# Breast milk ingredient could prevent necrotizing enterocolitis—deadly intestinal problem in preemies

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An ingredient that naturally occurs in breast milk might be used to prevent premature babies from developing a deadly intestinal condition that currently is largely incurable, according to researchers at the University of Pittsburgh School of Medicine and Children's Hospital of Pittsburgh of UPMC in this week's online early edition of the *Proceedings of the National Academy of Sciences*.

The story begins with a baby who is born too early, meaning before 36 weeks gestation, said senior author David Hackam, M.D., Ph.D., Watson Family Professor of Surgery, Pitt School of Medicine, and co-director of the Fetal Diagnosis and Treatment Center at Children's Hospital. Once stable, typically the baby is fed with formula because often breast milk is not readily available to premature infants.

"Within about 10 days of birth, the baby starts to vomit and a few hours later, the belly becomes distended and discolored," Dr. Hackam said. "It becomes clear that the child has developed a major problem in his or her tummy, and an X-Ray will usually confirm the diagnosis of necrotizing enterocolitis, or NEC, in which the intestinal tissue is dying. We have no choice but to remove the dead parts of the intestine, but despite surgery, half of these preemie babies still die from the condition."

Dr. Hackam and his team noted NEC occurs when the intestines start getting colonized with bacteria, a process that occurs normally after

birth. They focused on toll-like receptor 4 (TLR4), an immune protein that is involved in recognizing microbes and which they recently discovered plays a role in gut development. In the current work, Hackam and colleagues found that TLR4 is present in higher amounts in the blood vessel lining in preemies than in full-term babies.

The study shows that unlike normal mice, those bred to lack TLR4 in their blood vessels did not develop NEC in a model designed to induce the condition. The findings indicate that bacteria in the blood activate TLR4 leading to a reduction in nitric oxide, which in turn narrows blood vessels and decreases blood flow, Dr. Hackam said.

"This pathway can be dangerous when the preemie's immature gut becomes inflamed from exposure to the bacteria normally present in the intestine," he said. "Abundant TLR4 triggers a shutdown of the blood supply to the intestine, leading to tissue death or necrosis."

Premature babies who are nursed rather than formula-fed are more likely to survive NEC, so co-author and nitric oxide expert Mark Gladwin, M.D., chief, Division of Pulmonary Allergy and Critical Care Medicine, Pitt School of Medicine, and director of Pitt's Vascular Medicine Institute, and the team took a closer look at the components of breast milk.

They found that breast milk contains high levels of sodium nitrate, which is converted to nitrite by gut bacteria. Nitrite can be directly converted to the vasodilator nitric oxide, which can both protect the intestinal lining and improve blood flow.

"The additional nitrite appears to overcome the effects of TLR4 activation and corrects the blood flow problem," Dr. Gladwin said. "When we gave formula supplemented with a sodium nitrate and nitrite analog to the premature mice, we saw improved blood flow in the

intestine, and NEC did not develop."

Drs. Hackam and Gladwin are testing the compound, which is FDA approved for other uses, in other models of NEC with the hope that it could be routinely added to formula fed to premature infants to prevent NEC.

"This condition is frightening for parents and frustrating for doctors because currently there is little we can do to treat it," said Dr. Hackam, a pediatric surgeon. "I look forward to one day putting myself out of business and having a therapy that truly saves these children."

**More information:** Endothelial TLR4 activation impairs intestinal microcirculatory perfusion in necrotizing enterocolitis via eNOS–NO–nitrite signaling: www.pnas.org/cgi/doi/10.1073/pnas.1219997110

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