PARTNERS IN CARE

NEONATOLOGY UPDATE

FALL 2020

In these uncertain times, we at Children's Hospital of Philadelphia (CHOP) are doing everything we can to support our patients, staff, referring partners, and the communities that rely on us every day. We know COVID-19 has presented challenges for everyone. Our Division of Neonatology and our Harriet and Ronald Lassin Newborn/Infant Intensive Care Unit remain committed to caring for patients and continue to accept all referrals for ill or premature newborn infants.

As your partner, we are here for you as a resource to help coordinate your patient's care during this rapidly evolving situation. We know there are many questions during this uncertain time and want to assure you we are following best practice recommendations, in conjunction with Infection Prevention & Control at CHOP and the latest CDC guidance. We have put in place stringent protocols and procedures to keep babies, their families, and our staff safe, and will work with each family to meet their individual needs.

Our team of nurses, neonatologists, and other medical staff are among the most talented and dedicated in the care of fragile young babies. We continue to work around the clock using the most advanced resources available to ensure each baby receives the very best, most compassionate care and the best chance at a bright future.

Having a sick baby can be a particularly intense experience, even in normal times. In addition to the medical side of care, our team supports parents through any mental or emotional hardship they may experience. We continue to prioritize in-person parent/child bonding, and also offer state-of-the-art technology that allows parents to view their child remotely.

We value the opportunity to partner with you in providing expert care for your patients during this unpredictable time. This issue of *Neonatology Update* provides an in-depth look at some of our latest findings and advances. As always, we welcome your feedback. If you have any questions, please do not hesitate to reach out to us.

Stay well,

Eric C. Eichenwald, MD
Chief, Division of Neonatology

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Division of Neonatology

A COMPREHENSIVE APPROACH TO BECKWITH-WIEDEMANN SYNDROME

By Jennifer M. Kalish, MD, PhD, Attending Geneticist, and Evan R. Hathaway, MS, LCGC, Genetic Counselor

Beckwith-Wiedemann syndrome (BWS) is a complex multisystem overgrowth and cancer predisposition disorder that affects about 1 in 10,000 live births. Assisted reproductive technologies (ART) increases the risk to 1 in 1,100 live births. Improved clinical and molecular diagnostic guidelines have been developed with guidance from the BWS Clinic and Registry at CHOP, in conjunction with centers throughout Europe.

Several of the cardinal features of BWS, including macroglossia, omphalocele, hyperinsulinism, and an increased risk for embryonal tumors, require evaluation and management in the neonatal period. Additional features that would be unlikely to impact neonatal course but can lead to a diagnosis of BWS are facial nevus simplex, nephromegaly, hepatomegaly, placentomegaly, polyhydramnios, ear creases or pits, transient hypoglycemia, umbilical hernia, diastasis recti, and being large for gestational age (LGA).

Macroglossia

Approximately 90% of children with BWS have macroglossia. An enlarged tongue can cause feeding and respiratory issues in the neonatal period and beyond. Infants presenting with macroglossia should undergo a feeding evaluation and polysomnography which can be utilized as an objective measure for obstructive sleep apnea. An evaluation by a plastic surgeon familiar with macroglossia is also necessary to consider the utility of tongue reduction to improve immediate feeding and breathing concerns, as well as avoid potential speech development and structural jaw issues in the future.

Hyperinsulinism

While a significant percentage of neonates with BWS have transient hypoglycemia that resolves within the first few days of life, roughly 20% will have prolonged hypoglycemia due to hyperinsulinism (HI) that requires escalated treatment. Neonates with suspected or confirmed BWS should be screened for hypoglycemia, and infants with low plasma glucose levels should be evaluated by an endocrinologist familiar with HI. Treatment of HI can include medical therapies, pancreatectomy, and/or continuous feeds.

Embryonal Tumors

As children with BWS have an increased risk for developing embryonal tumors, specifically Wilms tumor and hepatoblastoma, tumor screening should be initiated immediately for any baby suspected to have BWS. The screening guidelines for BWS are complete abdominal ultrasounds every 3 months and serum alpha-fetoprotein (AFP) levels until the fourth birthday, followed by renal ultrasounds every 3 months until age 7.

Omphalocele

No specific recommendations for omphalocele management exist for babies with BWS, and standard practices should be observed.

Caring for infants with BWS

Careful and timely consideration of the recommendations is necessary for comprehensive care of neonates with BWS. One of the many newborns with BWS we have cared for at CHOP presented prenatally with an omphalocele on a 12-week ultrasound. His mother was referred to our Center for Fetal Diagnosis and Treatment at the time, and a diagnosis of BWS was highly suspected due to the additional prenatal features of being LGA along with enlarged kidneys and liver. The child was born via caesarean section at 34 weeks after his mother presented to our hospital's Garbose Family Special Delivery Unit with premature rupture of membranes. After birth, he was immediately transferred to our Harriet and Ronald Lassin Newborn/Infant Intensive Care Unit (N/IICU) where a clinical diagnosis of BWS was made based on features of omphalocele, LGA, macroglossia, hypoglycemia, and facial nevus simplex. This diagnosis was confirmed through molecular testing. Due to prolonged hypoglycemia, Endocrinology was consulted, and the child was confirmed to have hyperinsulinism. His blood glucose levels were maintained via total parenteral and enteral feeds with a background glucose infusion rate until he passed a cure fast prior to discharge. During his initial N/IICU stay, he was evaluated for feeding and breathing concerns due to his enlarged tongue, and it was determined that an early tongue reduction was not required. He later had a hemiglossectomy at 13 months of age. His first tumor screening through abdominal ultrasound and AFP was completed on the second day of life and was not concerning for any lesions. However, at approximately one and half months old, when the child was close to being discharged from the N/IICU, his AFP was noted to increase and a new liver mass was determined to be a hepatoblastoma. He underwent chemotherapy prior to surgical resection of the tumor and omphalocele repair.

Our experience with this child and many other children with BWS has enabled us to improve our clinical management of the neonate with BWS. In an effort to streamline our own practices and provide a resource for other institutions, we have developed a pathway describing the necessary evaluations and interventions for newborns suspected to have BWS. To view the pathway, visit **chop.edu/BWSpathway.** ■

Neonates with suspected or confirmed BWS should be screened for hypoglycemia, and infants with low plasma glucose levels should be evaluated by an endocrinologist familiar with HI.

For more information on BWS, including ongoing research, the BWS Registry, and educational resources for families and providers, please visit research.chop.edu/beckwith-wiedemann-syndrome-program-of-excellence.

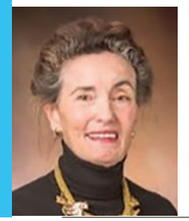
For inquiries about the BWS clinic, please visit chop.edu/BWSclinic.

To learn more about our Congenital Hyperinsulinism Center, please visit chop.edu/hyperinsulinism.

Evaluation and management checklist for suspected or confirmed Beckwith-Wiedemann syndrome (BWS) in the neonatal period.

CONSULT	EVALUATIONS/MANAGEMENT	BWS FEATURE
☐ Genetics	☐ Physical evaluation for consideration of clinical diagnosis ☐ Molecular testing including chromosome 11p15.5 methylation and copy number analysis, CDKN1C sequencing, and a genome-wide SNP array	One cardinal feature and/or multiple suggestive features
☐ Plastic Surgery	☐ Consideration of tongue reduction surgery based on clinical exam and sleep and/or feeding studies	Macroglossia
☐ Pulmonology	☐ Sleep study to evaluate for obstructive sleep apnea	
☐ Feeding Team	☐ Feeding evaluation including a swallow study	
☐ Endocrinology	☐ Screen blood glucose levels: **chop.edu/newborn glucosepathway** ☐ If persistent lows noted, consider diagnostic fast: **chop.edu/newbornhypoglycemiapathway**	Hypoglycemia/ Hyperinsulinism
☐ Surgery	☐ Standard omphalocele care	Omphalocele
☐ Cancer Predisposition/ Oncology	☐ Complete abdominal ultrasounds and alpha-fetoprotein every 3 months until the fourth birthday ☐ Renal ultrasounds from age 4 to 7	Embryonal tumor risk
☐ Pathology	☐ Placenta evaluation for placental mesenchymal dysplasia	Placentomegaly

Follow-Up Corner



MOVING TOWARD EARLIER DIAGNOSIS OF CEREBRAL PALSY

By Hallam Hurt, MD, Education Director, Neonatal Follow-up Program

Overview

Historically, the diagnosis of cerebral palsy (CP) occurs at ~18 months of age. The current endeavor seeks to identify CP as early as 3 months of age and certainly before 6 months corrected age. Why? The impetus is to intervene during the period of neuroplasticity, which is greatest in early infancy. The overarching aim of early detection is to provide optimal developmental trajectories of children, with interventions targeted not only to motor skills, but also to vision, hearing, sensory, pain, and sleep issues.

Instruments

What tools are utilized to provide early detection?

History: birth history, course in the intensive care nursery

Imaging: results of cranial ultrasounds or MRI, if available

Neurological examination: findings on an examination conducted in neonatal follow-up clinic or primary care office

Biomarkers:

- General Movement Assessment (GMA) - General movements are part of a spontaneous movement repertoire, present from fetal life to approximately 6 months of life. They are described as "fluent and elegant," waxing and waning in intensity, force, and speed *(Ment Retard Dev Disabil Res* rev 2005, 11(1): 61-67). With neurologic injury, movements become "monotonous and poor."

  Two specific patterns are associated with CP:
  - persistent pattern of cramped synchronized movements
  - absence of fidgety movements

  Each has a sensitivity and specificity of 95%. The GMA requires a 2-minute videotaping session to be reviewed by an individual certified in GM assessments. We initiated the GMA in our Neonatal Follow-up Program in January 2020.

- Hammersmith Infant Neurological Examination (HINE) - This 26-item evaluation was described in a prior "Follow-up Corner" article. Briefly, it assesses cranial nerves, posture, quantity and quality of movements, muscle tone, and reflexes and reactions. It is conducted by trained providers and physical therapists and includes optimality or "cut-off" scores for predicting cerebral palsy in both preterm and term infants.

Comment

As reported in *JAMA Pediatrics* in 2017, the 3 tools with the best predictive validity for detecting CP before 5 months corrected age are:

1. Neonatal MRI (86%-89% sensitivity)
2. GMA (98% sensitivity)
3. HINE (90% sensitivity)

Currently in CHOP Neonatal Follow-up Programs, we utilize the GMA and the HINE. Based on these tools, we identify some infants as at "high risk for CP" as early as 3 to 4 months, with future evaluations to confirm the diagnosis or not. The CP early detection initiative at CHOP follow-up clinics is being spearheaded by Andrea Duncan, MD, site investigator for this Cerebral Palsy Foundation-sponsored endeavor.

Communicating the diagnosis of cerebral palsy

Communicating the diagnosis of cerebral palsy to parents and families is a conversation that must be carried out with honesty and compassion. The following points regarding conduct of this communication were made at the Implementation of Early Detection and Intervention for Cerebral Palsy Conference in Spring 2018, and form the basis of our communication strategy.

- Be honest, realistic, and hopeful
- Use simple words; offer numbers if parents want more details
- Do not be too general or use platitudes
- High risk as a diagnosis is OK ... our conversations will continue and the diagnosis may be revisited
- Admit that we may be wrong
- Explain the whole spectrum for a child
- Explain why an early diagnosis is important
- Know that parents want earlier diagnosis; they prefer any information vs. none
- It is better to be wrong than not to have had the conversation

If you are making an early diagnosis ...

- Recap the clinical history
- Review what is noted during the current evaluation
- Demonstrate the abnormalities as you found them during evaluation
- Make certain the parent agrees
- Tell the truth
- Share hope
- Let the family share the event

Families want you to ...

- Have an upfront, transparent conversation
- Have both parents present
- Demonstrate respect for the child
- Allow quiet time
- Sit down
- Remind family of child's strengths; convey hope
- Provide a follow-up interview
- Take lead from the family; allow them control
- Acknowledge privacy of the diagnosis
- Help them in how to convey diagnosis to others
- Ask them to write down their questions

Pitfalls include ...

- Talking too much
- Beating around the bush
- Too much medical jargon
- Not being prepared for sadness or anger
- Assuming we know their fears rather than asking
- Not sitting down
- Forgetting to acknowledge that parents may be too overwhelmed to have questions at that moment
- No support person available
- Not having a prepared interpreter, if one is needed

Avoiding Pitfalls

- Listen
- Allow room for silence ... WAIT ... Why am I talking?
- Be honest regarding challenges and limits of our knowledge
- Give hope in specific ways
- Think about what the child can do rather than what they cannot
- Avoid prognostications
- Provide educational materials and support systems
- Establish follow-up

Next in Follow-Up Corner: Parental feelings regarding early diagnosis of CP. ■

Jacquelyn Evans, MD, FRCP(c), FAAP

HONORING AN IMPACTFUL CAREER

It is with mixed emotions that we bid farewell to long-time CHOP neonatologist, **Jacquelyn Evans, MD, FRCP(c), FAAP**, Associate Division Chief and Director of Quality and Patient Safety for our Division of Neonatology, who retired last fall.

"I would like to extend my sincere thanks to Dr. Evans," says Eric Eichenwald, MD, Chief of the Division of Neonatology at CHOP. "She has exemplified a strong dedication to advancing care for our patients ensuring they achieve the best possible outcomes."

Dr. Evans' areas of expertise include advanced ventilatory support in neonates, ethics in neonatal care, and the limits of neonatal viability. She frequently lectured around the globe on a variety of topics, most recently including Advanced Therapies in Neonatal Care.

In 2019, she was awarded the Neonatal Pioneer Award by the American Academy of Pediatrics. This distinction recognizes the pioneering achievements and contributions Dr. Evans has made to the health and well-being of newborns and infants. Beyond her role at CHOP, Dr. Evans also served as clinical professor of pediatrics at the Perelman School of Medicine at the University of Pennsylvania and chair of the Children's Hospital's Neonatal Consortium, a grassroots national benchmarking and quality improvement organization in children's hospitals NICUs.

We wish her the best in her retirement and miss her dearly. ■

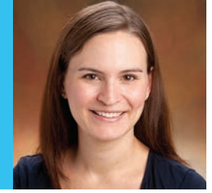
A NEW FACE ON THE CP FOUNDATION BOARD

Andrea F. Duncan, MD, MS, Attending Neonatologist and Medical Director of our Neonatal Follow-up Program, recently joined the board of the Cerebral Palsy Foundation. Dr. Duncan's main research interest is in long-term medical and neurodevelopmental outcomes of NICU graduates. This has included previous research on the effects of implementation of the international guidelines for early assessment for cerebral palsy (CP) on diagnoses and outcomes in high-risk infants. Her current research involves evaluation of executive functioning and brain connectivity in high-risk infants and infants with CP.

Dr. Duncan is the Principal Investigator for Neurodevelopmental Follow-up for the CHOP site of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. She is also the Principal Investigator for the CHOP site of the Cerebral Palsy Foundation Early Detection of Cerebral Palsy Network. ■

CLINICAL TRIAL HIGHLIGHTS

By Sara B. DeMauro, MD, MSCE, Program Director, Neonatal Follow-Up Program



Investigators in CHOP's Division of Neonatology have a robust portfolio of active clinical research in diverse patient populations, including preterm infants, infants exposed to opioids *in utero*, infants with chronic lung disease, and children who are considered high risk for longer-term disabilities because of neonatal illness. We are well-funded by both the National Institutes of Health (NIH) and private foundations. We take extreme pride in being able to offer our patients and their families the opportunity to participate in this exciting research, and we are hopeful that this work will continue to yield important insights into the optimal care of infants and young children. Below, we provide a few examples of actively enrolling studies led by the CHOP Neonatal Clinical Research team in several different patient populations.

Infants with Chronic Lung Disease

Inhaled Tobramycin • PI: Erik Jensen, MD, MSCE

Bronchopulmonary dysplasia (BPD), also known as chronic lung disease of prematurity, is a leading pediatric cause of lifelong disability and early death among very preterm infants. Strikingly, there are no drug therapies shown to improve outcomes for infants with BPD. Our research seeks to resolve this care gap.

An abundance of data support a causal link between pathologic microbial invasion of the lower respiratory tract (LRT) and worsening of respiratory health in chronic lung illness. Our work, and others', has shown the presence of pathogenic Gram-negative rod (GNR) bacteria in the lungs of ventilator-dependent very preterm infants with BPD is an independent risk factor for significant and enduring respiratory morbidity.

Systemically administered antibiotics do not adequately penetrate the lung epithelial lining fluid to eradicate these bacteria. In contrast, inhaled antibiotics deliver the drug directly to the site of infection, offering a safer and more effective alternative. Inhaled tobramycin is an antibiotic with proven efficacy in other chronic respiratory illnesses complicated by GNR infection of the LRT. However, inhaled tobramycin is only FDA approved for use in patients 6 years and older.

The purpose of our phase 1 trial (NCT04560179) of inhaled tobramycin is to establish the preliminary dose tolerability, efficacy, and pharmacokinetic data required to design and conduct the first randomized, placebo-controlled trial of this promising drug therapy in infants with BPD. This study is poised to identify the first drug therapy that improves long-term outcomes in this under-studied disease.

Opioid-Exposed Infants

Advancing Clinical Trials in Neonatal Opioid Withdrawal (ACT NOW) Longitudinal Study • PIs: Sara B. DeMauro, MD, MSCE, and Scott Lorch, MD, MSCE

Newborns exposed to opioids in the womb are at risk for neonatal opioid withdrawal syndrome (NOWS) or neonatal abstinence syndrome. NOWS symptoms can include tremors; excessive crying and irritability; and problems with sleeping, feeding, and breathing. The incidence of NOWS in the United States has increased more than five-fold since 2004 to almost 7 per 1,000 hospital births. Little is known about the long-term effects of this condition, and there are few standard, evidence-based treatments for NOWS.

The Advancing Clinical Trials in Neonatal Opioid Withdrawal (ACT NOW) Longitudinal Study — also known as the Outcomes of Babies with Opioid Exposure Study (OBOE) — is a longitudinal cohort study that aims to quantify the effects of antenatal opioid exposure and NOWS on the trajectory of brain development during the first 2 years of life, examine associations with developmental and neurobehavioral outcomes, and explore how specific factors (differing antenatal and postnatal exposures, severity of neonatal opioid withdrawal, maternal stress/depression/parenting) modify these effects. The study will also identify risk factors for adverse sequelae to optimize neurodevelopmental, behavioral, and family outcomes.

Premature Infants

Cycled Phototherapy Trial • Site PI: Eric C. Eichenwald, MD

The Cycled Phototherapy Trial is one of several ongoing trials at CHOP that is being conducted by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network. Were they not delivered early, extremely premature infants would normally develop in darkness within the uterus for 3 to 4 more months before birth. Yet, the routine care of these infants has involved the use of uninterrupted (continuous) exposure to bright light during phototherapy (PT). Immaturity, thin translucent skin, and a multitude of other problems may make extremely premature infants highly vulnerable to the photo-oxidative injury, lipid peroxidation, DNA damage, reduced cerebral and mesenteric blood flow, or other serious potential hazards of uninterrupted exposure to PT that have now been identified. Such hazards were not recognized when continuous PT was widely incorporated into neonatal care, and the survival rate of extremely premature infants was much lower than today.

PT rapidly photoisomerizes bilirubin in the subcutaneous tissues and vasculature. Six trials of cycled PT have demonstrated that use of cycled PT reduces the total hours of PT and results in minimal or no increase in peak total serum bilirubin (TSB) levels over that with continuous PT in term or moderately preterm infants. Recent findings from a pilot study (NCT01944696) support a PT regimen for this Cycled Phototherapy protocol.

Inborn infants ≤ 750 grams at birth and/or < 27 weeks gestation at birth are eligible for this study. Participants are randomized to either cycled PT or continuous PT. The cycled phototherapy begins with >15 min/h cycled PT regimen and is increased as needed based on the bilirubin level. Those randomized to continuous phototherapy will undergo standard therapy with continuous PT.

The goal of this randomized clinical trial is to test the hypothesis that cycled phototherapy will increase survival when compared to continuous phototherapy in extremely low birth weight (<=750 grams or <27 weeks gestation) infants. In addition, it will control total serum bilirubin levels while reducing phototherapy exposure.

NICU Antibiotics and Outcomes Trial • Site PI: Karen M. Puopolo, MD, PhD

The Division of Neonatology will soon be recruiting for the NICU Antibiotics and Outcomes (NANO) Trial, the first randomized, multicenter study to address the practice of universal empiric administration of intravenous antibiotics to extremely low gestation infants. Because intra-amniotic infection is believed to prompt as many as two-thirds of preterm births, such infants commonly receive antibiotics immediately after birth and often for prolonged periods thereafter, even in the absence of microbiologically-confirmed infection. Early antibiotic exposures are increasingly linked to poor long-term outcomes among preterm infants.

The NANO Trial is funded by the National Institutes of Health (NIH) and seeks to enroll 800 infants born ≤28 weeks gestation in a blinded, placebo-controlled multicenter randomized clinical trial of empiric antibiotics. The aims of the study are to determine if the composite incidence of late-onset infection, necrotizing enterocolitis, or death in infants that receive empiric antibiotics is significantly different than the incidence among infants that receive placebo, as well as to determine if the content of the intestinal microbiome differs among these infants. The results from this study may validate current clinical practice patterns regarding antibiotic administration, or they may provide a critical rationale for further reducing antibiotic usage in the NICU.

Early School-age Outcomes

Hydrocortisone for BPD Respiratory and Developmental (HYBRiD) Outcomes Study • PI: Sara B. DeMauro, MD, MSCE

Bronchopulmonary dysplasia (BPD) affects up to half of extremely preterm infants, and is associated with significant adverse respiratory, developmental, educational, and health economic outcomes. The Hydrocortisone for BPD Respiratory and Developmental (HYBRiD) Outcomes Study builds on the recently completed NICHD Neonatal Research Network (NRN) Hydrocortisone for BPD Trial to characterize the functional respiratory and developmental outcomes of this established trial population at 5 years corrected age, or early school age. Functional assessments, which cannot be performed before early school age, provide parents and schools with a realistic picture of a child's strengths and challenges in everyday scenarios, so that appropriate services can be provided to prevent school failure. In addition, CHOP is the lead site for a sub-study to HYBRiD utilizing impulse osillometry to evaluate early school-age pulmonary mechanics in HYBRiD participants as compared to healthy preterm and full-term children.

The HYBRiD Outcomes Study addresses several critical knowledge gaps about the early school-age outcomes of children with neonatal respiratory failure, based on both the severity of BPD and exposure to hydrocortisone (HC), as well as the relationships between respiratory and developmental outcomes. Results will have an immediate impact on counseling of parents in the neonatal intensive care unit and management of neonates in the unit and after discharge. In addition, data from this study will be essential for the development of future intervention studies aimed to improve the long-term outcomes of preterm infants with respiratory failure.

Transfusion of Prematures Trial 5-year Follow-up Study (TOP 5) • PI: Sara B. DeMauro, MD, MSCE

Up to 95% of premature infants undergo red blood cell (RBC) transfusion while in the intensive care unit, yet it is unknown whether more restrictive or more liberal transfusions will lead to optimal brain development. The Transfusion of Prematures (TOP) Trial is a multicenter study funded by the National Heart, Lung, and Blood Institute (NHLBI) and supported by the NICHD Neonatal Research Network (NRN). The primary objective of the TOP Trial is to assess survival and rates of neurodevelopmental impairment at 22 to 26 months corrected age in extremely low birth weight (ELBW) infants that are randomized to either liberal or restrictive RBC transfusion thresholds. CHOP was the lead site of the multicenter TOP Trial (PI Haresh Kirpalani, MD). The trial began enrollment in December 2012, reached the target sample size of 1,824 infants on time in April 2017, and completed 2-year follow-up of >93% of participants in February 2020.

Although major deficits in motor and cognitive function may be detected at 22 to 26 months of age, these infants are too young to assess cognitive, behavioral, and coordination skills that, if impaired, can lead to problems with academic skills, motor performance, or adaptive functioning in home or school environments, conditions that are far more prevalent in this population and create substantial morbidity for the children and their families. The TOP 5 Study will assess functional neurodevelopmental outcomes of infants randomized to 2 different transfusion thresholds in the TOP Trial at 5 years corrected age and provide evidence about which approach to neonatal transfusion (liberal or restrictive) minimizes damage to vulnerable neuronal circuits and, in turn, which transfusion strategy will improve both short- and long-term outcomes for these vulnerable premature infants. ■

Neonatal/Perinatal Health Services Research

Q-AND-A WITH SCOTT A. LORCH, MD, MSCE

Here, Scott A. Lorch, MD, MSCE, discusses his research group, which is one of the largest neonatal/perinatal health services research groups in the country, as well as a few recent publications and presentations.

What is health services research?

Health services research is a broad field that examines how social, financial, organizational, policy, and personal factors influence access to healthcare, the types and quality of care received, and ultimately the outcomes and costs of healthcare interventions. Neonatal health services and health policy research is unique because the dyad of mother and infant influence pregnancy and early infant outcomes. My research group has been funded continuously since 2004 to study a wide variety of topics focusing on the drivers of variation in outcomes of high-risk infants and mothers, answering the question, "Why, of these 2 newborns that have similar characteristics, did 1 of them experience a complication of preterm birth or a hospital readmission?" We have particular expertise in understanding the drivers of social and racial/ethnic disparities in health outcomes; assessing the quality of care received by infants; and understanding the importance of health policies and perinatal health systems on infant outcomes.

Can you describe some recent work your group has published in this domain?

One example pertains to racial segregation and intraventricular hemorrhage in preterm infants and was recently published in *Pediatrics* by Daria Murosko, MD, MPH, a first-year neonatology fellow at CHOP. She studied the impact of community segregation on a preterm infant's risk of developing intraventricular hemorrhage (IVH), comparing this risk between non-Hispanic Black and non-Hispanic white infants. This comparison is important because of several publications showing that the risk of IVH is higher in non-Hispanic Black infants compared to other racial/ethnic groups. She found that mothers living in a highly segregated area were associated with a 20% increase in the odds that a non-Hispanic Black preterm infant would develop IVH, compared to no significant increase for non-Hispanic white preterm infants whose mother resided in a highly segregated area. Such work provides needed information on how structural factors such as a mother's living conditions may explain some of the observed racial/ethnic disparities in neonatal and pregnancy outcomes here in the United States.

How does an infant's access to care, particularly high-quality care, both during their initial hospitalization and after discharge impact mortality and morbidity?

A publication last year by Gia Yannekis, MD, a third-year resident at CHOP, found that preterm infants of minority racial/ethnic status experienced greater benefits from delivering at a level 3 or 4 high-volume hospital compared to non-Hispanic white infants. This effect was most strongly seen in a reduction in the risk of common morbidities of preterm birth such as bronchopulmonary dysplasia (BPD) and intraventricular hemorrhage (IVH). A follow-up abstract published from this year's Pediatric Academic Societies meeting found that this finding occurred because the lower-level hospitals that cared for minority patients had substantially worse quality than lower-level hospitals that cared for non-Hispanic white infants. Such work parallels data that was published by the Vermont Oxford Network that I was fortunate to be a co-author on, which showed similar gaps in the quality of neonatal care provided to non-Hispanic Black infants compared to other racial/ethnic groups.

We have particular expertise in understanding the drivers of social and racial/ethnic disparities in health outcomes; assessing the quality of care received by infants; and understanding the importance of health policies and perinatal health systems on infant outcomes.

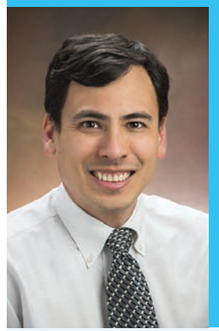
Are there other barriers to accessing high-quality healthcare?

Barriers to accessing high-quality care are not limited to racial/ethnic minorities; we have shown that only 40% of preterm rural pregnancies deliver at a hospital with any sort of neonatal intensive care unit (NICU), with even lower levels when there is no local hospital nearby that has a NICU. Given the work we and others have done that demonstrates a 600% to 300% improvement in mortality rates when preterm infants deliver at a hospital with the capability to care for the newborns immediately after delivery, such gaps in accessing high-quality care are an area for further investigation and intervention.

How are you using research to optimize outcomes?

Our group has a particular interest in developing and testing policies that may improve the outcome of high-risk mothers and infants. One example of such work is a recent publication by Diana Montoya-Williams, MD, examining the benefits of paid maternity leave, which is highlighted in this newsletter. We have also explored the importance of maternal levels of care on infant and pregnancy outcomes, as well as further refinements of the neonatal levels of care work that I have previously published, that shows the importance of the number of infants with a gestational age < 32 weeks on optimizing their outcomes. This work, presented in June as part of the Pediatric Academic Societies summer neonatology webinar series, showed that mortality rates were optimized when NICUs cared for at least 40 infants, and morbidity rates were optimized when NICUs care for at least 100 infants. However, we do not know how these findings translate in settings, such as rural communities, that live far from a high-level NICU. Such research, though, is important to present in order to overcome barriers to developing evidence-based policies for infants and children.

These recent publications and presentations are just a snapshot of the population health approach that our group uses to understand the many barriers to achieving the best outcomes for preterm infants and their mothers. By understanding all of the factors — medical and non-medical — that influence outcomes, we can begin to develop interventions and policies to improve care. In this current medical and social climate, such research is critical to address the particular issues for an individual child. ■



Scott A. Lorch, MD, MSCE, is an Attending Neonatologist, Associate Chief of the Division of Neonatology, Director of Clinical and Epidemiological Research, and Kristine Sandberg Knisely Professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania. He also has appointments in the Center for Clinical Epidemiology and Biostatistics, and is a senior fellow of the Leonard Davis Institute of Health Economics at the University of Pennsylvania. Dr. Lorch received his Master of Science degree in Clinical Epidemiology (MSCE) from the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania.

He currently is the principal investigator on the following 3 active federally funded projects:

- **Effect of Changing NICU Patient Volumes and Levels of Care on Neonatal Outcomes**, funded by the Agency for Healthcare Research and Quality (Grant Number R01HD084819)
- **Predicting and Preventing Pediatric Hospital Readmissions**, funded by the Agency for Healthcare Research and Quality (Grant Number R01 HS023538)
- **HEAL Initiative:** Antenatal Opioid Exposure Longitudinal Study Consortium (Outcomes of Babies with Opioid Exposure [OBOE] Study), Grant Number 1RL1HD104252/1PL1HD101059
- **Obstetric Volume, Regionalization, and Maternal and Infant Outcomes**

INTRODUCING OUR NEW DIRECTOR OF NEONATAL EDUCATION

We are pleased to announce **Mackenzie Frost, MD, MedEd**, has joined our team as Director of Neonatal Education in our Division of Neonatology, and Director of Fellowship Education for CHOP's Department of Pediatrics. Dr. Frost received her BA in biology from Rice University, her medical degree from Oregon Health Sciences University, and a master's in medical education from Cincinnati Children's Hospital. She completed her residency in pediatrics at Brown University Medical School, where she served as chief resident, and completed her fellowship in neonatal-perinatal medicine at the University of Colorado Health Sciences Center.

Since then, Dr. Frost has served as a critical care transport physician at Rhode Island Hospital/Hasbro Children's Hospital and an attending physician in pediatric/neonatal-perinatal medicine at Children's Hospital of Denver. She also served as attending physician in pediatric/neonatal-perinatal medicine and associate director of the neonatal-perinatal fellowship and the pediatric residency at St. Christopher's Hospital for Children. Most recently, she was an attending physician in pediatrics/neonatal-perinatal medicine at UT Southwestern Medical Center, where she also served as director of their neonatal-perinatal fellowship as well as their pediatric education fellowship. ■

EXPANDED NEWBORN CARE IN NEW JERSEY

We are pleased to announce the recent expansion of our Newborn Care footprint. CHOP's board-certified doctors now treat babies at Virtua Our Lady of Lourdes Hospital in Camden, N.J. This partnership allows us to provide 24/7 newborn and neonatal intensive care to the communities served by Our Lady of Lourdes. See a list of our new team members below.

For more information, contact us at **215-590-1653**.

Location:
1600 Haddon Ave.
Camden, NJ 08103

Referrals:
215-590-3083

WE ALSO WELCOME

Kamran Ahmed, MD
St. Mary Medical Center

Joseph Asaro, MD
AtlantiCare

Heidi Herrick, MD
Main Campus in University City
Instructor, Perelman School of Medicine at the University of Pennsylvania

Alina Ivashchuk, DO
Lancaster Women & Babies Hospital

Kuan-chi Lai, MD
Main Campus in University City

Sharadha Polam, MD
St. Mary Medical Center and Penn Princeton Medical Center

Kristin Ronan, MD
Lancaster Women & Babies Hospital

Amy Sloane, MD
Holy Redeemer Hospital

VIRTUA OUR LADY OF LOURDES HOSPITAL

Purvi Kapadia-Jethva, MD
Medical Director

Muhammad Anwar, MD
Yashvantkumar Patel, MD
Tomas Rotschild, MD
Smart Uko, MD

IMPROVING OUTCOMES FOR INFANTS WITH SEVERE CHRONIC LUNG DISEASE THROUGH INDIVIDUALIZED PATIENT CARE AND RESEARCH

By Erik Jensen, MD, MSCE, Assistant Professor of Pediatrics and Attending Neonatologist in the Division of Neonatology at Children's Hospital of Philadelphia and the University of Pennsylvania

Infant chronic lung disease, also known as bronchopulmonary dysplasia (BPD), is among the most common and consequential complications associated with prematurity. Roughly half of all extremely preterm infants develop BPD during their newborn hospitalization and most of those with the disease go on to suffer significant deficits in lung and cardiovascular health, growth, and neurodevelopment throughout childhood and even into adulthood. While considerable research has focused on the prevention of BPD, there is comparatively minimal available data on the best strategies to care for and improve outcomes among infants with established BPD.

In 2010, clinicians and investigators at Children's Hospital of Philadelphia (CHOP) created the CHOP Newborn/Infant Chronic Lung Disease (NeoCLD) Program to address this gap. One of the first of its kind in the world, the CHOP NeoCLD Program was designed to be a clinical and research home for infants with BPD receiving neonatal intensive care throughout the surrounding region and nation at large.

The 2 primary goals of the NeoCLD Program are:

1. Provide the best possible, evidence-based and patient-centered clinical care to infants and children with the most severe forms of BPD
2. Be at the forefront of clinical, translational, and basic science research that will improve care for this vulnerable population to achieve the best possible outcomes

Our team recognized early in the course of the NeoCLD Program that BPD is not one uniform disease. Rather, each infant with BPD is unique and requires an individualized care plan. Much of our research focuses on developing new strategies to understand each infant's pathophysiology and tailor appropriate therapies.

We are currently using next-generation sequencing techniques to characterize the lung microbiome in infants with established BPD and have been approved by the U.S. Food and Drug Administration to conduct a novel phase-1 trial of inhaled antibiotic therapy among infants with harmful bacterial pathogens identified in the airways. In addition to the injurious invasion of micro-organisms into the lungs, gastroesophageal reflux (GER) with pulmonary aspiration is an often cited but poorly understood potential contributor to ongoing respiratory disease in infants with BPD. Our research team is actively recruiting patients into a multifaceted study that will provide valuable new data on GER in BPD titled "Gastroesophageal reflUx in and the association with Lung disease in Preterms (GULP): A prospective cohort study." The GULP study employs 24-hour esophageal pH and multichannel intraluminal impedance (pH/MII) testing to diagnose and quantify GER in infants with BPD. This gold-standard technique is coupled with concurrent cardiac echocardiography, continuous cardiorespiratory physiologic monitoring, and videography. These diagnostic studies are then combined with the results from computed tomography (CT) imaging of the lungs and bronchoscopy of the airways to develop a detailed and individualized picture of each patient's disease. Our neonatal specialists in conjunction with a wide range of pediatric specialists use this information to select appropriate respiratory support strategies, medications, and feeding regimens, and, when needed, to recommend surgical interventions to families.

Additional recently completed and ongoing studies conducted by the NeoCLD team include:

- Single and multicenter cohort studies proposing new, evidence-based diagnostic criteria for BPD and BPD subtypes.
- Randomized clinical trial comparing 2 different goal oxygen saturation target ranges in infants with established BPD to help determine the optimal level and duration of oxygen therapy in this population
- Placebo controlled randomized trial of aerosolized albuterol in ventilator dependent infants with BPD
- Novel N-of-1 multiple crossover trial comparing cardiorespiratory stability during gastric and transpyloric feedings
- Optimization of positive end expiratory pressure (PEEP) level selection
- Development of dosage and duration informed treatment strategies for diuretic therapy in severe BPD
- Development of novel techniques to characterize and improve early motor development in infants with severe BPD

Investigators in the NeoCLD Program receive funding to conduct this research from the National Institutes of Health, the American Lung Association, the Thrasher Research Fund, Children's Hospital of Philadelphia, and other national organizations.

Our ability to perform state-of-the-art research and combine it in real-time with ongoing clinical care allows us to positively influence the health of our current patients and to design our next studies aimed at improving outcomes for our future patients. We take extreme pride in being able to offer our patients and their families the opportunity to participate in this exciting research, and we are hopeful that this work will continue to yield important insights into the optimal care of infants and young children with BPD. ■

RESEARCH SUMMARY

The Impact of Paid Family Leave in the United States on Birth Outcomes and Mortality in the First Year of Life

By Diana Montoya-Williams, MD, Attending Neonatologist

Paid parental leave has been tied to improvements in many pediatric health outcomes including breastfeeding, preterm birth, low birth weight, and infant mortality. However, most of the existing literature has come from international studies looking mainly at European countries. In 2004, California was the first state to pass paid family leave legislation in the United States. More than 10 years later, its effect on birth outcomes and risk of mortality in the first year of life is not known. Given the increasing number of states passing similar legislation and ongoing national discussions about optimal parental leave programs, it is crucial to better understand how such policies impact health outcomes in the U.S. specifically.

In our study, we evaluated the effect of the passage of paid family leave legislation in California on statewide rates of preterm birth, low birthweight, post-neonatal mortality (i.e., within the first 28 days) and overall infant mortality (within the first year). Using a quasi-experimental study design to compare the rates of these outcomes in California before and after implementation of the 2004 policy with rates in 2 states without paid family leave policies, we found that post-neonatal mortality rates decreased by 12% in California after 2004, after adjusting for maternal and neonatal factors. We also found there were no differences in the policy's effect by race/ethnicity or insurance status except for increased odds of low birthweight among privately insured women in California after 2004.

Our study thus found evidence that paid family leave policies are associated with reduced post-neonatal mortality in the U.S. Given that California has not seen any adverse effects on labor or economic-related outcomes to-date, recent federal legislation expanding paid family leave policies nationally should be explored as a strategy to improve infant health across the country.

Montoya-Williams D, Passarella M, Lorch SA.
The Impact of Paid Family Leave in the United States on Birth Outcomes and Mortality in the First Year of Life. *Health Serv Res.* *[Published online ahead of print April 5, 2020].* ■

SELECT PUBLICATIONS

Recorded Flexible Nasolaryngoscopy for Neonatal Vocal Cord Assessment in a Prospective Cohort. Chorney SR, Zur KB, Buzi A, McKenna Benoit MK, Chennupati SK, Kleinman S, DeMauro SB, Elden LM. *[Published online ahead of print Aug. 14, 2020] Ann Otol Rhinol Laryngol.*

IFNs Drive Development of Novel IL-15-Responsive Macrophages. Gordon SM, Nishiguchi MA, Chase JM, Mani S, Mainigi MA, Behrens EM. *J Immunol.* 2020;205(4):1113-1124.

Guidelines for Standardized Nomenclature and Reporting in Uterus Transplantation: An Opinion from the United States Uterus Transplant Consortium. Johannesson L, Testa G, Flyckt R, Farrell R, Quintini C, Wall A, O'Neill K, Tzakis A, Richards EG, Gordon SM, Porrett PM. *[Published online ahead of print May 7, 2020] Am J Transplant.*

Derivation of a Metabolic Signature Associated with Bacterial Meningitis in Infants. Gordon SM, Srinivasan L, Taylor DM, Master SR, Tremoglie MA, Hankeova A, Flannery DD, Abbasi S, Fitzgerald JC, Harris MC. *Pediatr Res.* 2020;88(2):184-191.

Neonatal Meningitis: Overcoming Challenges in Diagnosis, Prognosis, and Treatment with Omics. Gordon SM, Srinivasan L, Harris MC. Front *Pediatr.* 2017;5:139.

Placental Transfusion and Short-term Outcomes Among Extremely Preterm Infants. Kumbhat N, Eggleston B, Davis AS, Van Meurs KP, DeMauro SB, Foglia EE, Lakshminrusimha S, Walsh MC, Watterberg KL, Wyckoff MH, Das A, Handley SC; Generic Database Subcommittee of the NICHD Neonatal Research Network; undefined. *[Published online ahead of print July 30, 2020] Arch Dis Child Fetal Neonatal Ed.*

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Clinical Priority Line (24/7):
800-TRY-CHOP or
800-879-2467,
then press #2 to talk to the on-call CHOP specialist.

Need to reach a specific provider or a member of our clinical team caring for your hospitalized patient?

We can help arrange a return phone call!

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