

COMMENT

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# Sepsis management in pre-hospital care – the earlier, the better?

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## Abstract

Emergency medical services often serve as the initial point of contact for septic patients, offering crucial pre-hospital intervention opportunities. However, the efficacy of pre-hospital interventions remains uncertain. From this perspective, we'll talk about the available evidence of pre-hospital sepsis and septic shock treatment and the barriers to its implementation.

**Keywords** Sepsis, Septic shock, Sepsis, Pre-hospital emergency care, Antibiotics

## Main text

### Background

Sepsis is a clinical syndrome caused by a dysregulated host response to infection. Conversely, septic shock is characterized as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality [1]. Both situations have high prevalence and mortality that require prompt interventions. Early identification and prompt intervention are pivotal to optimizing outcomes [2].

The guidelines established by the Surviving Sepsis Campaign (SSC) have emerged as the universally endorsed benchmark for the management of individuals afflicted with sepsis and septic shock. The SSC 1-hour bundle includes five components: fluid resuscitation and vasopressors to maintain mean arterial pressure greater than 65mmHg, obtaining blood cultures before

antibiotics are administered, broad-spectrum antibiotics, and a lactate level measure [3].

Despite the suggested prompt initiation of these essential components, currently, treatment protocols describe the moment of hospital screening as the initial time to begin these interventions [3]. Nevertheless, emergency medical services (EMS) personnel frequently serve as the primary healthcare responders for individuals with sepsis. EMS professionals can administer various initial treatments before the patient's hospital arrival, anticipating and initiating potentially life-saving interventions. It is estimated that approximately half of all sepsis patients in the emergency department will arrive via EMS transport [4], showing that most of these patients could receive therapy earlier in pre-hospital care.

Pre-hospital care is a window of opportunity to recognize and treat severe sepsis before arrival at the hospital [5]. Previous studies have shown that EMS arrival is associated with a significantly reduced time to the initiation of fluids and antibiotics for septic patients [6, 7]. The reduction in time to treatment has already been associated with a decrease in the rate of intensive care unit admissions, which may reflect the impact of initial care [8].

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This time gain for initiating intervention by qualified pre-hospital service professionals could be even more significant for patients in remote areas where travel times to the receiving hospital are longer. For example, in rural areas hospitals continue to experience disparities in sepsis outcomes, with low-volume emergency departments having a 36% higher sepsis mortality rate compared to high-volume emergency departments [9]. Many variables contribute to this disparity, such as less experienced professionals in critical conditions, but also patients living in rural areas experience longer ambulance wait times, which is generally associated with severe adverse health events and worsens their survival rates [10].

Despite the potential for early intervention before hospital admission, it remains uncertain whether there are tangible clinical advantages to initiating interventions in the pre-hospital setting. Therefore, in this perspective, we will discuss the available evidence of pre-hospital sepsis and septic shock treatment, mainly concerning fluid therapy and antibiotics. In addition, we will discuss some of the barriers to implementing sepsis protocols in pre-hospital care.

### What is the evidence?

Despite the interesting rationale of pre-hospital treatment of sepsis and septic shock, doubts remain regarding pre-hospital effectiveness in delivering fluids and antibiotics.

#### Antibiotics

Prompt administration of antibiotic therapy is already an obligatory measure in patients presenting with septic shock; it is known that the mortality rate in this population increases by approximately 7% for every hour of antibiotic delay [11]. Therefore, the current recommendation is to initiate antibiotics early, within the first hour of septic shock onset. However, in sepsis, the body of evidence suggests that timing is more flexible [12], providing overall time for careful medical evaluation regarding the diagnosis of sepsis, definition of focus, and prescription of the best spectrum antibiotics. Thus, this approach allows differential diagnoses of sepsis to be better investigated and avoids the indiscriminate administration of antibiotics. It is interesting to observe that the same response appears to occur in the pre-hospital setting when antibiotics were administered for sepsis and septic shock.

The Pre-hospital Antibiotics against Sepsis (PHANTASi) was a randomized controlled trial (RCT) that evaluated septic patients to receive antibiotics in the emergency department versus pre-hospital care. The time-to-antibiotics difference was approximately 90 min between groups. Nevertheless, there were no differences in 28-day mortality, ICU admission, or hospital length of stay. In this trial, only 4% of participants had septic shock

[13]. This trial reinforces the idea that, in sepsis, antibiotics administration could wait until the diagnosis of infection is confirmed.

On the other hand, in septic shock patients, early intervention may improve outcomes even in pre-hospital care. Jouffroy et al. showed in two retrospective studies that pre-hospital antibiotic therapy reduced 30-day mortality [14, 15]. Likewise, Chamberlain et al. conducted a randomized study that evaluated 198 patients with septic shock in the pre-hospital setting and found that adjuvant treatment of patients with a guided prehospital-initiated broad-spectrum antimicrobial therapy and intravenous fluid reduced the delay in antimicrobial administration and significantly reduced the 28-day mortality rate [16]. The important point is that, although antibiotics were administered together with fluids in these studies, the control groups also received fluids; the only difference was antibiotics administration. Thus, the studies suggest that pre-hospital antibiotics administration in septic shock could reduce mortality.

#### Fluid therapy

Fluid therapy is a clinical practice easily available in pre-hospital care. In 2010, Seymour et al. [17] analyzed a retrospective cohort of pre-hospital medical services with inconclusive results regarding resuscitation of septic patients; however, the sample size was small, and type II errors could have occurred. In 2014, the same research group [18] published a study with a considerably larger number of patients ( $N=1,350$ ), and in the univariate analysis, fluid administration was associated with higher mortality. However, after statistical adjustments, the authors concluded that fluid therapy reduced the chance of hospital mortality. However, it is worth mentioning that the average volume of fluid administered was significantly low (approximately 500 ml), leading the authors to question whether the reduction in mortality was due to the small volume of fluid or if it was associated with improvements in pre-hospital recognition of sepsis. This argument was further supported by the finding that the insertion of an intravenous catheter, without any fluid administration, was also associated with in-hospital mortality reduction.

On the other hand, Lane et al. [19] found that mortality was higher among patients who received fluids in the pre-hospital setting. To elucidate this finding, a subgroup analysis was conducted based on the patients' initial systolic blood pressure values. In this analysis, mortality was decreased in patients who received intravenous fluids when the initial systolic blood pressure was below 100 mmHg. Reinforcing the idea that the response to fluid therapy depends on the patient's previous volume status, a cohort study with 1,871 patients found that administering fluids to patients presenting with a low initial systolic

blood pressure was associated with reduced odds of mortality [20].

Another study showed that pre-hospital hemodynamic optimization (mean arterial blood pressure >65 mmHg or >75 mmHg if previous hypertension history), with fluids and vasopressors, was associated with a decrease in 30-day mortality in patients with septic shock [21]. The authors suggest an individualized mean arterial pressure target can be considered from the pre-hospital resuscitation phase in septic shock. In addition, these studies suggest that fluid infusion should be titrated according to fluid responsiveness, as in other clinical scenarios.

Thus, the effects of fluid administration in the pre-hospital care of septic patients are inconsistent between different studies. The optimal volume and timing of fluid administration require further investigation, considering the risk of volume overload and its deleterious effects. The most appropriate approach would be an individualized approach, as recommended by an increasingly early assessment of fluid responsiveness in these patients.

A survey study evaluated the decision-making of EMS services and found that most decisions regarding fluid therapy were based on clinical intuition. The main parameters assessed were blood pressure, history, skin turgor, capillary refill time, and shock index. In the same survey, 97% of ambulance physicians agreed that they were interested in more education on fluid therapy for patients with suspected infection [22]. Reinforcing the impact of pre-hospital team training a study by Guerra and colleagues showed that by training EMS personnel in the recognition of severe sepsis, mortality was reduced from 27 to 14% for patients treated by the trained EMS personnel, it was not reported whether this education changed fluid strategies, but the educational measure was beneficial [23].

Ultrasound is a widely expanding tool in recent times. It can assess the patients' volume status and could be an alternative to aid in fluid therapy decisions even in the pre-hospital environment with team training. A 2018 cohort study evaluated the use of pre-hospital emergency ultrasound. Although it was not a specific study on sepsis, ultrasound findings correlated well with diagnostic outcomes in the hospital and helped in patient management without prolonging pre-hospital care time [24].

Regarding vasopressor use, their introduction is mandatory for patients with persistent hypotension refractory to volume expansion, which is also necessary as a criterion for defining septic shock. However, there is no conclusive study on their use in pre-hospital settings.

## What are the barriers?

In addition to addressing the efficacy of fluids and antibiotics in pre-hospital settings, we must highlight the challenges and barriers EMS teams face in delivering these interventions.

The first barrier is the recognition of sepsis. Despite the existence of several screening scores, the recognition and diagnosis of sepsis and septic shock is a challenge in the current scenario. Several attempts to implement screening protocols and their applicability in pre-hospital ambulance settings have been discussed over the years. In this regard, some studies have evaluated strategies, including team training for septic patient recognition [25–27], ambulance structuring with specific sepsis kits provision [28, 29], and the organization of viable care protocols [30].

Notwithstanding the difficulties associated with recognizing and diagnosing sepsis in the pre-hospital context, some studies sought to evaluate the impact of a pre-hospital sepsis protocol that optimized hemodynamics and antibiotic therapy. Two studies to date [15, 31] demonstrated a reduction in mortality with the implementation of the protocol compared to controls. Nevertheless, the discussion continues regarding the difficulty of standardizing assessment and making an assertive diagnosis of sepsis by pre-hospital teams. Additionally, there is a consensus regarding the necessity for more robust and prospective evidence to elucidate better which measures should be included in the therapeutic regimen for this population within pre-hospital settings. Although early antibiotics administration seems to be an obvious intervention, it is not routine in pre-hospital settings.

However, it is important to recognize that EMS teams lead to faster diagnosis and treatment for septic patients [20, 25]. Femling et al. [32] released a comparative analysis of outcomes for patients with sepsis and septic shock seeking healthcare spontaneously versus those attended by EMS, showing that those who came to the hospital by spontaneous demand take more time to receive initial treatment, which impacts mortality in this group.

Another diagnostic challenge that may arise in the EMS setting is the feasibility and reliability of collecting cultures in the ambulance. In 2021, Mikkelsen et al. [33] described that despite the high rate of culture contamination collected in ambulances, this procedure is feasible and may be followed by antibiotic therapy if indicated. Thus, despite all these challenges, we think that pre-hospital treatment of sepsis is feasible and may improve prognosis.

## Conclusion

Optimizing pre-hospital care for patients with sepsis and septic shock requires a multifaceted approach encompassing early recognition, appropriate triage, and timely

interventions. Antibiotic therapy studies found an association between time-to-antibiotics and mortality for septic shock but little or no association for sepsis without shock. Given the limited current evidence regarding pre-hospital therapy for septic patients, the administration of antibiotics is safe and could be considered in patients with septic shock. In addition, if the emergency medical team rules out sepsis diagnosis, the antibiotics could be discontinued. In sepsis, however, the lack of clear benefits allows us more time to clarify the focus and define the most appropriate therapy after hospital evaluation. Regarding fluid resuscitation, more evidence is needed to evaluate the impact of fluid therapy in the pre-hospital setting, and perhaps instead of investing in a fixed amount of fluid, individualized therapy guided by the patient's fluid responsiveness is a better strategy.

In addition, integrating novel diagnostic tools, implementing sepsis protocols, providing specialized training for EMS teams with standardized triage protocols, equipping ambulances with essential resources, and enhancing communication between pre-hospital providers and receiving hospitals hold promise for improving patient outcomes in this critical population.

Future research on pre-hospital treatment should focus on randomized controlled trials with standardized pre-hospital protocols and the impact of interventions like antibiotics, fluids, and vasopressors on patient outcomes. This would enhance pre-hospital care for septic patients and reduce the burden of sepsis-related morbidity and mortality.

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TL and RSB: Conceptualization, Writing – Original Draft. LZ, SET, SARP and PSA: Writing – Review & Editing, Visualization, Supervision. MFM: Team, Conceptualization, Writing – Review & Editing, Visualization, Supervision, Project administration. All authors made the final approval of the version to be submitted and agree to be accountable for all aspects of the work.

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