



Advancing Neonatal Outcomes Through Research and Clinical Care



**NATIONWIDE
CHILDREN'S®**

When your child needs a hospital, everything matters.



Dear friends and colleagues,

In a year unlike any other, we hope this letter finds you well. Together, we have navigated the many unknowns while continuing to ensure safe, quality care. Through it all, our focus has remained the same – the best possible outcome for our many patients and their families.

Like you, we have been working tirelessly to maintain patient and staff safety during the COVID-19 pandemic. Through extraordinary teamwork, we quickly developed enhanced safety measures, implemented telehealth, and were able to resume and ramp up all services throughout our division. This unique year has also provided us new opportunities to collaborate across divisions and overcome many challenges. To that, we celebrate!

You will see in the following pages how The Neonatal Network has continued to push forward and continue our journey to best outcomes. We invite you to learn more about some of this year's highlights:

- Advances in Neonatal GERD
- Novel Intervention to Help Infants with Cerebral Palsy
- Associations Between Kidney Injury and Fluid Imbalance in Premature Newborns
- Timing Steroids to Maximize Lung Benefit, Avoid Brain Harm in Premature Infants
- Prevention and Treatment of Early-Onset Sepsis in Newborns
- Systems Analysis Unravel Clinical Phenotypes in Infants With RSV

As we continue to navigate the challenges of COVID-19 in the coming year, we look forward to collaborating with our peers from around the world, to continue to provide the best care possible to our patients. From clinical care to cutting-edge research – we are all on the journey to best outcomes together!

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By The Numbers



In the Division of Neonatology at Nationwide Children's Hospital, we focus on improving outcomes for all of our patients, and research and clinical innovations are critical to that mission. Our physician-scientists are national leaders in areas such as bronchopulmonary dysplasia, infant feeding disorders, quality improvement and NICU follow-up programs – because we know neonatal care does not end when the hospital stay does. Our close association with the Center for Perinatal Research at The Research Institute at Nationwide Children's allows us to use basic science and translational research to develop cutting-edge clinical interventions.



Each year, more than **3,000 BABIES** receive the highest level of care in one of our **Newborn Intensive and Special Care Units**.



A DEDICATED critical care transport team ensures babies arrive safely.

With **275 NICU BEDS** we are one of the **largest neonatal centers** in the nation.

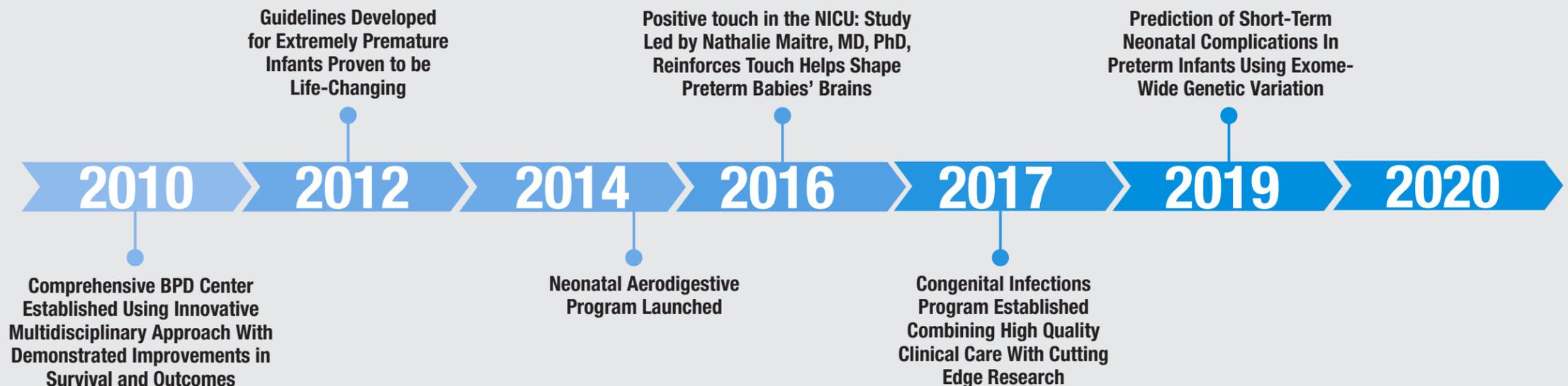
More than **5,300 TOTAL NEONATOLOGY** clinic visits each year.

Outstanding Outcomes **95% Survival Rate** for **small babies** (less than 27 weeks)



A Decade of Remarkable Transformation NEONATOLOGY

Throughout the past decade, we have made great strides in clinical care and research for neonates. Advancing strong collaborations, digging deeper into the treatment and prevention of prematurity, and leading in research and innovation, has enabled the size and strength of our program to be unmatched. Caring for more than 3,000 babies each year, we are the nation's largest neonatal center.



Advances in Neonatal GERD



Sudarshan Jadcherla, MD

Differentiating gastroesophageal reflux (GER), which is the passage of gastric contents into the esophagus, from GER disease (GERD), when troubling symptoms accompany reflux, remains challenging in infants. Symptom-based GERD diagnosis and treatment is widely practiced but fundamentally problematic.

Sudarshan Jadcherla, MD, principal investigator and director of the Neonatal and Infant Feeding Disorders Program at Nationwide Children's Hospital, says that feeding and airway-digestive problems are common in infants but may not always indicate GERD. Ambiguity lies in defining troublesome symptoms in newborns, making it difficult to determine whether symptoms are truly GERD-related.

Subsequently, infants receive numerous empiric therapies, such as prolonged acid-suppressive therapy.

Two new papers from Dr. Jadcherla's lab provide new evidence-based insights into diagnosing, classifying and treating neonatal GERD.



“Reflux often goes away with time and maturation, but when pathological, it requires careful evaluation and therapy. One has to be cautious in distinguishing normal from abnormal. That's where the need for testing comes in, and translation of evidence-based strategies will then be possible.”

- Dr Jadcherla

In the first study, Dr. Jadcherla and his colleagues used pH-impedance monitoring to differentiate esophageal sensitivity phenotypes in NICU infants referred for GERD symptoms. Symptoms may occur from esophageal sensitivity to acid, non-acid reflux or other non-GER causes. The researchers documented GERD symptoms and related their frequency to acid reflux.

Only vomiting and cough were caused by acid alone. Other common symptoms, including arching, could be related to non-acid reflux.

Dr. Jadcherla and his colleagues differentiated four esophageal sensitivity phenotypes. Identifying these phenotypes could lead to targeted treatments for neonatal GERD.

“The results highlight that many of the symptoms that are reported are not always acid-related and could be treated without using acid-suppressing medications,” says Zakia Sultana, a research assistant at Nationwide Children's and study author.

“You can't prescribe acid-suppressing medication just by looking at a baby,” she says. “You have to do some diagnostic testing, then determine if the symptoms might be related to other factors.”

There are risks to prolonged use of acid-suppressing medications in infants.

“These medications can alter the bowel flora, modify bone density, increase the risk of gut and airway infections, and cause other long-term consequences,” says Dr. Jadcherla. “Clinicians should investigate before they medicate.”

Sultana emphasizes the need for innovative treatment strategies to address non-acid-related symptoms.

“What comes up from the stomach to the esophagus? If it's not acid, what is it and how do we treat it?” she says.

In the second study, Dr. Jadcherla and his team tested the effectiveness of behavioral modifications for treating neonatal GERD. For decades, these non-evidence-based approaches were believed to modify GERD and its symptoms.

The researchers used objective testing to identify the infants who needed acid-suppressive therapy, then randomized them into two groups. One group received only acid-suppressive therapy. The other group received acid-suppressive therapy and underwent behavior modifications: restricted feeding volume and altered body position.

“There was no difference between these approaches in short- or long-term outcomes,” says Dr. Jadcherla. “After four weeks, the infants in both groups were okay and did not need other interventions.”

These findings suggest that maturation influences symptom resolution.

“We learned that infants can be fed what they can eat without imposing volume restrictions. Variabilities in feeding positions are common and do not effect GERD,” Dr. Jadcherla says. “Acid-suppressing medication should be used only in those who have evidence of acid-related GERD and for only a limited period of time.”

Future studies are needed to define true GERD and identify effective therapies to treat its symptoms or complications.

“Reflux often goes away with time and maturation, but when pathological, it requires careful evaluation and therapy,” he says. “One has to be cautious in distinguishing normal from abnormal. That's where the need for testing comes in, and translation of evidence-based strategies will then be possible.”

Dr. Jadcherla's research work is supported by R01 awards from the National Institutes of Health (NIDDK).

Reference:

1. Jadcherla SR, Hasenstab KA, Wei L, Osborn EK, Viswanathan S, Gulati IK, Slaughter JL, Di Lorenzo C. Role of feeding strategy bundle with acid-suppressive therapy in infants with esophageal reflux exposure: a randomized controlled trial. *Pediatric Research*. 2020 May 7. [Epub ahead of print]

2. Jadcherla SR, Sultana Z, Hasenstab-Kenney KA, Prabhakar V, Gulati IK, Di Lorenzo C. Differentiating esophageal sensitivity phenotypes using pH-impedance in intensive care unit infants referred for gastroesophageal reflux symptoms. *Pediatric Research*. 2020 May 6. [Epub ahead of print]

Novel Intervention Helps Infants With Cerebral Palsy Develop Arm and Hand Function

An intervention combining a patented soft restraint harness, therapist coaching and parent training reportedly increases reach smoothness, fine motor skills and tactile sensation in the more-affected upper extremity in infants with cerebral palsy (CP). For the first time in infants under 2 with CP, this intervention demonstrated safety for tactile processing of the restrained extremity and other motor skill development.

CP is characterized by sensorimotor impairments resulting from events that harm perinatal neural development, occasionally manifested as an upper extremity impairment that preferentially affects one arm.

A recent *Brain Topography* publication reports the results of the largest U.S. randomized controlled trial that evaluated the safety and efficacy of a parent-administered multimodal therapy in children with CP and asymmetrical upper extremity impairments.

The intervention involved using a loose, soft restraint harness (C-Mitt), which encouraged use of the more-affected arm by the less-affected arm. The C-Mitt allows sensory feedback, full-arm range of motion and use of the hand as an assist or for gross motor skills.

Wearing the C-Mitt encouraged use of the more-affected arm and facilitated sensory-motor reinforcement exercises and bimanual play. Therapists instructed parents on performing the therapies and instituted weekly challenge increases. An activity monitor measured restraint wear time.

“The developing sensory system is sensitive to long periods of neural input deprivation, making it imperative to study the safety of interventions leveraging neuroplasticity. We’re pleased that the NIH supported a high-tech mechanistic approach to studying a low-tech, inexpensive therapy,” says Nathalie Maitre, MD, PhD, lead study author and director of the NICU Follow-up Program at Nationwide Children’s Hospital.

Progress was evaluated using motion-capture measures of reach, high-density EEG measures of somatosensory processing in response to light touch, and standard motor function tests.

“It was a privilege to help empower families improve their children’s outcomes,” says Dr. Maitre. “Despite challenges, these families consistently and effectively delivered an intervention that improved their infant’s or toddler’s hand use. We are now studying increasing long-term effects in these children until age three.”

This trial is one of several conducted by the Baby Brain Optimization Project (BBOP), a collaborative team of various specialties, including neonatology and surgery, that performs patient-based neuroscience research.

“The BBOP team focuses on understanding and improving neurodevelopment for children with neural insults in early life,” says Dr. Maitre. “Our success is bolstered by a supportive hospital environment, incredible research institute, and a dedicated team of clinicians, scientists, engineers, therapists, international collaborators and, most of all, the participating families.”

Reference:

Maitre NL, Jeanvoine A, Yoder PJ, Key AP, Slaughter JC, Carey H, Needham A, Murray MM, Heathcock J. The BBOP group. Kinematic and somatosensory gains in infants with cerebral palsy after a multicomponent upper-extremity intervention: a randomized controlled trial. *Brain Topography*. August 2020. [Epub online]



“The developing sensory system is sensitive to long periods of neural input deprivation, making it imperative to study the safety of interventions leveraging neuroplasticity.”

- Dr. Maitre



What is the Association Between Kidney Injury and Fluid Balance in Premature Newborns?

According to new research, fluid balance is associated with outcomes in preterm newborns, with a negative fluid balance during the first week of life emerging as a potential therapeutic target.

Premature newborns can experience multi-organ dysfunction, frequently including kidney dysfunction. The international Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study showed that acute kidney injury (AKI) occurs commonly in preterm newborns and is associated with increased mortality and length of stay. AKI can also affect the function of other organs through its influence on fluid balance.

The AWAKEN study captured data on AKI, fluid balance and the impact of other kidney-related risk factors on short-term outcomes in premature newborns. Researchers from institutions including Nationwide Children's Hospital used these data to investigate changes in fluid balance in premature newborns during week 1 of life. They also investigated the association of fluid balance with AKI and mechanical ventilation at postnatal day 7, an important short-term outcome.

"The incidence of kidney issues in this population is much higher than we appreciated," says John Mahan, MD, professor of pediatrics in the Division of Nephrology at Nationwide Children's and The Ohio State University College of Medicine. He is also director of the Nationwide Children's Center for Faculty Development, program director of the Pediatric Nephrology Fellowship Program and a study author. "The inability to excrete water is a significant problem in these small babies. Among a large number of patients, we saw kidney involvement in many of them."

Over half the newborns weighed more than their birth weight during postnatal week 1, indicating a positive fluid balance. Those with a positive fluid balance at postnatal day 7 were more likely to require mechanical ventilation. Also, fluid balance was associated with AKI.

Dr. Mahan says kidney issues in premature newborns can go unappreciated without regularly testing kidney function.

"Those early signs of kidney issues, like the inability to excrete water, are easy to miss. Yet, these early signs of kidney issues can lead to significant and long-term problems," he says.

Elizabeth Bonachea, MD, program director for the Neonatal-Perinatal Medicine Fellowship at Nationwide Children's and another study author, says that detecting kidney issues early is crucial.

"Future studies will focus on prevention and early intervention. We are now working on developing a standard approach to detect and diagnose kidney injury in these babies. Looking forward, these studies will propose appropriate interventions to prevent or minimize kidney injury in premature babies."

- Elizabeth Bonachea, MD



Reference:
Selewski DT, Gist KM, Nathan AT, Goldstein SL, Boohaker LJ, Akcan-Arikan A, Bonachea EM, Hanna M, Joseph C, Mahan JD, Mammen C, Nada A, Reidy K, Staples A, Wintermark P, Griffin R, Askenazi DJ, Guillet R. Neonatal Kidney Collaborative. The impact of fluid balance on outcomes in premature neonates: a report from the AWAKEN study group. *Pediatric Research*. 2019 Sep 19. doi: 10.1038/s41390-019-0579-1. [Epub ahead of print]

Timing Steroids to Maximize Lung Benefit and Avoid Brain Harm in Premature Infants

Steroids are used to treat extremely premature babies with respiratory failure but could delay brain development. A recent study evaluated the age of first steroid administration and the risks of lung disease and neurodevelopmental impairment in preterm infants. The study's findings may help determine the optimal steroid treatment for improving long-term lung function and neurodevelopmental outcomes.

Premature babies are at risk for developing the chronic lung disease bronchopulmonary dysplasia (BPD). Steroids are sometimes used to prevent BPD in premature babies but can increase the risk of poor neurodevelopment. To complicate matters, BPD is a risk factor for neurodevelopmental impairment.

Researchers at National Institute of Child Health and Human Development (NICHD) Neonatal Research Network sites, including Nationwide Children's Hospital, sought to determine the optimal timing of steroid administration to maximize lung benefit without increasing neurodevelopmental risk. They analyzed outcomes of premature infants who received steroids between 8 days and 36 weeks old.

"Babies who received steroids between 8 and 49 days of age had similar rates of BPD. Infants receiving steroids after 50 days of age had a higher risk of BPD," says Jonathan Slaughter, MD, MPH, a neonatologist and principal investigator in the Center for Perinatal Research within The Research Institute at Nationwide Children's.

The risk for neurodevelopmental harm was similar throughout the time periods studied, regardless of when a baby received steroid treatment.

The results suggest that, for infants at very high risk of BPD, steroid treatment should be considered before 50 days of age for the lowest risk of severe lung disease. For ventilated infants at the highest risk for long-term lung disease, steroid treatment before 50 days of age could confer pulmonary advantages with no added neurodevelopmental risks.

Future studies are needed to determine the optimal type, dose and timing of steroids to safely prevent BPD. The NICHD Network is also trialing hydrocortisone (rather than the more traditionally used dexamethasone) to prevent BPD without hurting brain development.

"Treating early with steroids might be beneficial and does not appear to be more harmful to the brain than delayed treatment."

If you are thinking of treating a premature baby with steroids to improve their severe lung disease, it may be best to treat them early. Compared to waiting until their lung disease is more fully developed, treating early does not seem to increase their risk of neurodevelopmental delay."

- Jonathan Slaughter, MD, MPH



Reference:
Harmon HM, Jensen EA, Tan S, et al. Timing of postnatal steroids for bronchopulmonary dysplasia: association with pulmonary and neurodevelopmental outcomes [published online ahead of print, 2020 Feb 4]. *J Perinatol*. 2020. doi:10.1038/s41372-020-0594-4.

Prevention and Treatment of Early-Onset Sepsis in Newborns

Early-onset sepsis, defined as a positive blood or cerebrospinal fluid culture within the first 72 hours of life, remains a potentially fatal condition among newborns, particularly pre-term infants. According to a recent *JAMA Pediatrics* publication, ongoing surveillance is required to optimize prevention and treatment strategies.

Researchers evaluated data from 18 centers of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network from April 2015 through March 2017.

They identified cases of early-onset sepsis from a cohort of > 200,000 infants, including infants in the Nationwide Children's Hospital Neonatal Intensive Care Unit at The Ohio State University Wexner Medical Center.

There were 235 cases of early-onset sepsis in the cohort (rate: 1.08 cases/1,000 live births). The most frequent pathogens were *Escherichia coli* (37%) and group B Streptococcus (30%). *E. coli* infection primarily affected preterm infants, while group B streptococcal infection primarily affected term neonates. Importantly, 53% of group B streptococcal infections occurred in newborns whose mothers had negative group B streptococcal screening test results.

Neonatal empirical antibiotic treatment most frequently included ampicillin and gentamicin. Although these antimicrobial agents remained largely effective, ongoing surveillance should monitor antibiotic susceptibilities of early-onset sepsis pathogens.

“There has not been any resistance of group B Streptococcus to penicillin or ampicillin, which is reassuring,” says Pablo Sánchez, MD, a pediatric infectious diseases specialist and neonatologist, and director of Clinical and Translational Research in Neonatology at Nationwide Children's. “However, 6 of 77 *E. coli* isolates tested for susceptibility to ampicillin and gentamicin were resistant to both antibiotics.”

Compared with an earlier Neonatal Research Network study (2006-2009), there was no significant change in the rates of group B streptococcal infection or infection-associated mortality. However, the *E. coli* infection rate increased significantly among very low birth weight infants.

“*E. coli* can be a severe infection, associated with high mortality and morbidity,” says Dr. Sánchez.

He is currently working on comparing infants with early-onset *E. coli* infection to those without to identify differentiating characteristics and develop preventive strategies.

Continued surveillance is necessary to identify changes in pathogen distribution and antibiotic susceptibilities in this population. Also, innovative prevention strategies are needed to prevent additional cases of early-onset sepsis.

“This study highlights that we've made a lot of progress against group B streptococcal infections, although they remain a problem,” says Dr. Sánchez. “And we still have a lot of work to do to prevent *E. coli* infections.”

Reference:

Stoll BJ, Puopolo KM, Hansen NI, Sanchez PJ, Bell EF, Carlo WA, Cotton M, D'Angio CT, Kazzi SNJ, Poindexter BB, Van Meurs KP, Hale EC, Collins MV, Das A, Baker CJ, Wyckoff MH, Yoder BA, Watterberg KL, Walsh MC, Devaskar U, Laptook AR, Sokol GM, Schrag SJ, Higgins RD, Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Early-Onset Neonatal Sepsis 2015 to 2017, the Rise of *Escherichia coli*, and the Need for Novel Prevention Strategies. *JAMA Pediatrics*. May 04, 2020. [Epub ahead of print]



*“This study highlights that we've made a lot of progress against group B streptococcal infections, although they remain a problem. And we still have a lot of work to do to prevent *E. coli* infections.”*

- Dr. Sánchez



Systems Analyses Unravel Clinical Phenotypes in Infants With Respiratory Syncytial Virus Infection

Respiratory syncytial virus (RSV) is a leading cause of pediatric hospitalization, although most cases are mild. Developing effective antivirals and vaccines requires a better understanding of the clinical, immunologic and virologic factors in infants with mild versus severe RSV disease.

In a new study, researchers at Nationwide Children's Hospital sought to identify a "safe and protective" immunoprofile induced by natural RSV infection that protects infants from severe disease. Using a systems analysis approach, the researchers integrated blood transcriptional profiling and immune cell phenotyping with measuring viral loads and clinical data from children with RSV infection. The infants and young children spanned across age and disease severity spectrums.

"We identified complex interactions among RSV viral loads, the innate immune response and patients' age influencing disease severity," says Asuncion Mejias, MD, PhD, senior study author and an infectious disease specialist and principal investigator in the Center for Vaccines and Immunity at Nationwide Children's.

Children with mild disease (outpatients) had higher RSV loads in the upper respiratory tract. Those with more severe disease (inpatients) had higher levels of poorly activated monocytes.

Age-related differences in blood immune gene expression patterns emerged. Older children with mild disease showed greater interferon gene expression. Comparatively, inpatients with severe disease showed greater inflammation gene activation irrespective of age.

"Our data suggest mild RSV infection is characterized by robust interferon expression, adequate monocyte activation and higher viral loads," says co-senior author Octavio Ramilo, MD, chief of Infectious Diseases and principal investigator in the Center for Vaccines and Immunology at Nationwide Children's.



Asuncion Mejias, MD, PhD

Study findings demonstrate how disease severity and age are important in children with RSV infection.

"We found that RSV infection is associated with distinct patterns of innate immune response activation according to disease severity, and that age influences these patterns," says Dr. Ramilo. "A robust interferon response is protective, while an uncontrolled inflammatory response is detrimental."

Identifying a "safe and protective" immunoprofile induced by natural RSV infection across age groups could be clinically important.

Also, these findings could be used to help design and evaluate new vaccines and antivirals directed against RSV and inform other infectious disease research.

"This study can be a template for future research of RSV and other respiratory viral infections," says Dr. Mejias.

"For instance, we don't understand how COVID-19 activates or suppresses the immune response in infected children or how age influences responses to infection in COVID-19 at this point. We can still learn a lot."

This work was supported by NIH grant #AI112524.

"Our data suggest mild RSV infection is characterized by robust interferon expression, adequate monocyte activation and higher viral loads."

- Octavio Ramilo, MD



Reference:

Heinonen S, Velazquez VM, Ye F, Mertz S, Acero-Bedoya S, Smith B, Bunsow E, Garcia-Mauriño C, Olivia S, Cohen DM, Moore-Clingenpeel M, Peeples ME, Ramilo O, Mejias A. Immune profiles provide insights into respiratory syncytial virus disease severity in young children. *Science Translational Medicine*. 22 Apr 2020;12(540):eaaw0268.

Referrals and Consultations

Online: [NationwideChildrens.org/Neonatology](https://www.NationwideChildrens.org/Neonatology)

Outpatient Scheduling Phone: (614) 722-6200 or (877) 722-6220

Fax: (614) 722-4000

Physician Direct Connect Line for 24-hour urgent physician consultations, referrals and transfers: (614) 355-0221 or (877) 355-0221.

