Medical News & Perspectives

In Treating Sepsis, Questions About Timing and Mandates

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In 2012, Rory Staunton, a 12-year-old boy from Queens, New York, died from sepsis after his pediatrician and an emergency department (ED) physician reportedly misinterpreted warning signs—a high fever and vomiting, but also a cut on his arm, and severe leg pain—as an intestinal illness and dehydration. He was discharged from the ED, but his condition deteriorated. He was readmitted the next day. However, he died in the hospital's intensive care unit (ICU) 2 days later.

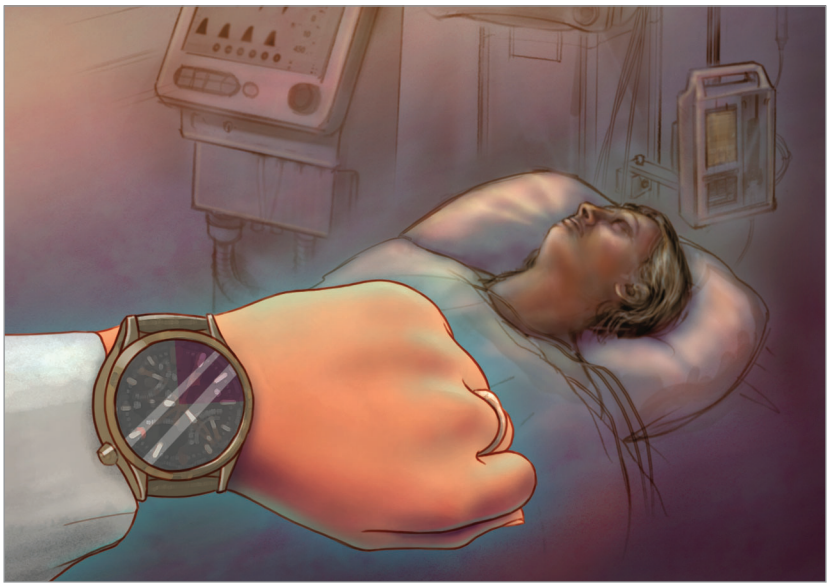
Staunton's story, although tragic, is not necessarily surprising to physicians. "Sepsis in its early throes, even if dire under the surface, can masquerade as a far milder problem," said Derek Angus, MD, MPH, chair of the department of critical care medicine at the University of Pittsburgh Medical Center, who was not involved with Staunton's care. "The trick is helping physicians to raise their index of suspicion in the 'right' cases—no easy task."

Staunton's death inspired the passage of Rory's Regulations in New York state the following year. The initiative requires New York hospitals to have evidence-based protocols for the early recognition and treatment of sepsis, now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The regulations stipulate that hospitals collect sepsis data and report it to the state annually.

Now, investigators have mined the data to see how much timing really matters in sepsis care. Researchers led by Christopher Seymour, MD, of the University of Pittsburgh's Clinical Research, Investigation, and Systems Modeling of Acute Illnesses (CRISMA) Center, recently published a report based on data from more than 49 000 adult patients with sepsis and septic shock treated at 149 New York hospitals from April 2014 to June 2016, after the state adopted Rory's Regulations.

Under the regulations, hospital sepsis protocols must contain a 3-hour bundle of care that includes serum lactate testing and administration of broad-spectrum antibiotics after obtaining a blood culture. A mandated 6-hour bundle includes fluid resuscitation—the administration of intravenous fluids to increase blood volume—for patients with low blood pressure (hypotension) or elevated lactate levels, which indirectly indicate low oxygen levels in the body's tissues and organs.

The data revealed that administering antibiotics and completing the 3-hour bundle of care more quickly appeared to save lives—but rapid completion of an intravenous fluid bolus did not.



The mixed findings highlight the ongoing uncertainty around sepsis management at a time when additional states are moving to mandate hospital protocols for the challenging condition. Some experts caution that regulating sepsis care, although well-intentioned, could have unintended consequences.

"The idea that we should be paying attention to this disease that kills hundreds of thousands of people per year—absolutely we should," said Michael Howell, MD, an associate professor of medicine and chief quality officer at the University of Chicago Medicine, who was not involved with the new study. "Regulation and legislation helps with that, but there can be a downside to it if the regulation or legislation mandates the wrong thing."

Every Hour (Probably) Matters

The mortality improvements associated with rapid antibiotic administration and completion of the 3-hour bundle in the study were small but clinically meaningful. Because so many patients die from sepsis—approximately 215 000 annually in the United States—even a small improvement in the risk of death is valuable, said Howell, who specializes in critical care and pulmonary medicine.

Most of the patients in the study—83%—had the 3-hour bundle completed within 3 hours. For a typical patient, the odds of dying in the hospital increased 4% for every hour longer it took to complete the 3-hour bundle. Patients had 14% higher odds of dying in the hospital if their 3-hour bundle was completed or antibiotics were administered between 3 and 12 hours compared to before 3 hours. And the predicted risk of dying was approximately 3 percentage points higher, on average, among patients whose 3-hour bundle was completed within 6 hours than within 1 hour.

"I think these data suggest to us that hours, if not minutes, matter in our sickest patients with sepsis and that we need to get treatment started as soon as possible," Seymour said.

The findings are generally consistent with updated international practice guidelines for sepsis management in adults, which recommend the administration of broad-spectrum antibiotics within 1 hour of sepsis recognition. (Pediatric sepsis guidelines are currently in development.)

However, Seymour said, the lack of association between the timing of completion of the fluid bolus and in-hospital mortality suggests the need for further study, particularly because the guidelines recommend aggressive fluid administration within 3 hours in patients with sepsis-induced hypotension.

"In my mind it's disappointing because I think that most of us feel that a key aspect of these early treatments should be fluid resuscitation," said Damon Scales, MD, PhD, an intensivist at Sunnybrook Health Sciences Centre in Toronto, Ontario, Canada.

Seymour, who is also an assistant professor in the departments of critical care and emergency medicine at the University of Pittsburgh School of Medicine, noted that hospitals or study teams may have documented completion of fluids inconsistently, which could have affected the results. Or there may be no real association between fluid timing and mortality.

It's also plausible that early fluids helped some patients and harmed others, resulting in no net gain or loss, Angus said.

"These are the things we need to tease out in a larger, prospective trial that randomizes patients' different fluid strategies," Seymour said. "In the absence of any new evidence, I do think we should continue to lean on our clinical practice guidelines and our policies that are in place."

The Case for Randomized Trials

In fact, no large studies have randomized the timing of antibiotics in sepsis, and most trials of fluid timing have randomized patients after administration of the initial fluid bolus. The core elements of the sepsis management guidelines—early recognition, early antibiotics, early fluids—are largely based on a mixture of common sense and observational studies, Angus said, and not every clinician agrees with all aspects of them.

The uncertainties could have important clinical implications. A standard of less aggressive sepsis treatment could result in more patient deaths, whereas widespread aggressive management could contribute to antibiotic resistance and previously reported increases in negative outcomes associated with liberal fluid resuscitation, such as longer ventilator use, pulmonary edema, and death.

The guideline recommendations for early fluids are on particularly shaky ground. Although Seymour's recent study didn't note increased morbidity or mortality with earlier fluid resuscitation, others have.

"We don't really know what type of fluid, how much fluid, or how fast to give intravenous fluid to the septic patient," Seymour said.

The recent Protocolized Resuscitation in Sepsis Meta-Analysis (PRISM) study—a collaboration between US, Australian, New Zealand, and UK investigators—showed that an aggressive 6-hour resuscitation protocol had similar mortality outcomes as usual care but was associated with greater use of intensive care and cardiovascular support and higher hospitalization costs. Usual care varied, but there was no apparent benefit of introducing a timed protocol even in EDs with the least aggressive resuscitation practices.

In light of those results, Howell said a randomized trial directly comparing a conservative vs a liberal fluid strategy in the early management of patients with sepsis and septic shock is needed. Such a study is in the planning stages through the National Heart, Lung, and Blood Institute–funded Prevention and Early Treatment of Acute Lung Injury (PETAL) Network and is slated to begin enrollment by mid-2018.

Meanwhile, although most physicians agree that earlier antibiotics are probably better for sepsis outcomes, many might harbor skepticism about just how linear the relationship is. Can even a 1-hour delay truly increase the odds of death? "Some might think, better to wait an hour or 2 while collecting information to be more sure the person really is infected," said Angus, who oversees the CRISMA Center but was not involved with Seymour's recent study.

One commonly cited 2006 study of medical records from more than 2700 adult patients with septic shock found that each hour of delay in administering antibiotics decreased survival by 7.6% on average. In contrast, a 2015 systematic review and meta-analysis of observational studies found no significant mortality benefit of administering antibiotics within 3 hours of ED triage or 1 hour of septic shock recognition.

Even in Seymour's study, which supports the use of early antibiotics, small odds ratios raise concerns about possible confounders, Howell said: "It gives me a little bit of pause about whether future studies may contradict this."

Although it's highly plausible that earlier antibiotics save lives, other scenarios can't be definitively ruled out without randomized trials. For instance, it's possible that antibiotics were unintentionally delayed in cases where the diagnosis was difficult. In those cases, all care—not just antibiotics—might have been delayed, increasing the risk of death. Or, patients for whom the diagnosis is difficult may be, on average, sicker and therefore at higher risk of death.

Angus said the study underscores that time really is of the essence when it comes to antibiotics in the first few hours of sepsis, but that "as long as there's not a randomized trial… people's opinions may swing back and forth."

There is a problem, however, with planning those investigations: Now that a standard of care has been established, randomized trials of antibiotic timing for hospital patients with sepsis may be considered unethical.

There is more uncertainty around sepsis management in the out-of-hospital setting—and no guidelines—which make it a less fraught opportunity for randomized trials investigating treatment timing. At least 3 trials in the out-of-hospital setting are under way or in the planning stages, including a study led by Scales that will evaluate whether paramedic-administered antibiotics, fluids, or both, improve sepsis survival compared with usual care. These trials could usher in a new approach for the diagnosis and treatment of sepsis that starts in the ambulance, not the ED.

Angus believes that in the future, randomized trials could be possible in a "Goldilocks" cohort of hospital patients with low or intermediate suspicion of infection and sepsis who might be harmed by aggressive treatment. "There may be an 'on-the-fence' group in whom clinicians would agree there is adequate equipoise" to conduct a trial, he said. However, he added that identifying these patients quickly will require more rapid diagnostics than are currently available—likely a combination of clinical tests and pathogen or host response biomarkers.

A Lifesaving Law?

The question of whether Rory's Regulations save lives isn't asked or answered in

the recent study. Sepsis deaths were already decreasing in the United States before the mandate, and determining its contribution to the trend in New York will require a comparison with national data over the same time period.

Last year, Illinois passed Gabby's Law, requiring hospitals to adopt evidence-based sepsis protocols, and the Rory Staunton Foundation is seeking mandatory sepsis protocols in every state by 2020.

Yet "the certainty of evidence in what to do in sepsis has declined year over year," Howell said. In this climate of uncertainty, statewide mandates may be premature. Although public policies can create much-needed awareness around sepsis, experts say they may rob physicians of their clinical discretion at a time when best practices are still evolving and antibiotic stewardship is top of mind.

"It's really hard to simultaneously say, 'Give antibiotics as early as possible in patients before you even know if they're infected or not,' and at the same time, 'Please be judicious with the use of antibiotics so as not to promote antimicrobial resistance,'" Angus said. "That's sort of driving with a foot on the accelerator and the brake. It's really challenging."

In the end, physicians will err on the side of antibiotics, warned Emily Ko, MD, PhD, a hospitalist at Duke Regional Hospital who conducts research on biomarkers for sepsis and infectious disease at the Duke Center for Applied Genomics and Precision Medicine. "Protocol-driven care that mandates early antibiotic use will likely push physicians to prescribe antibiotics or face penalties even when a noninfectious or viral etiology is felt to be more likely the cause of symptoms," she said.

Mandating rapid sepsis treatment may also force ED staff to deprioritize other life-threatening conditions, Angus said: "If I put sepsis to the top of the list, what drops down on the list? This is where a lot of this contentiousness and controversy arises." ■

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