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Improving newborns' bacterial environment could fend off infections, animal study suggests

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Mothers give a newborn baby a gift of germs—germs that help to kick-start the infant's immune system. But antibiotics, used to fend off infection, may paradoxically interrupt a newborn's own immune responses, leaving already-vulnerable premature babies more susceptible to dangerous pathogens.

A new animal study by neonatology researchers at The Children's Hospital of Philadelphia (CHOP) sheds light on immunology in newborns by revealing how gut microbes play a crucial role in fostering the rapid production of infection-fighting white blood cells, called granulocytes.

"At birth, newborns move from a largely sterile environment to one full of microorganisms," said CHOP neonatology researcher Hitesh Deshmukh, M.D., Ph.D., first author of the study published online today in *Nature Medicine*. "Animals and humans adapt to this new situation by ramping up the production of granulocytes within the first days of life."

The current study, said senior author and CHOP neonatalogist G. Scott Worthen, M.D., suggests that exposure to the mother's microbes initiates the immunological transition. As in human babies, neonatal mice have a spike in white blood cells, but this response was reduced when their mothers had prenatal and postnatal exposure to antibiotics. This left the neonatal mice much more vulnerable to life-threatening sepsis caused by

the bacterium *E. coli* K1, especially when they were born prematurely.

The study team showed that signaling mechanisms within the gut microbiome—the vast colony of microorganisms in the gastrointestinal tract—regulate the production of white blood cells in neonatal mice. Exposing both the mothers and neonatal mice to antibiotics reduced the diversity of gut bacteria, many of which are beneficial, and also impaired resistance to infection in the newborn animals, in comparison to control mice.

The researchers reversed these abnormal effects by taking normal intestinal microbes from mice that were not exposed to antibiotics and transferring them to mice that had received antibiotics. This improved the animals' resistance to *E. coli* infection.

When a similar procedure is performed in humans, it is called a fecal transplant, and has recently shown success in treating severe bacterial infections in adults. Such transplants have not been performed in human newborns, and the researchers caution that a great deal of work remains before they can determine what implications these animal results may have in guiding human treatment.

Because it is very difficult to determine whether critically ill newborns are infected with bacteria, these babies will continue to be treated with antibiotics, even as clinicians strive to decrease antibiotic use as a long-term goal. However, added Worthen, further investigation may reveal appropriate combinations of microbes that could be used to reconstitute infants' immune systems after they complete a course of antibiotics.

More information: "The microbiota regulates neutrophil homeostasis and host resistance to Escherichia coli K1 sepsis in neonatal mice," *Nature Medicine*, published online April 20, 2014. doi.org/10.1038/nm.3542

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