Study begins to reveal clues to the cause and progression of sepsis

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Not all patients with sepsis mount the same immune response, even when they look the same clinically, according to findings from the first large-scale natural history study of sepsis. The results, published by University of Pittsburgh School of Medicine researchers in the August 13/27 issue of the *Archives of Internal Medicine*, indicate that past interpretations of how the immune system responds to infection – interpretations on which many experimental treatments were based – were incorrect.

This year, nearly 1 million Americans will develop sepsis, a result of the body's inflammatory response to an infection, which can lead to organ failure and death. More than 30 percent will die, making sepsis the 10th leading cause of death. While incidence rates of sepsis have been steadily increasing over the years, little is known about the condition. Past investigational treatments have been based on data from small studies, and most of these therapies have failed.

Researchers at the University of Pittsburgh believe that these treatments failed, at least in part, because of insufficient data to fully understand the complexity and variability of the inflammatory response to sepsis. To gain a better understanding into the mechanisms behind the condition, the researchers conducted the Genetic and Inflammatory Markers of Sepsis study (GenIMS), which collected extensive clinical and laboratory data geared to help analyze the risks of a person developing sepsis and dying. Data were collected from 2,320 subjects who came to hospital emergency rooms at 28 sites nationwide.

“With sepsis, we’re dealing with one of the deadliest diseases, yet we know so little about the condition. The situation is similar to what this country experienced over 50 years ago with heart disease and stroke – we knew that too many people were dying of cardiovascular disease, but we didn’t know enough about the disease to effectively treat and prevent it,” said Derek C. Angus, M.D., M.P.H., professor and vice chair of research, department of critical care medicine, University of Pittsburgh School of Medicine. “In response, the National Institutes of Health embarked on the Framingham Heart Study, the results of which have influenced everything we know about the prevention and treatment of cardiovascular disease. With our study, we’re hoping to do the same for sepsis, providing a greater understanding of the disease on which future treatment and prevention strategies can be based.”

For this analysis, researchers evaluated data from 1,886 of the study participants who were hospitalized with community-acquired pneumonia (CAP), the leading cause of severe sepsis. More than 30 percent of the subjects developed severe sepsis, of whom 26 percent died.

To determine the inflammatory response in the participants with CAP, the researchers measured cytokine levels daily for the first week of hospitalization and then weekly thereafter. They found that 82 percent of the participants with CAP had elevated cytokine levels. Levels were highest when the subject presented at the emergency room, tapered down over the first few days, but remained elevated throughout the first week of hospitalization – even after the clinical signs of infection had subsided. Levels were highest in those with fatal severe sepsis, lowest in those with CAP but no sepsis.

“Our data show that much of what we previously thought about the role the inflammatory response plays in sepsis was wrong or incomplete. We had thought the inflammatory response to infection was relatively short-lived, just a few days, and that it was similar in patients with similar

clinical signs. Instead, we found that the inflammatory response was extremely variable across patients—more than 50-fold differences were seen in some markers. Additionally, we found that the inflammatory response extends past the outward symptoms, far longer than previous data would suggest, and far longer than the courses of therapies used in unsuccessful clinical trials of experimental agents," said John A. Kellum, M.D., professor, department of critical care medicine, University of Pittsburgh School of Medicine. "We also found that the difference between the inflammatory response in a patient with a good outcome and a patient with a bad outcome is only a matter of degree."

The Pitt researchers say that in light of their results, treatments that completely abolish a specific component of the inflammatory response would be ineffective, and could be dangerous, since the inflammatory response is needed to address the underlying infection. Instead, they believe that therapies that address the chronic inflammatory response after sepsis and those that act more broadly on multiple components may yield better results.

"No one really knows why some people develop sepsis following an infection," said Scott Somers, Ph.D., who oversees sepsis grants at the National Institute of General Medical Sciences, which partially funded the work. "This large study gives us a much clearer picture of sepsis—and shows us that it's even more complicated than we thought."

The researchers plan to release several other reports from the GenIMS study in the coming months, which they hope will provide more clues to the condition.

Source: University of Pittsburgh Schools of the Health Sciences