In March 2012, Rory Staunton, a 12-year-old boy in Queens, New York, cut his arm playing basketball in school. The next day, his parents, worried about his fever and leg pain, took him to see his pediatrician and then, the day after, to the emergency department at NYU Langone Medical Center. He was discharged with a diagnosis of an upset stomach and dehydration but died 3 days later from sepsis (http://nyti.ms/1P8l3uR). His parents later founded the Rory Staunton Foundation to increase public awareness of the condition (http://bit.ly/1ZEB798).

Rory’s story illustrates the stealth and rapid progress of sepsis, which affects about 1 million people a year in the United States and kills about a quarter of those affected (http://1.usa.gov/1Ig4SDq). New guidelines published in this issue of JAMA, which are intended to increase the precision and speed of sepsis diagnosis, shift the diagnostic focus from infection with systemic inflammation to infection-triggered organ dysfunction, eliminate the distinction between sepsis and severe sepsis, and refine the definition of septic shock (Singer M et al. JAMA. 2016;315[8]:801-810).

The task force defined sepsis as a “life-threatening organ dysfunction caused by a dysregulated host response to infection” (Singer M et al. JAMA. 2016;315[8]:801-810).

[The task force] felt very strongly that we needed to differentiate a straightforward infection from one that can cause organ dysfunction or death,” said Mervyn Singer, MD, the guidelines’ co-lead author and director of the Bloomsbury Institute for Intensive Care Medicine at University College London. He explained that this new emphasis on organ dysfunction, rather than infection, stems from an evolving understanding of the pathophysiology of sepsis that encompasses both inflammatory and anti-inflammatory responses.
and coagulation, metabolic, and hormonal changes. Such changes cause a dysregulated response to infection and can lead to organ dysfunction.

In addition, the systemic inflammatory response syndrome (SIRS) criteria, which have been used to diagnose sepsis for more than 20 years, can occur in normal disease processes such as the common cold or even when a person vigorously exercises.

"Sepsis is much more nuanced than previously appreciated," explained Derek Angus, MD, MPH, one of the guidelines' coauthors and a professor and chair of the department of critical care medicine at the University of Pittsburgh School of Medicine. "Certain parts of the inflammatory response are overactive, and some are underactive."

**Diagnostic Criteria**

To identify clinical diagnostic criteria that best reflect this new definition of sepsis, the task force analyzed the SIRS criteria, Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score, and Logistic Organ Dysfunction system (LODS) for validity in predicting mortality for patients with suspected hospital- or community-acquired infections (Seymour CW et al. JAMA. 2016;315(8):762-774). The SOFA and LODS have been developed and used clinically to evaluate organ dysfunction among patients in the intensive care unit (ICU) based on clinical and laboratory measurements of several physiological parameters, including coagulation, blood gases, and oxygen level (Ferreira FL et al. JAMA. 2001;286(14):1754-1758; Le Gall JR et al. JAMA. 1996;276(10):802-810).

A retrospective cohort analysis of EHR data found that among adult patients with suspected infections in the ICU, the predictive validity of SOFA and LODS for patient mortality was statistically similar, and both were higher than SIRS. For example, in a pair of patients with similar characteristics who are in the ICU with an infection, there would be a 74% chance that the one who died had a higher SOFA score than the one who lived, but only a 64% likelihood that the one who died had a higher SIRS score, meaning lower predictive validity for SIRS. Patients in the ICU with a SIRS score that increased by 2 points or more had a 1- to 2-fold rate of hospital mortality, compared with a 3- to 11-fold increase in hospital mortality among patients with a SOFA score that increased by 2 points or more.

"Conceptually, [SIRS as diagnostic criteria for sepsis] no longer has any legs... it sounded like a good idea in 1992, but it has lost steam," said Angus.

Given these findings, new guidelines recommend that clinicians use SOFA to assess patients in the ICU with a diagnosed or suspected infection. With the new guidelines, a patient with a diagnosed or suspected infection with an increase of 2 points or more from the baseline SOFA score meets the criteria for sepsis.

Because SOFA requires laboratory tests, the task force also recommended that clinicians use a streamlined process called quick SOFA (qSOFA) to evaluate patients for possible sepsis outside of the ICU. Using multivariate logistic regression, the task force developed the qSOFA model, in which a clinician assesses a patient for an altered mental state, systolic blood pressure of 100 mm Hg or less, and respiration rate of 22 breaths/minute or greater. If a patient meets any 2 of the qSOFA criteria, the guidelines recommend that the patient be more closely monitored, given more intensive treatment as needed, and possibly referred to a specialist as needed (SOFA score)." said Angus. "It could be done in an ambulance, it could be done by Marines on the battlefield... it very quickly identifies among infected patients those who have a far greater chance of doing badly."

Both qSOFA and LODS have a high predictive ability for mortality outside of the ICU, but qSOFA is much quicker and easier to do, said Christopher W. Seymour, MD, MSc, assistant professor of critical care and emergency medicine at the University of Pittsburgh School of Medicine, a task force member, and lead author of the statistical analysis of the sepsis data.

"It is really remarkable that a model with 3 vital signs could return results [similar] with a model that has so many lab tests that may take a long time," Seymour said.

Based on Delphi consensus processing of results from a systematic literature review and meta-analysis of observational studies, surveys, and cohort studies of EHR databases and the SCCM and ESICM’s Surviving Sepsis Campaign’s registry of 28,150 patients in 18 countries, the guidelines also updated the definition of septic shock to sepsis with "underlying circulatory and cellular/metabolic abnormalities" that can result in substantially greater mortality (Shankar-Hari M et al. JAMA. 2016;315(8):775-787). The clinical criteria were also redefined as sepsis with hypotension needing vasopressor therapy after fluid resuscitation to elevate mean arterial pressure to 65 mm Hg or greater.

The new definition of septic shock will result in more precise diagnoses and better epidemiological tracking of septic shock, said Singer. "Fewer patients will be diagnosed, but it will have a more robust characterization."

**Adoption in the Clinic**

Jeffrey A. Kline, MD, a professor of emergency medicine and a vice chair of research at Indiana University School of Medicine, had mixed thoughts about the new sepsis guidelines. While the guidelines use more concrete physiological criteria for diagnosing the condition, which he said may reduce overdiagnosis, he questioned whether the gain in clinical precision will be worth the need to re-educate clinicians.

"It took us 5 to 10 years to get physicians to understand what sepsis is, and now we will have to change it," said Kline. "I'm not sure if it is worth the complexity of adding the SOFA score."

Angus and Singer predict that the guidelines will not be the final word in sepsis diagnosis but, rather, serve as a starting point for ongoing discussions and additional research into the often deadly condition.

Seymour added that prospective studies would need to be conducted to validate the newly developed qSOFA scoring once it starts being used by clinicians.

"[The task force] recognized that it can't please everyone on every point," said Singer. "It is an iterative process. As our knowledge expands, we will be able to refine [the guidelines] even further."