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Prehospital Emergency Care in Sepsis: From the "Door-to-Antibiotic" to the "Antibiotic-at-Door" Concept?

To the Editor:

In the December 2018 issue of *AnnalsATS*, Peltan and colleagues reported that for patients with sepsis without hypotension, antibiotic initiation is faster when patients are cared for by a prehospital advanced life support team, but not a basic life support team (1). Although the authors did not report the effect on a strong outcome parameter (i.e., mortality), their results promote systematic care of patients presenting with sepsis symptoms by an advanced life support team.

Nevertheless, as underlined by the authors (1), for sepsis, long antibiotic delays are associated with poorer outcomes. To date, no results are available from randomized controlled trials to determine the effect of prehospital antibiotic administration for patients presenting with sepsis (2). Unfortunately, previous studies that evaluated this strategy have shown negative results (3), but this could be at least partly explained because most of these trials have recruited patients with varying levels of septic severity, and not only those presenting with septic shock (4). Furthermore, from an emergency medical service point of view, the criteria proposed by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) do not seem to be appropriate (3). Indeed, excluding the most caricatural septic cases, early identification of the sepsis and assessment of its severity during the phone call to the emergency medical service dispatch center are difficult (4), but conversely, it represents the prerequisite needed to determine the appropriate care response (advanced life support vs. basic life support) for an individual patient.

Finally, beyond early sepsis recognition, functional and survival prognosis of patients could be much more improved not only after an isolated specific intervention such as prehospital antibiotic administration (5), but also after introduction of a "bundle of care" strategy, including hemodynamic optimization. To date, the SAMU Save Sepsis is the only trial that evaluates the effect of prehospital initiation of a bundle-of-care strategy on mortality in severely septic patients (6). This French prospective multicentric study aims to determine whether an aggressive therapeutic option, with early antibiotic administration, fluid loading, and eventually catecholamine administration, initiated early "at the door" of the patient by a prehospital medical emergency medical service team, could allow for a reduction in the mortality of patients suffering from severe sepsis and/or septic shock.

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Reply: From the "Door-to-Antibiotic" to the "Antibiotic-at-Door" Concept?

From the Authors:

We appreciate the thoughtful comments from Jouffroy and Vivien regarding our study. We agree completely regarding the need for validated methods to risk stratify likely patients with sepsis well before the Sequential Organ Failure Assessment score becomes available. We are also eager for results from SAMU Save Sepsis and other innovative trials in early sepsis care that will help guide quality improvement efforts and also address persistent concerns that early antibiotic initiation is a marker of overall better sepsis care, rather than a direct driver of improved sepsis mortality (1). Data from these studies should also inform the debate currently raging on the potential adverse effects of accelerated antibiotic initiation (2–4) by quantifying any adverse effects and distinguishing between the process outcome of antibiotic overtreatment and actual patient harms (e.g., anaphylaxis, antibiotic-associated infections).

On a side note, similar to other recent authors (4, 5), Jouffroy and Vivien describe as "negative" Alam and colleagues' pioneering randomized trial of prehospital ceftriaxone for patients with infection plus the systemic inflammatory response syndrome (6). Setting aside the fact that 20% of patients were already receiving antibiotics and the unfortunate and extensive failures of randomization, this trial was powered for control group mortality fivefold higher than observed and an effect size 20–100% too large, given the achieved difference in antibiotic timing and the effect predicted from observational data. We would advise sepsis clinicians and researchers that referring to this randomized trial as "negative" without also noting that it was severely underpowered implies the trial provides considerably stronger evidence against early or prehospital antibiotics than it does in reality, particularly when the goal is to argue for more cautious efforts to accelerate antibiotics (4, 5).

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