Researchers investigate cell-free DNA as early sepsis marker in foals

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It's hard to be a horse. It's especially hard to be a newborn foal, dropped into a world of microbes and bacteria with your sole initial defense against devastating infections being the antibodies you get from your

mother's milk, or colostrum. Researchers at North Carolina State University wanted to learn whether a biomarker that correlates with severe infection in humans could do the same in foals, to potentially identify sick foals early.

"Foals are dependent on colostrum for antibodies, but they have to get it within the first 12 to 24 hours of their lives," says Katie Sheats, associate professor of equine primary care at NC State. "So many things can go wrong—maybe the foal doesn't stand up fast enough, nurse enough, or the quality of the colostrum is bad—then the foal doesn't get enough antibodies. We call that 'failure of passive transfer.'"

Inadequate passive transfer happens in up to 25% of foals. About 10% of foals end up with serious infections, or sepsis, and between 40% to 60% of those septic foals die.

You can see why early detection is key.

One promising method for early detection is cell-free DNA (cfDNA), which refers to fragments of DNA that get released from cells into body fluids like blood. In both infant and adult humans with sepsis, cfDNA levels in the blood increase because of activation of neutrophils.

Neutrophils are the first responders of the immune system. They're white blood cells that kill bacteria. One method neutrophils use to kill bacteria is through a process called NETosis, which is exactly what it sounds like. Picture a host of tiny Spider-Men, casting out webs, or nets, made of their own DNA. The nets are sticky, like Spider-Man's webs, and they contain destructive enzymes that kill the bacteria that get stuck in them.

"Neutrophils are always present in the bloodstream, but they remain inactive until they receive signals of infection," Sheats says. "Really

severe infections—like sepsis—can cause overwhelming neutrophil activation, and some of those neutrophils release NETs. The strands of the NETs are cfDNA, which is why we expect to see elevated levels cfDNA during sepsis. We have some early data suggesting this is true in adult horses, so we wanted to see if we could use cfDNA as a marker for early sepsis detection in foals."

Sheats and a research team from NC State looked at levels of cfDNA in blood plasma samples from 60 foals. The foals were divided into three groups: healthy, sick but non-septic, and septic.

Surprisingly, the researchers found that cfDNA levels did not differ between the three groups. One explanation could be that a foal's net-throwing neutrophils are simply less effective.

"We know that when it comes to neutrophil functions, age matters," Sheats says. "Studies show that neutrophils from human infants aren't as good at releasing NETs as neutrophils from adults. As a next step for this project, we want to find out how age, and conditions like failure of passive transfer, affect foal neutrophil NETosis.

"Based on the results of our current study, we hypothesize that foal neutrophils aren't good at making NETs. If this is true, it could help explain why foals are so susceptible to infection and ultimately lead to a better understanding of how foals' immune systems work."

The study is published in *Veterinary Sciences*. Sheats is the corresponding author and NC State graduate student Kallie J. Hobbs is the first author. Graduate research assistant Bethanie L. Cooper and Assistant Professor of Equine Medicine Katarzyna Dembek, both from NC State, also contributed to the work.

More information: Kallie J. Hobbs et al, Investigation of Extracted

Plasma Cell-Free DNA as a Biomarker in Foals with Sepsis, *Veterinary Sciences* (2024). DOI: 10.3390/vetsci11080346

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