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Study shows biomarker accurately diagnoses deadly infant disease

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A diagnostic study of 136 premature infants found that a protein involved in managing harmful bacteria in the human intestine is a reliable biomarker for the noninvasive detection of necrotizing enterocolitis (NEC). Led by researchers and clinicians at LSU Health New Orleans School of Medicine, this is one of the largest prospective clinical studies in premature infants yet. Results of the study are published online in *JAMA Network Open*.

According to the National Institutes of Health, necrotizing enterocolitis is a life-threatening illness almost exclusively affecting neonates. NEC has a mortality rate as high as 50%. Inflammation of the intestine leads to bacterial invasion causing cellular damage and cell death, which causes necrosis of the colon and intestine. As NEC progresses, it can lead to intestinal perforation causing peritonitis, sepsis and death. To date, no clinical test has been established as the gold standard to diagnose NEC. X-rays are used to diagnose advanced disease, but their sensitivity can be as low as 44%.

The gut disease is one of concern in Louisiana, as it has one of the highest rates of premature birth in the country, and it disproportionately affects African American infants.

"This study exemplified academic medicine at its best," notes Sunyoung Kim, Ph.D., Professor of Biochemistry and Molecular Biology at LSU Health New Orleans School of Medicine and senior author. "It creates linkages between unexplained patient presentations and scientific

inquiry. We were driven by the desire to build unique and useable tools to fight a disease that has been unexplained for nearly 200 years in the most fragile patient population—preemie babies."

Previous research suggested that NEC is preceded and accompanied by changes in the complex and dynamic collection of microorganisms called gut microbiota, which live in the intestine. In this study, the research team measured and analyzed the activity of the protein, intestinal alkaline phosphatase (iAP) obtained from stool samples from the babies enrolled in the study at Children's Hospital of New Orleans, Touro Infirmary, and St. Louis Children's Hospital. Clinical data collected included gestational age, birth weight, Apgar scores, delivery type, race, gender, feeding, antibiotics, laboratory and radiology results, as well as surgical notes. Eighteen percent of the babies were classified as having severe NEC; 14% had suspected NEC; and 68% were NEC control.

Since iAP activity precedes the chemical process triggering inflammation, the researchers studied the abundance and enzyme activity of iAP shed in stool to assess the correlation of two iAP biochemical measures with disease severity. They found that elevated levels of iAP protein linked to NEC were shed in the samples, but the proteins were dysfunctional in the NEC patients. The accuracy rates using iAP levels and iAP activity as markers for severe NEC were 97% and 76%, respectively. The accuracy values were similar for suspected NEC—97% and 62%, respectively.

These results indicate that iAP biochemistry and abundance can be used as diagnostic biomarkers for both severe and suspected NEC. Significantly, iAP measures were not biomarkers for sepsis, another potentially fatal condition that can exhibit symptoms similar to NEC. A correct diagnosis is crucial to treatment decisions.

The biomarker has doubled the diagnostic identification of the disease, compared to the current gold standard—a milestone important at both the bench and the bedside.

"Intestinal AP is the first candidate diagnostic biomarker, unique in its predictive value for NEC," reports Dr. Kim. "It is correlated only with NEC and is not associated with sepsis or other non-GI infections. The clinical potential of this noninvasive tool lies in its use to identify infants most at risk to develop NEC, to facilitate management of feeding and antibiotic regimens, and monitor response to treatment."

Besides Kim, other members of the research team from LSU Health New Orleans included Drs. Maya Heath, Zeromeh Gerber, Brian Barkemeyer and Duna Penn in the Section of Neonatology in the Department of Pediatrics; Rebecca Buckley, Ph.D., and Porcha Davis in the Department of Biochemistry and Molecular Biology; and Zhide Fang, Ph.D., in the Department of Biostatistics in the School of Public Health. Misty Good, MD, Laura Linneman, RN, and Qingqing Gong, Ph.D., from Washington University School of Medicine and St. Louis Children's Hospital, also participated in the research.

The research was supported by funding from the National Institutes of Health, National Science Foundation, March of Dimes, Louisiana Board of Regents, Children's Discovery Institute at Washington University and St. Louis Children's Hospital, Department of Pediatrics at Washington University School of Medicine, LSU Health New Orleans School of Medicine and LSU Health Foundation.

Kim is the founder of a spin-out company, Chosen Diagnostics Inc., whose business interests are related to this project. The company is considering an option to license its diagnostic test developed from this work. Dr. Misty Good has financial relationships with Abbott Laboratories and Astarte Medical Partners.

"What began as a collaboration between Biochemistry and Pediatrics at LSU Health New Orleans School of Medicine to address a life-threatening condition has grown into a multicenter national partnership," concludes Kim. "We are working hard here at LSU Health to create solutions for people in our state and to use our discoveries to help infants across the country."

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