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Immune function predicts infection risk among child trauma patients

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Researchers studying critically ill children with traumatic injuries have identified an immune marker that predicts which patients are likely to develop a hospital-acquired infection. The study, led by clinician-scientists at Nationwide Children's Hospital and published online in June in the journal *Shock*, is part of several larger efforts that could lead to the clinical implementation of quick-turnaround immune function tests and treatments to prevent or reverse immune system damage following critical illness or injury in pediatric patients.

Hospital-acquired, or nosocomial, infections pose a threat to any patient, but people who've suffered a traumatic injury have the highest risk of all, says Mark W. Hall, MD, senior author of the new study and division chief of Critical Care Medicine at Nationwide Children's. Dr. Hall and his colleagues have spent more than a decade studying this phenomenon and have honed in on a problem within the immune system as a possible contributor.

"With a normal immune response, the body responds to pathogens and eliminates them before they cause an infection. But in many forms of critical illness, we see the immune system unable to do those things," he says. Studies in adults with traumatic injuries have found that immune function is decreased in those patients, but this is the first data to show that the same thing happens in critically injured children.

For the study, the researchers collected blood samples from 21 healthy children and 76 critically injured children 18 years of age or younger. In

a test tube, they exposed each sample to lipopolysaccharide (LPS), a known stimulant of the immune response. When healthy cells are exposed to LPS, it prompts the production of TNF-alpha, a type of protein called a cytokine that is part of the first line of defense in the body's innate immune system.

When they analyzed the immune response in the lab, they found that blood cell samples from the healthy children responded normally when exposed to LPS, producing high levels of TNF-alpha. Samples from the patients with critical injuries all showed at least a moderate decrease in the production of the cytokine. However, the children who went on to develop an infection showed a much more severe and persistent drop in immune function following injury.

"It's as if we put the blood cells on a treadmill, forcing them to work in the test tube by exposing them to LPS, and then we measure how much TNF-alpha they are capable of making," Dr. Hall says. While the findings strongly suggest that infection risk is associated with immune system function after critical injury, they don't offer any answers about what's causing the malfunction. Dr. Hall's team is studying that question now.

The research also highlighted another interesting issue that may affect the immune response in critical illness. The team found that patients who received a transfusion of blood that had been stored for more than two weeks prior to transfusion had a lower level of TNF-alpha production than kids whose transfused blood was less than two weeks old, regardless of the severity of their original injury. This supports a study published by the same group in 2012 in Transfusion that found the same immunosuppressive effect in a human cell culture model.

Dr. Hall plans to look into this further through his work with a multi-institutional effort called The Pediatric Critical Care Blood Research

Network (BloodNet) that is studying, among other things, what impact blood transfusions have on immune function.

"There's a whole line of research in which we're involved that is dedicated to understanding the effects of transfusion in critical illness," he says. "It's not clear yet if blood transfusions are immunosuppressive, but our work so far suggests that blood becomes more immunosuppressive the longer it sits on the shelf."

Yet another element to the recently published study involves reversing the immunosuppression that follows critical injury or illness. The researchers took three blood samples in which TNF-alpha production was decreased and cultured them with GM-CSF, a drug used to stimulate white blood cell growth in bone marrow transplant patients. Once treated, the cells began to produce normal levels of TNF-alpha—an indication that the immunosuppression had been reversed.

Dr. Hall is currently leading a phase IV clinical trial of GM-CSF to reverse immunosuppression in critically injured patients age 1 to 21 years old. The trial is funded by a five-year, $1.5 million grant from the National Institutes of Health and is enrolling patients in the Pediatric Intensive Care Unit at Nationwide Children's and the Surgical Intensive Care Unit at The Ohio State University Wexner Medical Center. Although findings from that project won't be ready for another year or so, the results in the *Shock* article seem to offer yet another weapon in physicians' arsenal when caring for critically ill and injured children, Dr. Hall says.

"We have certainly made headway in reducing preventable infections through programs such as our own Zero Hero initiative," says Dr. Hall, who also is a principal investigator in the Center for Clinical and Translational Research in The Research Institute at Nationwide Children's and an associate professor of pediatrics at The Ohio State

University College of Medicine. "But what this paper suggests is that it's also important to consider the patient's immune system and how well they are able to fight off infection. We believe that critical illness- and injury-related immune suppression may be reversible with beneficial effects of clinical outcomes."

More information: Muszynski JA1, Nofziger R, Greathouse K, Nateri J, Hanson-Huber L, Ccrn LS, Nicol K, Groner JI, Besner GE, Raffel C, Geyer S, El-Assal O, Hall MW. Innate immune function predicts the development of nosocomial infection in critically injured children. Shock. 2014 Jun 21. [Epub ahead of print]

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