The Quest for Evidence on Time to Antibiotics in Children With Sepsis—Finding the Sweet Spot

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DOI: https://doi.org/10.1001/jamanetworkopen.2024.13926

JAMA Network Open

Invited Commentary | Pediatrics

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Timely recognition and management of sepsis in children remains a major challenge in pediatric emergency care, where most patients with sepsis present. Avoiding delays in antimicrobial treatment for children with sepsis, such as delays in recognition, escalation, prescription, or administration, represents a core feature of quality improvement initiatives; at the same time, the quest for the optimal threshold in relation to time to antimicrobials continues to stir controversy. The Surviving Sepsis Campaign[1] advocates that broad-spectrum antibiotics should be administered as soon as possible upon recognition of septic shock. Although constrained by practical and ethical considerations that preclude randomized clinical trials in this field, the available observational evidence consistently indicates that early antibiotic treatment for children with septic shock improves outcomes, such as mortality, severity in terms of duration and extent of intensive care unit support, and length of hospital stay.[2-4] However, translating the biologically obvious urgency for early antibiotic treatment in a child with proven sepsis of bacterial origin into actionable, timely recommendations applicable to larger patient groups in empirical settings where emergency department (ED) physicians need to make rapid decisions—often based on best educated guesses and in the absence of detailed laboratory results—poses considerable challenges. The heterogeneous and commonly nonspecific presentations of children with sepsis, along with milder viral infections dominating epidemiology in pediatric EDs, the potential for rapid clinical deterioration, and need to ensure optimal use of resources such as staff, hospital beds, laboratory tests, and antimicrobials, necessitate a delicate balance between immediate action and accurate diagnosis, complicating the establishment of broad, generally applicable treatment timelines.

The retrospective cohort study conducted by Lane et al,[5] which leverages data from the Improving Pediatric Sepsis Outcomes (IPSO) collaborative across 51 US hospitals, provides new insights concerning the critical issue of antibiotic timing and its association with sepsis-related mortality in pediatric patients. The main goal was to identify time points when delays in antibiotic administration are associated with increased risk of mortality outcomes in children with sepsis. The study included 19 515 children aged 29 days to less than 18 years with a diagnosis of sepsis over a 5-year period. The authors observed that delays in antibiotic administration beyond 330 minutes after ED presentation were associated with significantly increased mortality. Patients who received antibiotic treatment within 330 minutes of presentation (19 164 patients) had sepsis-attributable 3-day mortality of 0.5% and 30-day mortality of 0.9%. Patients who received antibiotics at 330 minutes or later (351 patients) had 3-day sepsis-attributable mortality of 1.2% and 30-day sepsis-attributable mortality of 2.0%.

The study[5] is commendable for its sample size compared with previous work,[3,4] capturing a range of US hospitals that participate in the largest pediatric sepsis quality improvement effort globally.[6] The IPSO collaborative focuses on enhancing pediatric sepsis outcomes by promoting earlier recognition and treatment of children, with rigorous quality metrics based on established criteria prospectively captured in a well-described database. Unlike the previous International Pediatric Sepsis Consensus Conference criteria, which relied on systemic inflammatory response syndrome markers, and the Phoenix criteria,[7] which use a quantifiable sepsis score indicating organ dysfunction, IPSO criteria are pragmatically built on clinical indicators and interventions, as well as

coding to identify sepsis cases post hoc, and have been validated internally. However, this intention-to-treat approach inevitably includes many children treated for suspected sepsis with less severe presentations compared with those identified by the more stringent Phoenix criteria. The operationalization of sepsis, septic shock, and time to treatment, which is central to the analysis of the work by Lane et al,[5] relies on how IPSO captured the time of sepsis recognition (which is the earliest time of a sepsis screen, huddle, order set use, first intravenous fluid, or antibiotic administration), labeled as functional time zero. Given the inherent difficulties with labeling sepsis onset, the authors defined time from presentation to ED to first antibiotic administration as the primary exposure. The authors intentionally limited the cohort to patients who were recognized within the first hour of arrival to the ED to minimize confounding by delayed recognition. Of 57 643 patients meeting the required age criteria presenting directly to the IPSO sites (ie, 70 296 patients total minus 7667 excluded for age restrictions and 4986 from other hospitals), 7247 had various missing data (1254 came from centers with missing data, 5190 were missing data for age, and 830 had antibiotic time not documented), 14 541 had sepsis recognized outside the ED, 11 529 had sepsis recognized 1 hour or longer after presentation, 4335 were excluded because the recognition was based on administration of antibiotics and/or fluids, and 449 were excluded because the antibiotic was given more than 7 hours after presentation.[5] Although the authors provide rationales for these exclusions, such procedures in an observational cohort risk the introduction of selection bias. Generalizability of the findings is further hampered because the data stem from an established collaborative aiming to improve recognition and time to treatment (the median time to antibiotics in Lane et al[5] was 69 minutes), are restricted to the US health care system, and are dominated by large specialized children's hospitals. Furthermore, consistent with many pediatric ED studies, overall mortality was low (0.9% 30-day mortality),[5] limiting the power to estimate effect sizes for the primary outcome of sepsis-attributable 3-day mortality associated with incremental 30-minute time-to-treatment windows.

Optimal cutoffs were derived from logistic regression models adjusted for site, demographics, major comorbidities, and bacteremia using an interrupted time series model, which resulted in an inflection point of 330 minutes, after which mortality increased. Of note, serum lactate levels and meeting IPSO critical sepsis criteria were the only severity features used for risk adjustment. The interpretation of results must thus consider confounding by severity and/or indication because patients facing imminent mortality owing to the severity of their condition might receive prompt treatment yet manifest higher mortality rates. This likely explains the paradoxically elevated mortality rate for antibiotics administered within 30 minutes. In addition, the lack of detailed data on the prevalence of microbiologically confirmed sepsis diagnoses in this cohort makes it difficult to distinguish who improved because of timely administration of antibiotics, as opposed to who received unnecessary treatment in the presence of viral infections or noninfectious disease. The authors were unable to draw firm conclusions because of the small number of outcomes in patients in the bacteremia subgroup included in their post hoc analysis. Although the authors should be commended for endeavoring to improve care for children with sepsis, their observations illustrate methodological and practical challenges to be considered for future studies and warrant careful consideration in relation to the impact of these findings, even more so for settings with different resources, epidemiology, and patient mix.

The optimization of sepsis management ideally would focus on identifying those patients with predicted bacterial infection who need rapid antibiotic therapy and who are likely to deteriorate, warranting escalation of care (eg, intensive care support or transport to a more specialized facility). Although novel transcriptomic biomarkers perform well to discriminate bacterial from viral infection in children developing organ dysfunction,[8] they are not yet available on point-of-care platforms or used outside research studies. Thus, although it appears biologically plausible that in less severely ill children, allowing up to approximately 330 minutes as per the findings of Lane et al[5] for investigations and observations may not necessarily result in increased mortality, future studies should attempt to assess temporal relationships by focusing on patients who are most likely to

benefit from early intervention. The question to balance will then be to decide on the acceptable number of children with uncertain sepsis who get treated as a result of mandates for early care, vs the benefit of timely treatment in those most likely to have bacterial infection progressing to organ or multiorgan dysfunction.

ARTICLE INFORMATION

Published: June 5, 2024. doi:10.1001/jamanetworkopen.2024.13926

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Conflict of Interest Disclosures: None reported.

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