Modeling sepsis in newborns

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Sepsis, or bacterial infection of the bloodstream, is a grave, hard-to-diagnose threat in premature newborns in the NICU. Even when it's detected and treated with antibiotics, its inflammatory effects can harm fragile babies' development. Now, researchers at Boston Children's Hospital have modeled the effects of sepsis on the unique newborn immune system, using mice. They and others have begun using the model to identify diagnostic markers and better treatments.

The new model is described September 6 in the online open-access journal PLOS ONE.

Premature infants typically are kept alive with catheters and intravenous lines that are vital for their care, but that also carry a risk of bloodstream infection, most commonly from the bacterium Staphylococcus epidermidis. Preventive measures can now avoid many of these infections, but those that slip through can be hard to spot and treat.

"When infection occurs, it's hard to detect in newborns, who can't speak and, due to their unique immune systems, tend not to have fevers or show clinical signs," explains Ofer Levy, MD, PhD, of the Division of Infectious Diseases at Boston Children's and senior author on the paper. "There may be irregular breathing or increased heart rate, or the baby may be acting a little 'off,' but these signs are pretty nonspecific. There's a tremendous need for better diagnostics in this field."

Mouse models of intravenous infections in newborns have been lacking, due to the technical challenge of working with tiny newborn mice. With

great manual dexterity, Kenny Kronforst, MD, MPH, a clinical Newborn Medicine fellow working in Levy's lab and first author on the paper, was able to inject live S. epidermidis into the tiny animals' jugular veins, simulating what happens when an IV or catheter infection occurs in an hours-old preemie in the NICU.

The findings surprised the team—and gave hope.

"Newborns have traditionally been considered immunologically immature and distinct from adults in their ability to fight off infection," says Kronforst, now an attending physician in neonatology at Lurie Children's Hospital of Chicago. "Through our model, we have shown that there is a robust inflammatory response to bacterial challenge even at the earliest hours of life. Additionally, we were able to reproduce many clinical features of sepsis that we see in human infants. Because of these features, our model is ideal for exploring novel diagnostic and therapeutic possibilities—something we're extremely excited about."

For example, one part of the inflammatory response, also known to occur in human newborns, was increased production of a molecule called Toll-like receptor-2 (TLR2). Levy's team and others are now evaluating TLR2 as a potential biomarker for detecting sepsis, as well as a potential target for treatments to suppress the inflammation.

"We can now try to block TLR2 in our model, to see if we can clear bacteria faster and prevent inflammatory damage," Levy says.

Even when babies with sepsis are treated with antibiotics, the inflammatory response to the infection can be just as harmful. "Infants spend a lot of energy fighting the infection, and the inflammatory response impairs weight gain," says Levy.

Impaired weight gain was also seen in the mouse model. A separate

study with the model, presented at last May's Pediatric Academic Society meeting, linked increased TLR2 production with another kind of damage: impaired development of the brain's white matter.

"There's an emerging literature showing that having bacteria in the bloodstream is harmful to the newborn brain, and that the inflammatory response harms the brain even if the infection is cleared," Levy says. "That raises the bar tremendously for detection and treatment."

Levy and his colleagues have been invited to apply for funding to develop new treatments using their mouse model.

More information: dx.plos.org/10.1371/journal.pone.0043897

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