in the ambulance was not the most commonly used antibiotic when patients were admitted for sepsis so this may have differed the results. A limitation of the study is that SOFA is the preferred measure for sepsis identification but due to lack of diagnostic testing in the ambulance SIRS was the one that was used for identification instead.

Study 2: *Randomised feasibility study of prehospital recognition and antibiotics for emergency patients with sepsis (PhRASe)*[10]

Objective

To develop a method for screening septic patients, create a protocol for blood culture collection, administration of IV antibiotics and handing off care to the emergency department.

Study Design

Five ambulance stations in the vicinity of the University Hospital of Wales participated in this study for 118 patients from December 1, 2017, to May 21, 2018. Paramedics were trained in the recognition of sepsis, how to collect blood cultures and how to administer the IV antibiotic. The participants were randomized in a 1:1 ratio for treatment or usual care. Each paramedic received a batch of cards and when they identified an eligible patient would scratch off the card that reviewed the patient's study ID number and randomization status.

Usual care was described as maintaining oxygenation saturations over 94% or 88-92% if the patient was known to have a chronic obstructive pulmonary disease. The patients also received a 250 mL 0.9% sodium chloride bolus or up to 2000 mL if the patient has a systolic blood pressure less than 100 mmHg. The treatment group included the usual care as well as the patient received 2g of cefotaxime after blood cultures were collected.

Study Results

62 patients were randomized into the treatment group where 48 of these patients completed the treatment protocol. 52 patients were randomized into usual care where 51 of these patients completed the usual care protocol. Of the 114 patients participating in the study, 51 were diagnosed with sepsis (45%). 39 of the 114 had a diagnosis of a non-viral infection therefore the study concluded that 90 of 114 recruited patients had sepsis or a likely bacterial infection. There was no statistical difference in deaths, ICU admissions, ED readmissions or health care related quality of life between the treatment group and usual care group. The number of hospital admission post 3 months was significant for 87 in the treatment group and 56 patients in the usual care group ($p=0.0002$). There was a 13% absolute difference in 90-day mortality between the treatment group and the usual care group. The treatment group received their antibiotics on average 24 minutes before arrival into the emergency department.

Study Critique

The study was very thorough in their calculations and included all data so the reader could verify the results. The study was also modeled after Study 1 as previously discussed but with different antibiotics and a different population.

A limitation of the study was that it was with a small sample size which can skew the results and reduce the power of the study. Another limitation was that they did not classify their patients based on severity of sepsis which could be a reason for using the antibiotics earlier.

Study 3: *Prehospital administered intravenous antimicrobial protocol for septic shock: a prospective randomized clinical trial*[11]

Objective

To compare the mortality of hypotensive patients with suspected severe septic shock when administered broad-spectrum, intravenous antibiotics in the prehospital setting with that of patients who are given intravenous broad-spectrum antibiotics in the hospital setting.

Study Design

198 patients meeting the SIRS criteria for septic shock on initial clinical presentation prehospital were randomized to receiving broad-spectrum intravenous antimicrobial therapy and fluid per guided protocol or to receiving intravenous fluids only. Then an intensive care unit (ICU) mortality prediction score, APACHE II, was then used to assess baseline risk in groups being compared in clinical trials.

Study Results

Of the 198 septic shock patients, 99 received prehospital antimicrobial therapy with blood cultures being taken prior to administration. Both control and treatment groups were comparable in all aspects. 83 males and 26 females received the treatment while 79 males and 20 females were in the control group (P =0.021). Mean age was 67.9 ± 10.5 years in the treatment group and 63.8 ±11.0 years in the control group (P =0.186).

The APACHE II scores in both the test group and in the control groups were statistically not significant with a P value of 0.661. 28% of the test group, versus 53% of the control group, had community-acquired pneumonia. The mean ICU stay in the test group was 6.8 ± 2.1 days and in the control group it was 11.2 ± 5.2 day (P =0.001). The first antimicrobial administration after emergency department admission time in the control group was 3.4 ± 2.6 hours for a P=0.02. The 28-day mortality was significantly reduced to 42.4% in the test group compared with the 56.7% in the control group (P = 0.049, OR = 0.56; 95% = CI = 0.32 to 1.00).

When assessing the result of this study, D. Chamberlain concluded that the adjuvant treatment of patients with a guided prehospital-initiated broad-spectrum antimicrobial therapy with intravenous fluids reduces the delay in antimicrobial administration and significantly reduces the 28-day mortality rate in patients with septic shock.

Study Critique

Strengths of this study include the relatively straight-forward design and similar group demographics. The sample size is relatively large which also adds to its strengths. The randomized study directly compared the administration of intravenous antimicrobials in the prehospital setting with a control group which is precisely what we are trying to analyze in our meta-analysis.

This study has many limitations, such as its overall vague descriptions. While not specifically stated, it is assumed that this study was unblinded due to the risk of antimicrobial adverse side effects, allergies and consent which lessens its statistical significance. In addition, there was no exclusion and inclusion criteria stated, and it appears hypotension was the sole criteria used for suspecting septic shock in patients. D. Chamberlain did not specify which antibiotics were used, which would have further affected the inclusion and exclusion criteria based on the patient's medical history, if they have had sepsis before, any allergies to Penicillins, etc. Finally, the study correlates length of hospital stay with mortality which seem unrelated. While the treatment group did have a statistically significant decrease in length of hospital stay when compared to the control group, it seems a stretch to equate that to a decrease in mortality.

DISCUSSION

Based on the research, administering antibiotics in the prehospital setting does not appear to have an immediate impact on patient mortality. However, prehospital intravenous antibiotics might instead affect how long the patient will be in the hospital. All three studies have concluded that short term there is no mortality benefit to providing antibiotics in the prehospital setting. Study 1 found a statistical difference in the 28-day readmission rate with the intervention group who received the earlier antibiotics coming in less[9]. Study 2 found that the intervention group who received the earlier antibiotics came into the hospital more post sepsis recovery however it was not classified what these visits were for, their other comorbidities, or how severe the sepsis event was[10]. Study 3 concluded that prehospital administration of intravenous antibiotics reduces the 28-day mortality by correlating mortality with length of ICU stay, which can be misleading as the mortality is then due to hospital procedures rather than the sepsis itself[11]. In theory earlier antibiotic administration seems beneficial, but in reality, most ambulance rides, care, and treatment are less than 30 minutes as based on the time to antibiotic treatment in the studies[9,10]. This short amount of time does not seem to impact mortality of the patient[9,10].

Strengths of the articles include many different populations being observed and randomization of patients. Limitations of the articles for this meta-analysis is that each antibiotic administration for the studies were different and there is limited amount of data in one of the studies. Another limitation is that even though the antibiotics were received prehospital it was not a big-time difference from administration to emergency department time which may skew the results. This study may produce different results in a more rural area where the transport time is longer. Another limitation is that in some studies the paramedics were previous nurses which is different than in the United States and may dictate different care standards than a patient receives in the United States.

CONCLUSION

Sepsis is a life-threatening condition that can be corrected with the early recognition of SIRS criteria and administration of empiric antibiotics[1]. Even though the studies analyzed in this paper do not appear to show a concrete correlation between prehospital recognition of sepsis with subsequent intravenous antibiotics, there is more information that can be acquired before completely ruling out this option. For example, research is lacking for patients who will arrive at the hospital within less than twenty-five minutes of antibiotic administration which could have different results. The same could be said for more rural settings, where ambulance rides might take upwards or more than an hour, in which case it would be expected that prehospital administration of antibiotics might be crucial. Another gap in the knowledge includes an inconsistency in antibiotic administration and if that makes a difference in how patients responded to early antibiotic administration. These gaps in knowledge affect the useability of early antibiotic administration for septic patients.

In future studies, instead of early antibiotic administration, it may be more worthwhile to spend resources on publicizing the signs and symptoms of sepsis to the general population rather than focusing solely on the role of EMS. This is in part due to the increasingly urbanized cities of America which is only decreasing ambulance ride-time nationwide. More universal recognition of what sepsis is- how to identify it, what actions to take, and the severity of the situation- may aid in reducing the mortality rate rather than receiving medications twenty minutes or so early. This brings to mind the National Institute of Neurological Disorders and Stroke (NINDS) and their “Know the Stroke” campaign, where they educated the public about the signs and symptoms of stroke and the importance of getting to the hospital quickly[12]. If something similar to “Know the Stroke” could be applied to sepsis, then this could have a profound impact on reducing the high mortality rate associated with it and save countless lives[12].

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