Pediatric Septic Shock in the Emergency Department: Can We Set the Alarm Clock a Little Forward?*

How did it get so late so soon?—Dr. Seuss

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Septic shock is a complex clinical condition, which affects several thousands of children yearly, both in industrialized and developing countries (1–3).

Although septic shock is relatively infrequent in pediatric patients presenting in the emergency department (ED), it may constitute a life-threatening condition, which can often be difficult to recognize, particularly in the early phase. Clinical studies have shown that early and appropriate therapy is associated with improve outcomes, although persistent septic shock adversely affects survival in a time-dependent way (4, 5). Thus, timely diagnosis and treatment are essential for septic shock reversal (6). Current management guidelines, including those promoted by the Surviving Sepsis Campaign (SSC) initiative, emphasize the role of early recognition and timeliness of treatment, including broad-spectrum antibiotics, IV fluid resuscitation, and vasoactive therapy, among others (7).

Despite recent large, randomized trials in adults reported no clear benefits in adopting protocol-based sepsis management (8), in the pediatric ED setting, sepsis protocols and quality improvement (QI) strategies have been associated with improved process measures, such as time to antibiotic administration and time to IV fluid resuscitation (9–11). Similar improvements have been observed also for outcome measures, such as an increased number of cases of septic shock between each death, or reduction of hospital length of stay (LOS) (10, 12).

Consistent positive results were generally observed in large tertiary centers but have been reported from medium-sized centers as well (13).

In this issue of *Pediatric Critical Care Medicine*, Workman et al (14) report interesting findings from a selected population of 321 children with septic shock, presenting in a pediatric ED and requiring admission to the PICU. The objective of the study was to evaluate the association between timely delivery of therapy and several outcomes, the primary outcome being the development of new or progressive multiple-organ failure (NP-MODS). To this end, by following the SSC guidelines, they chose three elements of a bundle, all to be accomplished within 1 hour of arrival in the ED: 1) administration of antibiotics; 2) administration of at least 60 mL/kg IV resuscitation fluids; 3) administration of an inotropic or vasoactive agent for fluid-refractory patients.

Plausibly, the authors were expecting better results in the group of patients receiving SSC compliant care, compared with patients receiving the same therapy but at a slower pace, that is, beyond the first hour since arrival in the ED. Overall, only 36% of patients received all bundle measures within 1 hour. However, the majority of remaining patients did so within 2 or 3 hours. Interestingly, primary and secondary outcomes were not significantly different in the two groups. These apparently unexpected findings may have several explanations, such as the relatively small sample size and the low occurrence of NP-MODS observed in the study population. In addition, even though all patients were admitted to the PICU, most of them had a relatively short PICU and hospital LOS (median values were 1.7 and 5 d, respectively), although only one third of patients did need mechanical ventilation and/or had to be supported with continuous infusion of vasoactive drugs. In addition, overall mortality was rather low (5.3%), increasing to 14.4% when considering the subgroup of patients with complex chronic conditions but decreasing to 0.9% in the subgroup of previously healthy subjects (14). All these features suggest that the majority of these patients were affected by a moderately severe form of septic shock, and this may have reduced the potential of timely therapy to demonstrate any superiority on efficacy endpoints, such as the development of new or progressive MODS.

Even more importantly, as previously mentioned, patients who did not receive the bundle interventions within the first hour, did so within 2 or 3 hours in most cases. Therefore, a reasonable doubt arises: do we expect that such a relatively small delay in getting appropriate care could translate in any relevant effect on clinical outcomes? Further research is needed to properly address this question.

Of note, other authors have reported marked improvements in the care of children with septic shock presenting in ED, by implementation of QI initiatives (9, 10, 12). In a prospective cohort study, Paul et al (12) reported improved adherence to a five-component sepsis bundle, with increased adherence to Pediatric Advanced Life Support guidelines.

In another prospective cohort study of children with sepsis, presenting to a tertiary ED in Australia, a before-after

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study design was used to monitor changes in targeted process measures, aimed at improving compliance with current sepsis guidelines (15). The primary outcome was hospital LOS. Through a preliminary analysis, the authors could identified several systematic delays in providing critical interventions in the early phase of treatment in the ED, including antibiotic administration, fluid resuscitation therapy (FRT) and/or scarce use of pressure bag, rapid infuser, or manual push, and venous blood sampling for gas analysis and lactate.

An ad hoc comprehensive educational and QI initiative was administered to all clinicians, resulting in a marked reduction in time to antibiotic administration, rapid administration of FRT, and early measurement of venous blood gas analysis. Of note, the combination of these improvements was associated with a significant reduction in hospital LOS (15). Unfortunately, the authors could not discern which of the study interventions was responsible for the observed reduction of hospital LOS. Furthermore, how the level of timeliness of each intervention could have impacted on the ultimate outcome was unknown. Indeed, well-designed, randomized controlled studies would be needed to clarify this matter. However, the feasibility of such studies may not be obvious, for practical reasons and for inherent ethical issues.

After all, early recognition of a child with septic shock remains key to ameliorating the timeliness of any possible intervention in these vulnerable patients. Indeed, particularly in most critically ill patients, even few minutes of delay in providing care may have unfavorable consequences. Conversely, less severe cases may allow the clinicians a wider temporal window for initiating the bundle interventions. However, currently recommended timing metrics should be still considered as measures of quality of care.

Thus, let's keep the "septic shock clock" set at 1 hour, until proven otherwise.

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