



Children's Foundation
Research Institute

Research Matters

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Ajay Talati, MD

Mycobiome in preterm infants predicts development of bronchopulmonary dysplasia

In very low birth weight preterm newborns, the composition of the gut mycobiome, or the naturally occurring fungi in the intestines, predicts later development of bronchopulmonary dysplasia (BPD), according to research published in *Microbiome* by Le Bonheur Chief of Neonatology Ajay Talati, MD, and other researchers. The results of this research suggest the existence of a gut-lung axis and position the gut mycobiota as a potential therapeutic target for newborn lung disease. It is known that intestinal microbes can influence the lung directly, but previous research focused on bacteria, leaving the role of fungi not well known. This is one of the most extensive studies of the multi-kingdom intestinal microbiome in preterm newborns.

"This research is incredibly meaningful for a patient population that currently has limited available interventions," said Talati. "Our findings suggest the causality of the fungal mycobiome in the

development of BPD as well as a potential therapeutic strategy for the future."

BPD is a chronic lung disease found in premature infants and the most common morbidity of prematurity, according to researchers. Lungs that are already small and underdeveloped at birth can be injured by the supplemental oxygen required for survival. Researchers used a two-part study to measure if the intestinal microbes had an influence on the potential for injury to the lungs and if this effect was transferable and modifiable.

First, researchers collected the first available true stool sample from 102 very low birth weight preterm newborns within the first two weeks of life. They compared the intestinal microbiomes of those who later developed BPD and those who did not.

Results from this comparison showed that the gut mycobiome of infants who later develop BPD is unique several weeks to months



Bronchopulmonary dysplasia is a chronic lung disease found in premature infants that currently has few interventions.

before diagnosis. The mycobiomes between the two groups differed in community diversity, composition and connectivity, with those developing BPD being the least connected and with the most types of rare fungi. In addition, babies who were assigned male at birth and later developed BPD had the least interconnected mycobiomes, which could be a cause for the worse outcomes seen in male infants with BPD.

"Through our results, we found

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Recently published research from Le Bonheur Chief of Neonatology Ajay Talati, MD, identifies a potential therapeutic target for bronchopulmonary dysplasia in the gut mycobiota.

that baseline compositional differences in the gut mycobiome predicted the eventual development of BPD, including sex-specific differences," said Talati.

The second phase of the study was to determine if this effect was transferable and modifiable. Using a murine model, researchers conducted a fecal microbiota transplant (FMT) from infants who did develop BPD and those who did not. Those who received the FMT from an infant with BPD had worse lung injury after exposure to excess oxygen measured by increased pulmonary resistance and changes in blood vessels consistent with pulmonary hypertension. These results showed that the gut microbiome of an infant with BPD can augment lung injury after exposure to excess oxygen.

Finally, researchers inhibited the development of fungi and augmented it in two different groups. Inhibiting fungi development reduced the extent of lung injury after excess oxygen exposure and improved lung development and function. Augmenting the fungal development increased the severity of lung injury. This further suggests that changing fungal colonization modulates the extent of hyperoxia-induced lung injury.

"All of our findings suggest the existence of a gut-lung axis, where the mycobiome is directly influencing the potential for lung injury and altering the mycobiome can alter the extent of lung injury," said Talati.

Ultimately, researchers uncovered through this study that the compositional differences in the gut mycobiome can predict the development of BPD. Analyses demonstrated that those who did not develop BPD had more uniform composition of the mycobiome, while those who did develop BPD were more disparate. This effect was transferable, where modifying fungal colonization could modulate the severity of lung injury.

"More research is needed into the ways that the mycobiome impacts the development of BPD, but, through this work, we have identified a potential therapeutic strategy for this growing group of babies who desperately need viable interventions," said Talati.

LE BONHEUR ENROLLS FIRST PATIENT IN THE COUNTRY IN MULTI-CENTER PREEMIE TRIAL



Interventional Cardiologist Neil Tailor, MD, leads the PREEMIE study at Le Bonheur.

Le Bonheur Children's was the first center in the country to enroll a patient in the PREEMIE trial, a study that is evaluating the safety and efficacy of the Bloom™ Micro Occluder System.

Led at Le Bonheur by Interventional Cardiologist Neil Tailor, MD, the PREEMIE study will investigate the clinical benefit of the device to treat patent ductus arteriosus (PDA) – a birth defect where a small blood vessel near the heart does not close after birth – in premature infants who weigh as little as 600 grams. This patient population has no other approved device on the market.

The Bloom™ Micro Occluder System is intended to streamline treatment in this high-risk patient population, and provide solutions to common procedural challenges, such as flexibility to minimize distortion on the heart and to avoid catheter exchanges.

APPENDECTOMY VS. ANTIBIOTICS: STUDY FROM LE BONHEUR SURGEON CONFIRMS SURGERY SUPERIOR FOR APPENDICITIS

Since 1886, when the operation was first described, appendectomy has been the standard for treating appendicitis, the most common surgical emergency for children (with a lifetime risk of 7-8%); only recently have antibiotics alone been explored in place of surgery, according to research recently published by Le Bonheur Pediatric Surgeon Tim Jancelewicz, MD, in *The Lancet*.

With the decision between appendectomy and antibiotics for best treating patients, Jancelewicz and his colleagues sought to determine which treatment for uncomplicated appendicitis (meaning an appendix that is inflamed but has not yet ruptured) was inferior. Their research showed that ultimately an appendectomy is the better choice for kids over antibiotics.

"The APPY Trial shows that around a quarter to a third of kids that are treated with antibiotics and don't get their appendix removed will get recurrent appendicitis within a year," stated Jancelewicz. "That may sound like a risky proposition if you're a surgeon. Now we have the numbers for them to make an informed decision."

While several studies have claimed that antibiotics alone is a more effective treatment plan, this study was the first "large, pragmatic, randomised trial to compare antibiotics and appendectomy for the treatment of uncomplicated appendicitis



Tim Jancelewicz, MD, (above in surgery and below in clinic) published research in "The Lancet" confirming appendectomy as the best treatment option for kids over antibiotics.



in children." To compare these treatments side by side, they had to first decide what "failure" meant for each of them. For antibiotics, failure was defined as the need for appendectomy within one year. For appendectomy, it was defined as a negative appendectomy, which is when an appendix is removed that is not inflamed.

The study ran from 2016 to 2021 and consisted of 936 children ages 5 to 16 from 11 children's hospitals across Canada, the United States, Finland, Sweden and Singapore with non-perforated appendicitis. Patients were randomly assigned to either antibiotic treatment or appendectomy.

They found the failure rate to be 34% in the antibiotic group compared to only 7% in the appendectomy group. In addition, the appendectomy group had a shorter initial hospital stay compared to the antibiotic group. While the antibiotic group returned to normal activities faster and required fewer pain medications, complications were more frequent for them overall.

The conclusion made in this rigorous study led Jancelewicz and his colleagues to determine that for uncomplicated appendicitis in children, antibiotics alone were

inferior to appendectomy and had a higher failure rate. Their findings, combined with past results in previous studies, show that additional comparative studies in this vein are not likely to produce different results. Appendectomy remains the best choice for most patients more than a century later.

EDWARDS RECEIVES OXNARD FOUNDATION GRANT



Price Edwards, MD

Le Bonheur Gastroenterologist Price Edwards, MD, received a grant from the Oxnard Foundation for his project “Downstream Analysis of Upper Gastrointestinal Biopsies in Pediatric Patients.” Many disorders that cause pain and abnormal motor activity of the stomach are poorly understood. New technologies allow analysis of gastrointestinal samples to identify the genetic activity in individual cells of the tissue.

Pediatric samples from the stomach have not yet been used for this type of analysis. By using biopsies from patients already undergoing a scope for clinical care, Edwards will use these samples to solidify preparation procedures and reveal differences between the regions of stomach. This data will then be used to compare in different disease states to show how genetics and protein production may cause these disorders. Better understanding of these disorders will improve both diagnosis and treatment.

NOORIZADEH RECEIVES JUNIOR INVESTIGATOR AWARD FROM AMERICAN EPILEPSY SOCIETY

Le Bonheur Neuroscientist Negar Noorizadeh, PhD, recently received a junior investigator award from the American Epilepsy Society (AES) for her project “Improving the Accuracy of TMS Language Localization Using Tractography.” Transcranial magnetic stimulation (TMS) is utilized as a non-invasive method of mapping language cortices prior to surgical resection for epilepsy or brain tumors but suffers from high false-positive rates. This project aims to improve the accuracy of TMS by integrating it with diffusion tensor imaging (DTI) tractography, an MRI technique, to create a more reliable, individualized tool for presurgical planning.

Noorizadeh hypothesizes that areas showing both TMS activation and tractography-defined connections are true language sites, while non-aligned regions may be false positives. Research will validate this tractography-optimized TMS approach against cortical stimulation mapping and postsurgical language outcomes.



Negar Noorizadeh, PhD

BEARDEN RECEIVES GRANTS THROUGH THE PEDIATRIC EPILEPSY RESEARCH CONSORTIUM



Donald J. Bearden, PhD

Le Bonheur Neuropsychologist and Chief of Pediatric Psychology and Behavioral Health Donald J. Bearden, PhD, recently received grants for two projects as a co-principal investigator from the Pediatric Epilepsy Research Consortium (PERC). The first, “A delphi consensus on best practices for identifying and treating early life epilepsy,” aims to develop consensus recommendations for standards of care for early life epilepsy patients three years or younger.

The second, “From Assessment to Action: Optimizing neuropsychological and neurosurgical communication in epilepsy surgical planning,” will use a multi-site approach to develop streamlined communication recommendations between neuropsychologists and neurosurgeons/epileptologists for surgical planning.

CONTACT US

If you have any research news or announcements you would like to include in an upcoming issue of Research Matters, please email research@lebonheur.org.