

# Early Recognition of Sepsis Saves Lives, but a 1-Hour Antibiotic Target Misses the Mark

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Sepsis is a dysregulated host response to infection that causes shock and multiorgan dysfunction.<sup>1</sup> Of the estimated 50 million people worldwide who develop sepsis annually, ~10 million die, and survivors can have lasting or permanent organ damage.<sup>2</sup> Long-term effects include renal failure, cardiac damage, and neurocognitive dysfunction.<sup>3-6</sup> Quick recognition and resuscitation of sepsis including antibiotic administration has been championed by acute care and infectious disease specialties in both adult and pediatric medicine. In the pediatric population, there is some evidence to support these efforts, showing that shorter time to recognition of sepsis, initiation of treatment, and completion of a sepsis bundle lead to improved outcomes.<sup>7-9</sup> However, one component of many sepsis quality-improvement recommendations, the goal of antibiotic administration within an hour of sepsis recognition, is not well supported by available evidence and should be challenged.<sup>1</sup>

Since 2004, the Surviving Sepsis Campaign's "International Guidelines for Management of Sepsis and Septic Shock" have included a strong recommendation for administration of intravenous antibiotics within 1 hour of recognition of sepsis, citing published evidence that empirical antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour.<sup>1,10,11</sup> This recommendation has been applied to management of both children and adults despite an acknowledgment that "the feasibility with which clinicians may achieve this ideal state has not been scientifically evaluated."<sup>1</sup> In response, many institutions and collaboratives have adopted systematic measures to improve rapid recognition of sepsis, such as universal sepsis screening and "1-hour sepsis bundles" that include urgent antibiotic administration in addition to laboratory testing and fluid resuscitation or vasopressors as appropriate.<sup>12-14</sup> Despite these efforts, antibiotic administration is still often delayed beyond 1 hour.<sup>7</sup> Should this be cause for distress?

There is a growing body of evidence that a 1-hour target for antibiotics in pediatric sepsis might be not only difficult to achieve but also unnecessary or even counterproductive. In the current issue of *Hospital Pediatrics*, Lane et al<sup>15</sup> used a single-center retrospective cohort study to evaluate the effect of delays in antibiotic administration on clinical outcomes for pediatric patients with suspected septic shock. The study, conducted between 2007 and 2015, included 1377 episodes of suspected sepsis. The investigators used a pragmatic definition of suspected septic shock, which included signs of hypotension, poor tissue perfusion, or altered mental status and applied a multivariable analysis to attempt to control for confounders. Almost all participants (93%) received antibiotics within 3 hours of sepsis recognition. The main finding of the study is that a longer time to antibiotics was not

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significantly independently associated with an increase in the risk of ICU admission, the duration of ICU care, persistent organ dysfunction on day 2, or mortality. This finding persisted after controlling for identified confounders. The authors conclude that the optimal target for time to antibiotics in pediatric sepsis is not yet defined.

Although controversial, the finding that delays in administration of antibiotics (within a reasonable margin) might not affect sepsis outcomes in children is not new. In an analysis of pediatric sepsis episodes in New York state, Evans et al<sup>9</sup> found that outcomes were similar for antibiotic therapy given between 15 minutes and 4 hours. Similarly, in a study that did find that delayed antibiotic therapy for pediatric sepsis was associated with poorer outcomes, Weiss et al<sup>16</sup> noted that the risk increase was not apparent until antibiotics were delayed for at least 3 hours after recognition. Although all of these studies suffer from the possibility of confounding by indication (the tendency to give more aggressive therapy to patients who are sicker), the result is consistent across studies and persists after attempts to control for confounders. In contrast to the lack of apparent benefit from earlier antibiotics, Lane et al<sup>15</sup> did find that early recognition of sepsis and immediate administration of crystalloid fluid resuscitation seemed to improve outcomes. These data suggest that the most important aspects of sepsis management within the first hour of diagnosis are protocolized management, appropriate level of care, and rapid fluid resuscitation. This is consistent with the theory that correcting metabolic defects, hypoxia, and tissue hypoperfusion are more urgent than killing bacteria.

Knowing whether it is safe to delay antibiotics for up to 3 hours in pediatric patients with suspected sepsis is important.<sup>17</sup> Because most patients presenting to pediatric emergency departments meet criteria for systemic inflammatory response syndrome,<sup>18</sup> failing to allow for time to thoughtfully discriminate between those who have viral illnesses or focal infections and those with

sepsis can mean widespread use of broad-spectrum antibiotics “just in case.” And pressure to ensure administration of antibiotics within the first hour for patients with sepsis will inevitably lead to administration of inappropriate antibiotics to a large number of patients without sepsis,<sup>19</sup> which will increase the risk of antibiotic-resistant infections at a personal and community level.<sup>20</sup> This is especially important in pediatrics because many children with suspected sepsis have at least one complex chronic condition that puts them at high risk of repeated antibiotic exposures and acute care presentations.<sup>7</sup>

So, what is to be done? One hopeful note comes from quality-improvement work that aims to help clinicians use available tools and their clinical experience to identify and treat sepsis rapidly but not thoughtlessly. Scott et al<sup>21</sup> recently reported single-institution experience with an emergency department intervention in which pediatric patients with suspected sepsis were stratified as “sepsis stat” or “sepsis yellow” depending on clinical features at presentation. This allowed them to delay treatment long enough to determine that 1 in 4 of the sepsis yellow patients did not require antibiotics and could safely be discharged from the hospital. This example shows how a careful approach to risk stratification can improve care for patients with suspected sepsis without encouraging overuse of antibiotics.

As we go forward, it will be vital to resist pressures to mandate administration of antibiotics in an arbitrary and nonevidence-based time frame to all children with suspected sepsis. Although early data suggested a 1-hour antibiotic target might be appropriate, we should continually reevaluate the evidence and revise our interventions and goals accordingly to optimize patient outcomes. We also must focus on continuing to develop tools that not only help us to recognize sepsis but also differentiate it from the haystack of other serious and benign conditions that surround it. In evaluating interventions to improve care of patients with sepsis, we must concurrently measure and report their effects on patients without sepsis.<sup>22</sup> As

we do this, we can thank Lane et al<sup>15</sup> for adding to the evidence that it is safe to take a little breathing room for thoughtful decisions about antibiotics in children with suspected sepsis.

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