Gut bacteria can cause life-threatening infections in preterm babies

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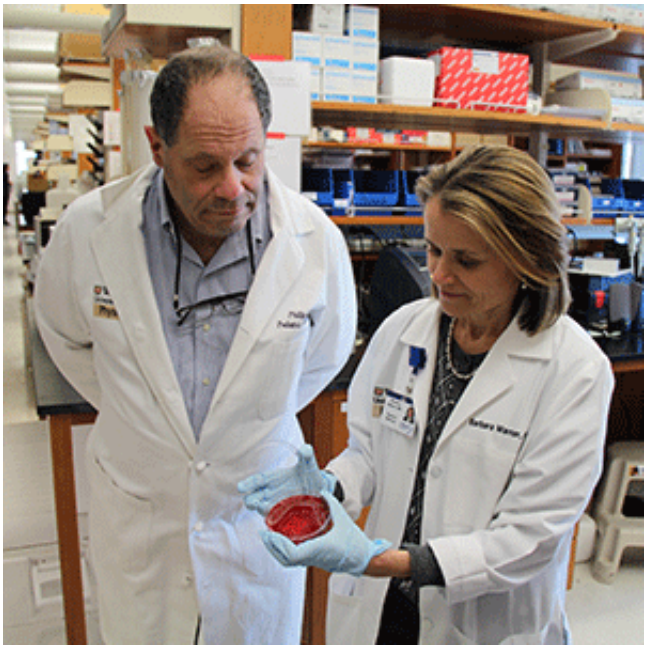

Phillip I. Tarr, M.D., and Barbara B. Warner, M.D., view an agar dish containing organisms sequenced in their study of gut bacteria in preterm babies. The researchers found that premature babies' guts harbor infectious microbes that can cause life-threatening late-onset sepsis. Credit: E. Holland Durando

Babies born prematurely are surviving in increasing numbers. But many withstand complications of early birth only to suffer late-onset sepsis—life-threatening bloodstream infections that strike after infants reach 72 hours of age.

While early-onset sepsis often is caused by pathogens acquired from the amniotic sac or birth canal, the causes of late-onset sepsis have been far less clear.

But now, researchers at Washington University School of Medicine in St. Louis have discovered that preterm babies' guts harbor infectious microbes that can cause late-onset sepsis.

The research is published March 19 in *Clinical Infectious Diseases*.

"There is a tremendous emphasis in intensive-care units throughout the world on stopping infections related to the insertion of IVs, catheters or other tubes, but that leaves a sizable subset of people who get bloodstream infections from germs that don't necessarily reside on the skin," said senior author Phillip I. Tarr, MD, the Melvin E. Carnahan Professor of Pediatrics. "It's been suspected that these other infections come from the gut. This research proves that."

The researchers, in collaboration with scientists at Michigan State and the University of Minnesota, found three types of potentially harmful gut microbes in the bloodstreams of most babies in the study who developed late-onset sepsis: *E. coli*, group B strep and *S. marcescens*.

The findings suggest new strategies to detect and prevent severe bloodstream infections in neonatal intensive care units (NICUs)—and that such strategies include the gut as a target.

The findings also are relevant to other patient populations, said study co-author Barbara B. Warner, MD, a professor of pediatrics who treats patients at St. Louis Children's Hospital.

"Although our study was in preterm infants, its applicability is much more broad and may include people who are susceptible to bloodstream

infections, for example, people in intensive care units or with chronic illnesses, or cancer patients who take medicine that may suppress their immune systems," Warner said. "Late-onset sepsis is not just a disease in preterm infants—it's a cause of serious illness and death among many acutely ill and immunocompromised patients."

Sepsis, which contributes to billions of dollars in health-care costs each year, occurs when the immune system has an overwhelming response to a bacterial infection. The body releases chemicals into the blood to fight the infection, but this triggers widespread inflammation that can lead to blood clots and leaky blood vessels. In severe cases, sepsis causes shock, organ failure and death.

It's widely accepted that preterm babies—and patients of all ages—can acquire such infections via IVs, catheters and other tubes. These infections are thought to be hospital-based or otherwise associated with health care.

About 20 percent of preterm babies develop late-onset sepsis. Overall, about 10 to 20 percent of infants whose infections aren't successfully treated with antibiotics die because of the condition. This death rate varies according to the bacteria causing sepsis; some gut organisms result in higher death rates, in the range of 20 to 30 percent.

The Washington University investigators, including first author Mike A. Carl, a medical student at Saint Louis University, studied 217 premature infants from whom they collected all stool samples, beginning as soon as possible after birth. The babies had been admitted to the NICU at St. Louis Children's Hospital, which has stringent infection-control practices and sepsis rates that fall below the national average. Still, at or after three days of age, 11 of the infants developed sepsis.

The researchers, working with scientists at The Genome Institute at

Washington University School of Medicine, used genome sequencing to compare bacteria in the blood samples of the 11 affected infants with bacteria found in their stool samples, which are a proxy for microbes in the lower intestine, or gut. To assess whether sepsis-causing infections spread between infants, the scientists also compared stool-based bacteria with bacteria in stool samples from two groups of infants without sepsis.

In seven of the 11 infants who developed sepsis, the researchers found that bacteria in stool samples taken days to weeks before the onset of sepsis matched bacteria in the blood samples taken later, suggesting that bacteria from the gut – rather than from other parts of the body – quite likely caused the bloodstream infection.

"We obtained the organism from the blood and then isolated the organism from the stool and then sequenced both," Warner explained. "We could tell, because the sequences were genetically identical, that the source of that organism was the same in the blood as what was in the stool."

They also found the same microbes in the stool samples of infants whose NICU stays overlapped, suggesting that such bacteria occasionally are transmitted from infant to infant, though the bacteria don't always lead to illness.

"No one can be completely sterile; it is inevitable that bacteria will be encountered by infants in these settings," said Tarr, who is also a professor of molecular microbiology. "We do not know the origin of these bacteria in most cases. However, this study tells us that at least in a subset of infants who develop bloodstream infections, the germ that invades their blood flourishes in their gastrointestinal tracts for at least a few days before it causes sepsis.

"That's an opportunity to be on top of colonization and to be aggressive

in preventing dissemination between infants in NICUs and within infants who are colonized. The concept of sepsis as gut infection offers a new strategy to prevent this serious, hospital-acquired condition independent of assiduous skin care, which we continue to endorse."

Warner stressed that the findings indicate a need to consider infection-control steps outside of those taken regarding the insertion of IVs and other tubes into patients. "We could be spending millions of dollars to decrease line-related sepsis, but health-care and infection-control experts haven't addressed this other component," she said. "Considering our findings, this should be looked at more broadly and more intensively."

More information: Carl MA, Ndao M, Springman AC, Manning SD, Johnson JR, Johnston BD, Burnham CD, Weinstock ES, Weinstock GM, Wylie TN, Mitreva M, Abubucker S, Zhou Y, Stevens HJ, Hall-Moore C, Julian S, Shaikh N, Warner BB, Tarr PI. Sepsis from the gut: The enteric habitat of bacteria that cause late-onset neonatal bloodstream infections. *Clinical Infectious Diseases*. March 19, 2014.

Provided by Washington University School of Medicine