SELECT PUBLICATIONS

Te Pas A, Roehr CC, Foglia EE, Hooper S. **Neonatal resuscitation research: closing the gap**. *[Published online ahead of print Feb. 24, 2021] Pediatr Res.*

Seabrook RB, Grover TR, Rintoul N, Weems M, Keene S, Brozanski B, DiGeronimo R, Haberman B, Hedrick H, Gien J, Ali N, Chapman R, Daniel J, Harrison HA, Johnson Y, Porta NFM, Uhing M, Zaniletti I, Murthy K; Children's Hospitals Neonatal Consortium Congenital Diaphragmatic Hernia Focus Group. **Treatment of pulmonary hypertension during initial hospitalization in a multicenter cohort of infants with congenital diaphragmatic hernia (CDH).** *J Perinatol.* 2021;41(4):803-813.

Grover TR, Weems MF, Brozanski B, Daniel J, Haberman B, Rintoul N, Walden A, Hedrick H, Mahmood B, Seabrook R, Murthy K, Zaniletti I, Keene S; Children's Hospitals Neonatal Consortium (CHNC) Congenital Diaphragmatic Hernia Focus Group. **Central line utilization and complications in infants with congenital diaphragmatic hernia.** *[Published online ahead of print Feb. 3, 2021] Am J Perinatol.*

Lorch SA, Rogowski J, Profit J, Phibbs CS. **Access to risk-appropriate hospital care and disparities in neonatal outcomes in racial/ethnic groups and rural-urban populations.** *[Published online ahead of print March 21, 2021] Semin Perinatol.*

Ying T, Golden TN, Cheng L, Ishibashi J, Seale P, Simmons RA. **Neonatal IL-4 exposure decreases adipogenesis of male rats into adulthood.** *[Published online ahead of print April 19, 2021] Am J Physiol Endocrinol Metab.*

van Heesewijk AE, Rush ML, Schmidt B, Kirpalani H, DeMauro SB. **Agreement between study designs: a systematic review comparing observational studies and randomized trials of surgical treatments for necrotizing enterocolitis.** *J Matern Fetal Neonatal Med.* 2020;33(12):1965-1973.

Burris HH, Passarella M, Handley SC, Srinivas SK, Lorch SA. **Black-white disparities in maternal in-hospital mortality according to teaching and Black-serving hospital status.** *[Published online ahead of print Jan. 13, 2021] Am J Obstet Gynecol.*

Sivieri EM, Rub DM, Abbasi S, Eichenwald EC. **Preserved pressure delivery during high-frequency oscillation of bubble CPAP in a premature infant lung model with both normal and abnormal lung mechanics.** *Pediatr Pulmonol.* 2021;56(5):1136-1144.

Mukhopadhyay S, Puopolo KM, Hansen NI, Lorch SA, DeMauro SB, Greenberg RG, Cotten CM, Sanchez PJ, Bell EF, Eichenwald EC, Stoll BJ; NICHD Neonatal Research Network. **Neurodevelopmental outcomes following neonatal late-onset sepsis and blood culture-negative conditions.** *[Published online ahead of print Jan. 21, 2021] Arch Dis Child Fetal Neonatal Ed.*

SAVE THE DATE • SEPT. 29, 2021
Advances in Neonatal-Perinatal Medicine Virtual Conference

LEARN MORE
cloud.chop-cme

CONNECT WITH US

One Call, One Number! Clinical Priority Line (24/7): 1-800-TRY-CHOP or 1-800-879-2467, 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!

www.chop.edu/neonatology

Children's Hospital of Philadelphia®
Division of Neonatology

PARTNERS IN CARE

NEONATOLOGY UPDATE

SUMMER 2021

As one of the largest Neonatology practices of any pediatric hospital in the world, we care for thousands of critically ill infants with health issues related to birth defects, pulmonary, cardiac and gastrointestinal issues, and other disorders every year. Our goal is to provide each patient the highest quality care in their earliest hours, days, weeks, and months of life in an effort to ensure their best long-term health.

We take a holistic approach toward the respiratory and health needs of preterm infants while providing individualized care to optimize long-term respiratory outcomes. Today, about half of extremely preterm infants who survive to 36 weeks post-menstrual age have bronchopulmonary dysplasia (BPD). Infants with BPD are at increased risk for poor respiratory health, developmental delay, and cerebral palsy.

In this issue of our newsletter, you'll find a deep dive into our team's efforts to improve therapies and care strategies for neonates with BPD. This work runs the gamut, from developing a treatment-based classification of BPD disease severity, to investigating the connection between oxygen therapy in the neonatal period and the lung circadian clock to pave the way for novel therapeutic strategies for this vulnerable population. We also provide a link that allows you to access our inpatient and ICU clinical pathway for pulmonary hypertension screenings in patients with BPD, which may be helpful in guiding you.

Also featured within are fascinating pieces on:

- the rate of preterm birth and stillbirth during the COVID-19 pandemic
- the biological functions of nitric oxide in the cardiovascular and neuronal systems
- parental perspectives on learning a child is at high risk for cerebral palsy
- ways to improve management of infants with life-threatening airway anomalies
- use of Aquadex FlexFlow® to support small infants with early renal insufficiency or renal failure who are unable to receive peritoneal dialysis
- between-center variation in loop diuretic use of preterm infants with BPD

Our team values the opportunity to partner with you and is ready at a moment's notice to provide the best possible outcome for every child entrusted to us. I hope you enjoy this edition of *Neonatology Update*. As always, I welcome your feedback.

Stay well,

Eric C. Eichenwald, MD
Chief, Division of Neonatology

Children's Hospital of Philadelphia®
Division of Neonatology

SEEKING A BETTER UNDERSTANDING OF BRONCHOPULMONARY DYSPLASIA TO OPTIMIZE CHILDHOOD OUTCOMES

By Sara B. DeMauro, MD, MSCE, Program Director, Neonatal Follow-Up Program, and Associate Director, Neonatal Clinical Research

Preterm infants with bronchopulmonary dysplasia (BPD), particularly those who require prolonged mechanical ventilation during the neonatal period, are at high risk for poor medical and developmental outcomes throughout childhood. Today, about half of extremely preterm infants who survive to 36 weeks post-menstrual age (PMA) have BPD. Infants with BPD have increased risk for poor respiratory health, developmental delay, and cerebral palsy. As children with BPD mature beyond infancy, they continue to demonstrate important developmental sequelae. BPD is associated with approximately one-standard deviation decrease in childhood intelligence and significantly increased risk for cerebral palsy. In addition, children and adolescents with BPD have poorer performance than other children across multiple domains, including academic skills, visual-motor integration, executive function, motor coordination, and social function.

Our team of investigators in the Children's Hospital of Philadelphia Chronic Lung Disease Program, in collaboration with the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network, developed a treatment-based classification of BPD disease severity. This new definition of BPD is based on the level of respiratory support at 36 weeks PMA, regardless of oxygen administration *(see chart below)*. This definition has high predictive accuracy for both death or serious respiratory morbidity and death or moderate to severe neurodevelopmental impairment at 18-26 months corrected age. A higher grade of BPD is associated with more severe developmental impairment.

BPD GRADE	RESPIRATORY SUPPORT AT 36 WEEKS PMA
No BPD	No support
Grade 1	<=2L nasal cannula
Grade 2	>2L or noninvasive positive pressure
Grade 3	Mechanical ventilation

Impact of strategies to prevent or treat BPD

Over the past several decades, many therapies and care strategies—including prenatal therapies, immediate postnatal medications, and respiratory strategies to prevent BPD and later approaches to treat or decrease severity of BPD—have been rigorously evaluated and introduced into the bedside armamentarium. The hope is that by preventing or treating BPD, these strategies will also improve longer-term outcomes.

The key perinatal strategy to prevent BPD is administration of **antenatal corticosteroids**, which reduce mortality, respiratory distress syndrome, and several other important neonatal morbidities. Unfortunately, however, antenatal steroid treatment does not reduce the incidence of BPD or improve the developmental outcomes of survivors. In the immediate postnatal period, **noninvasive respiratory support** as an alternative to routine intubation in the delivery room, **early surfactant treatment** of intubated infants, and **vitamin A** all lead to reductions in the combined endpoint of death or BPD in very preterm infants. However, none of these approaches has been demonstrated to improve developmental outcomes at 2 years.

The impact of **postnatal corticosteroids** on both BPD and longer-term developmental outcomes is uncertain due to heterogeneity in existing research as well as in clinical practice, including the type of steroid used, timing of administration, dosing regimen, route of administration, and baseline risk for adverse outcomes in the treated children. When given during the second week or beyond, this therapy may reduce risk for adverse developmental sequelae. However, much remains to be learned about how to best use postnatal steroids to reduce BPD while protecting neurodevelopment. Lastly, **inhaled steroids** have also been studied both for prevention and treatment of BPD. When initiated in the first 2 weeks of life, inhaled steroids reduce BPD but may increase mortality without clear developmental benefits or harms. Later initiation of inhaled steroids does not reduce BPD and longer-term impacts are unknown.

In the neonatal intensive care unit, **caffeine** is standard of care for infants at risk for apnea. Caffeine is the only neonatal intervention that has been clearly proven to reduce BPD and provide lasting developmental benefits, with particular benefit for motor outcomes. Importantly, at least half of the improvement in motor impairment that is observed until 11 years in children treated with caffeine is attributed directly to shorter duration of mechanical ventilation.

As BPD progresses, it becomes increasingly difficult to differentiate the impact of the lung disease itself from the impact of therapies to manage or treat the lung disease. The relative risks and benefits of available therapies must be weighed against one another to determine the best care plan for each individual infant.

Next steps for BPD research and clinical care

New strategies for prevention and treatment of BPD are always being evaluated. For example, budesonide instilled with surfactant is likely to significantly reduce BPD, and effects on longer term outcomes are currently under investigation. State-of-the-art approaches, such as the artificial placenta, stem cell therapies, and liquid ventilation, all have the potential to alter the landscape of BPD epidemiology and, hopefully, the subsequent adverse sequalae of BPD.

After discharge, intensive developmental interventions and comprehensive multidisciplinary care are essential for improving medical and neurodevelopmental outcomes for this high-risk population. Yet much remains to be learned about how best to support infants with BPD and their families throughout childhood, in order to help them obtain their maximum developmental potential and reduce childhood functional impairments. ■

Jackson, 7 months

References:

Jensen EA, Dysart K, Gantz MG, et al. **The diagnosis of bronchopulmonary dysplasia in very preterm infants. An evidence-based approach.** *Am J Respir Crit Care Med.* 2019;200(6):751-759.

DeMauro SB, D'Agostino JA, Bann C, et al. **Developmental outcomes of very preterm infants with tracheostomies.** *J Pediatr.* 2014;164(6):1303-1310.e2.

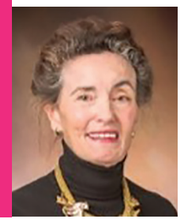
Schmidt B, Roberts RS, Anderson PJ, et al. **Academic performance, motor function, and behavior 11 years after neonatal caffeine citrate therapy for apnea of prematurity: An 11-year follow-up of the CAP randomized clinical trial.** *JAMA Pediatr.* 2017;171(6):564-572.

Sriram S, Schreiber MD, Msall ME, et al. **Cognitive development and quality of life associated with BPD in 10-year-olds born preterm.** *Pediatrics.* 2018;141(6).

Gou X, Yang L, Pan L, Xiao D. **Association between bronchopulmonary dysplasia and cerebral palsy in children: A meta-analysis.** *BMJ Open.* 2018;8(9):e020735.

To access our Inpatient and ICU Clinical Pathway for Pulmonary Hypertension (PH) Screenings in Patients with Bronchopulmonary Dysplasia (BPD) visit **www.chop.edu/bpdpathwayph**.

Follow-Up Corner



PARENTAL PERSPECTIVES ON DIAGNOSIS OF CEREBRAL PALSY

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

Case: Hospital course

Your second child, Anna, was a 25-week preterm infant. She was delivered by C-section due to abruptio placentae. Apgars were 5 and 8. She initially required ventilator support, but she was extubated on day of life 10. She had midline head positioning, judicious use of fluids, and no episodes of acute deterioration. A patent ductus arteriosus was diagnosed on day of life 3; it was successfully closed with indomethacin. She transitioned from total parenteral nutrition to enteral feeds of breast milk without significant problems. Serial cranial ultrasounds showed the following:

- day of life 7 - bilateral grade 2 intraventricular hemorrhage
- days of life 10 and 30 - no change
- time of discharge - resolving grade 2 hemorrhages, no periventricular leukomalacia

Anna was discharged home on day of life 96 on full feeds, vitamin D and iron, and breast milk fortified to 22 calories. You are delighted. Throughout Anna's course, you have frequently been updated by Anna's treatment team.
Early on, especially with the news that Anna had grade 2 hemorrhages, you asked many questions regarding her developmental outcome. While grade 2 hemorrhages are not as severe as grades 3 and 4, the team could not assure you that Anna's development would not be affected. Moreover, Anna was born at 25 weeks, a risk factor for altered developmental outcome. In a meeting when Anna was 34 weeks corrected age, you re-discussed her current status, ongoing needs, and prognosis. You were informed that Anna, in addition to seeing her primary care provider, would also be seen in Neonatal Follow-up Clinic. This clinic would assess her developmental progress, her muscle tone, and any ongoing medical issues. An appointment was given for several months after discharge, when Anna was 3 months corrected age. A referral to early intervention was made at the time of discharge.

First neonatal follow-up visit at 3 months corrected age

Anna is gaining weight nicely. She is receiving Synagis® as immunoprophylaxis against RSV. She is smiling and follows your face. You have noticed that her legs seem "strong" and that she "loves to stand." Early intervention has contacted you; her evaluation is scheduled for the end of the week.
At her clinic visit, an examiner takes a 2-minute video of Anna as she rests on her back. The video is a General Movement Assessment (GMA) to assess her movement of her arms and legs, called fidgety movements. Anna has some movements, but not as many as would be expected for her age. She also is examined with the Hammersmith Infant Neurological Examination (HINE). The providers invite you to watch them as they go through various checks of Anna's tone, reflexes, posture, and movement. The examiners say that Anna's HINE score is "OK"; she is making progress but they, too, notice stiffness in her legs, that her toes curl under, and that her head control is not quite as good as would be expected. In regard to meeting developmental milestones, she is on target for baby thinking and language. The providers sit down with you and discuss their concerns and the importance of starting early intervention/physical therapy as soon as possible. Anna is making progress, but it is critical to initiate therapies now. Anna will be seen again in 3 months at which time it will be important to reassess her progress.

Second neonatal follow-up visit at 6 months corrected age

You report that physical therapy has begun, once a week. The therapist is concerned that the stiffness in Anna's legs is not improving; she crosses her legs when held in vertical suspension and appears to tiptoe when held in standing position. You report to the team that Anna is not sitting independently, even briefly, and that her head control is not as good as her older sister's when she was 6 months old. The team again performs the HINE and examines Anna. They note the stiffness or increase in tone in the lower extremities. You ask, "Why are her legs stiff and why can't she control her head better? My family has noticed that Anna is different from her older sister. What is it? Does it have a name?" The medical provider and physical therapist sit down with you. The doctor says, "Have you ever heard of cerebral palsy or CP?" You feel tears coming to your eyes. You ask, "Does she have it?" The doctor responds, "We do not know for certain right now, but we can tell you that based on our evaluation today, she is at high risk for developing CP. When we look back at Anna's history, first, she was an extremely preterm baby. And you recall that she had the bleeding in the brain on her head ultrasound. Those issues put her at risk. Then, at her 3-month visit, she didn't have those fidgety movements we talked about, plus we noted the stiffness in her legs. We wanted to see if the therapy would make a difference, but at this point we still note the stiffness. And today, on the HINE, she has a score that puts her in a category of children at high risk for CP. While this obviously is a difficult topic for you and your family, we feel it is important for you to know that she is at risk. We are not giving her the diagnosis today, but we want to see her back in 3 months for a reassessment."

The conversation continues. You are given more information. The providers ask if they can meet with other members of your family to answer questions. You are tearful but grateful to be aware of the at-risk status, putting a name on what you and your family have noticed is different about Anna from her older sister. You are encouraged to call the team at any time prior to the next visit. Physical therapy is increased to twice a week.

How would you want this scenario to play out?

Would you want to hear that your child is at high risk for CP and worry about it for months, perhaps unnecessarily?

Would you definitely prefer NOT to hear that your child is at high risk and just wait until a diagnosis is firm?

Suppose you had never heard of CP? Would this be too much information to process if it is not a firm diagnosis?

What do we know about parents' perspectives on the diagnosis of cerebral palsy?

A number of articles have addressed parents' perspectives on the diagnosis of cerebral palsy. In brief, one investigator found that parental dissatisfaction with how the diagnosis was disclosed related to the diagnosis being made later, rather than earlier.[1] In some cases, parents were frustrated and angry that there was a delay in diagnosis when they previously had expressed concerns to their provider. Another response was "everyone knew before I did." Interestingly, one investigator found that some families actually are relieved to receive the diagnosis of a special need, and that they "are not crazy." This same investigator found that parental response to disclosure related not so much to the information that is given as to the manner in which it is imparted. Additionally, parents told at earlier time points were most likely to be satisfied, with earlier diagnosis allowing for earlier adjustment and acceptance of their child.

In a recent investigation, Katherine Guttmann, MD, MBE (former fellow in the Division of Neonatology at Children's Hospital of Philadelphia), explored parental perspectives on diagnosis and prognosis of neonatal intensive care unit graduates with cerebral palsy.[2] In this select population, she found that the diagnosis was rarely seen as early, with 40% of parents surveyed (162/401) feeling the diagnosis was "a little too late" or "very delayed." Interestingly, 59% of these parents felt the diagnosis provided benefits. This data suggests clinicians should aim for earlier diagnosis when appropriate.

In this regard, the diagnosis of CP currently occurs in children between 12 months to 24 months of age. The Cerebral Palsy Foundation is committed to moving the age of diagnosis to much earlier, as early as < 5 months. Why? Neuroplasticity of the brain is at its height in a child's earliest months and years. The opportunity for robust responses to interventions diminishes as time passes. Thus, the earlier the diagnosis, the more likely the child will benefit from interventions.

NOTE: In the past year, utilizing the tools and training received with the endeavor "Toward the Earlier Diagnosis of Cerebral Palsy," led by Andrea F. Duncan, MD, MS, Attending Neonatologist and Medical Director of our Neonatal Follow-Up Program, we have changed the time of diagnosis of cerebral palsy from 17 months to 8 months.

ON A PERSONAL NOTE: Regarding timing, in a totally informal, random sampling of young adults during pediatric resident teaching sessions, the author of this column posed the question as to whether these young trainees would or would not prefer to know if their own child was at high risk for CP. In 5 separate sessions with 5 to 7 trainees per session, every participant stated they would prefer to know, even if the diagnosis was not firm. Yes, it would be anxiety-provoking, but they would much rather know their child is at high risk than be in the dark.

Finally, in my experience, in addition to parents shedding many tears when discussing/conferring the diagnosis of CP, I have experienced the following reactions:

"CP? No, I never heard of it, except maybe on TV."

"So, now I know. I knew something was not right. It helps to have a name for it."

"CP. Yeah, I've heard of it. My cousin's kid goes to that clinic."

"I don't understand how he got it."

Given this set of responses, I hope it is clear that providers must, with great humility and sensitivity, adapt these difficult conversations accordingly. ■

References:

1. Baird G, McConachie H, Scrutton D. **Parents' perceptions of disclosure of the diagnosis of cerebral palsy.** *Arch Dis Child.* 2000;83(6):475-480.
2. Guttman K, Flibotte J, DeMauro SB. **Parental perspectives on diagnosis and prognosis of neonatal intensive care unit graduates with cerebral palsy.** *J Pediatr.* 2018;203:156-162.

RESEARCH SPOTLIGHT: BIOLOGICAL FUNCTIONS OF NITRIC OXIDE IN THE CARDIOVASCULAR AND NEURONAL SYSTEMS

By Haralambos Ischiropoulos, PhD, Investigator and Gisela and Dennis Alter Endowed Chair in Pediatric Neonatology

The long-term research objective of my laboratory at Children's Hospital of Philadelphia's Research Institute is to understand the biological functions of nitric oxide in the cardiovascular and neuronal systems.

The discovery of nitric oxide as a "short-lived, endogenously produced gas that acts as a signaling molecule in the body" was recognized with the 1998 Nobel Prize in Physiology and Medicine. Our early work discovered novel nitric oxide-mediated post-translational protein modifications that informed on the biological fate of nitric oxide during disease states. Armed with this new knowledge, we developed and implemented biochemical platforms to detect and quantify nitric oxide-mediated protein modifications. One of the first applications of these technologies was to test if inhaled nitric oxide induced adverse effects. Inhaled nitric oxide, a therapy that is still in clinical use, was originally tested as a therapy for pediatric persistent pulmonary hypertension. Our early work in models of inhaled nitric oxide enabled the testing of this treatment in prematurely born infants with bronchopulmonary dysplasia.

Our more recent work aims to elucidate the nitric oxide signaling pathways at the proteome level in the cardiovascular system. Proteome is the complete set of proteins expressed by an organism and includes several post-translational modifications. Utilizing innovative mass spectrometry-based approaches, we are generating precise maps of nitric oxide signaling in the heart and blood vessels. This is the first comprehensive attempt to elucidate how the various biological signaling events mediated by nitric oxide are coordinated, prioritized, and integrated at the proteome level. Completion of this work will provide an understanding of how reduced signaling resulting from debilitated production of nitric oxide leads to the pathogenesis of cardiovascular disorders and identify potential therapeutic strategies.

Another contribution of our recent work relates to observations that nitric oxide signaling regulates metabolic pathways during development and aging. We identified nitric oxide signaling as a key regulator of metabolic efficiency that allows cells to manage the use of carbohydrates and specifically long-chain fatty acids to generate energy. This is important for the heart, which requires large amounts of energy and relies on the oxidation of long-chain fatty acids to produce energy. It is also important for the muscle, liver, and other organs.

The clinical significance of these findings relates to a collection of rare inherited autosomal recessive diseases of fatty acid β-oxidation that present with cardiomyopathy, intermittent muscle breakdown, and liver failure. Notwithstanding the advances in detection and clinical management of these disorders, patients still experience lifelong complications such as recurrent myopathy, rhabdomyolysis, and cardiomyopathy. We have developed and are currently testing novel small molecule therapeutics for long-chain fatty acid oxidation disorders. The ultimate goal of our efforts is to bring these small molecules to the clinic, aiming to reduce symptoms and improve quality of life. ■

BASIC SCIENCE RESEARCH: CIRCADIAN RHYTHM AND LUNG BIOLOGY

By Shaon Sengupta, MBBS, MPH, Attending Neonatologist

A new preclinical study by researchers in our division has found that side-effects of oxygen therapy in the neonatal period increase susceptibility to influenza infection by eliminating protection via the lung circadian clock. Premature infants are born with very immature lungs, which necessitates lifesaving oxygen therapy. However, the inadvertent side effect of this therapy is hyperoxia, the key risk factor for developing bronchopulmonary dysplasia (BPD). BPD is a chronic condition that results from the lungs not developing appropriately. Patients with BPD are more susceptible to other diseases of the lung—including asthma, COPD, and respiratory infections like influenza—later in life.

Previous research done at our hospital and the University of Pennsylvania has shown that circadian rhythms offer a protection against influenza, with mortality 3 times lower if animal models are infected in the morning rather than in the evening. However, until now, researchers had not established a connection between neonatal hyperoxia, circadian clock disruption, and influenza infection.

To do so, we analyzed adult mice who had been exposed to neonatal hyperoxia and in adulthood were exposed to influenza at different times of day. We found that adult mice exposed to hyperoxia as neonates lose the time-of-day protection from circadian regulation of influenza infection. On the other hand, adult mice exposed to hyperoxia in adulthood did not lose the time-of-day protection. This led us to conclude that the neonatal period represents a uniquely vulnerable window for development of circadian networks and thus exposure to hyperoxia in the neonatal period alters this function.

Although the suprachiasmatic nucleus (SCN) is the master circadian pacemaker in the body, peripheral tissues, including the lungs, also have their own circadian clocks. To identify the location of the clock responsible for the increase in susceptibility to influenza, we knocked out the core clock gene Bmal1 in adult mouse models. We found that disrupting Bmal1 in alveolar type II (AT2) cells, which are critical in maintaining lung function and integrity, produced the same phenotype as mouse models that had been exposed to neonatal hyperoxia, suggesting that early life hyperoxia disrupts the circadian regulation of the pulmonary response to hyperoxia through the AT2 clock.

Our work here suggests that a unique window exists in the lung in the early neonatal period that affects circadian regulation throughout life. Children born prematurely and suffering from even mild BPD have persistent adverse effects on their lung function into adulthood and beyond, so this study could pave the way for novel therapeutics and chronobiological strategies for this vulnerable population. ■

Reference:
Issah Y, Naik A., et al. **Loss of circadian protection against influenza infection in adult mice exposed to hyperoxia as neonates**. *Elife*. 2021;10:e61241.

TRIAL FINDS NO BENEFIT TO HIGHER RED CELL TRANSFUSIONS IN PRETERM INFANTS

By Haresh M. Kirpalani, MD, Professor Emeritus of Neonatology

A trial led by our team found that a higher hemoglobin threshold for red blood cell transfusions in anemic, extremely-low-birth-weight newborns does not improve survival or reduce neurodevelopmental impairment by age 2. The study, which is the largest on this topic to date, was recently published in the *New England Journal of Medicine*.

For the randomized controlled trial, we analyzed 1 824 infants between 22 and 29 weeks of age who weighed less than 1 000 grams at birth. The infants were randomly assigned to 1 of 2 groups:
- A group that would receive higher red blood cell transfusions
- A group that would receive lower red blood cell transfusions

We followed both groups until they were about 2 years old and monitored for death or neurodevelopmental impairment, such as cognitive delay, cerebral palsy, and hearing or vision loss.

In comparing the 2 groups, we found no statistically significant difference in outcomes. The higher and lower hemoglobin threshold groups had similar rates of death, neurodevelopmental impairments, and serious adverse events.

The results of this trial support the notion that we can use less blood when transfusing very low-birth-weight babies. Given the potential hazards associated with blood transfusions in an already vulnerable population, these data support the notion that less is more, and we should not be transfusing infants unnecessarily. This also shows how therapies commonly thought of as "standard care" may require further testing to assess their true value. ■

Reference:
Kirpalani H, Bell EF, Hintz SR, Tan S, Schmidt B, Chaudhary AS, Johnson KJ, Crawford MM, Newman JE, Vohr BR, Carlo WA, D'Angio CT, Kennedy KA, Ohls RK, Poindexter BB, Schibler K, Whyte RK, Widness JA, Zupancic JAF, Wyckoff MH, Truog WE, Walsh MC, Chock VY, Laptook AR, Sokol GM, Yoder BA, Patel RM, Cotten CM, Carmen MF, Devaskar U, Chawla S, Seabrook R, Higgins RD, Das A; Eunice Kennedy Shriver NICHD Neonatal Research Network. **Higher or lower hemoglobin transfusion thresholds for preterm infants**. *N Engl J Med*. 2020;383(27):2639-2651.


Jeramiah, 2 months

CHOP EMERGENCY AIRWAY PROGRAM FACILITATES RAPID INTERVENTION BEFORE AND DURING PANDEMIC

By Janet Lioy, MD, Director, Neonatal Outreach Program, and Medical Director, Neonatal Airway Program; and Christopher Thom, MD, PhD, Attending Neonatologist

A new study published in the *International Journal of Pediatric Otorhinolaryngology* shows that our Emergency Airway Program facilitates rapid airway intervention in our N/IICU and was successful both before and during the COVID-19 pandemic.

Managing infants with life-threatening airway anomalies can be challenging due to their unique anatomy. Unexpected airway emergencies occur frequently in the neonatal intensive care unit and must be addressed immediately and with meticulous care, often with specialized equipment and multidisciplinary expertise.

To address this need, in 2008 CHOP developed a Neonatal and Infant Emergency Airway Program to improve medical responses, communication, equipment usage, and outcomes for all infants requiring emergency airway interventions in the N/IICU. By 2016, the program had been well established, and its standardized measures and streamlined procedures were in regular use, including a multidisciplinary airway response team of pediatric ENT, neonatology, respiratory therapy, and anesthesia-critical care physicians, as well as a specialized pager notification system and an emergency equipment cart.

In order to assess the program's effectiveness, we analyzed all airway emergency events that occurred in our N/IICU from 2008 to 2019. Respiratory therapists present at each emergency event recorded specialist response times, as well as equipment use and patient outcomes.

Of the 159 airway emergency events included in the study, the mean specialist response time from 2008 to 2019 decreased by more than 1 minute, and the number of incidents with response times greater than 5 minutes decreased by approximately a third. Equipment availability and subspecialist communication also improved. For example, the emergency equipment cart did not initially include a 2.2 mm flexible fiberoptic laryngoscope, but after program implementation, the emergency airway team recognized it was the main bronchoscope used in both diagnosis and airway access. Once we recognized this, a 2.2 mm flexible fiberoptic laryngoscope was written into the budget process and made available during all emergency events.

In response to COVID-19, our Emergency Airway Program team also outfitted a separate cart with extra N95 masks, eye protection, gloves, hand sanitizer, and gowns for all responding personnel. Rapid COVID-19 tests were performed on patients, and appropriate personal protective equipment (PPE) was worn by all members of the team. The effectiveness of this program, both during the pandemic and before, could serve as a model for other similar centers. ■

Reference:
Thom CS, Deshmukh H, Soorikian L, Jacobs I, Fiadjoe J, Lioy J. **Airway emergency management in a pediatric hospital before and during the COVID-19 pandemic**. *Int J Pediatr Otorhinolaryngol*. 2020;139:110458.

STUDY OF LOOP DIURETICS IN SEVERE BPD SHOWS VARIATION BETWEEN CENTERS

We recently completed a retrospective cohort study measuring between-center variation in loop diuretic use for preterm infants at <32 weeks of gestational age with severe bronchopulmonary dysplasia (BPD). The primary outcome was cumulative loop diuretic use, defined as the proportion of days with exposure between admission and discharge. Infant characteristics associated with loop diuretic use at $P < .10$ were included in multivariable models to adjust for center differences in case mix. Hospitals were ranked from lowest to highest in adjusted use and dichotomized into low-use centers and high-use centers. We then compared mortality and postmenstrual age at discharge between the groups through multivariable analyses.

We identified 3 252 subjects from 43 centers. Significant variation between centers remained despite adjustment for infant characteristics, with use present in an adjusted mean range of 7.3% to 49.4% of days ($P < .0001$). Mortality did not differ significantly between the 2 groups (aOR, 0.98; 95% CI, 0.62-1.53; $P = .92$), nor did postmenstrual age at discharge (marginal mean, 47.3 weeks [95% CI, 46.8-47.9 weeks] in the low-use group vs. 47.4 weeks [95% CI, 46.9-47.9 weeks] in the high-use group; $P = .96$).

Our findings, which were published in the *Journal of Pediatrics*, show marked variation in loop diuretic use for infants developing severe BPD exists among U.S. children's hospitals, without an observed difference in mortality or age at discharge. More research is needed to provide evidence-based guidance for this common exposure. ■

Reference:
Bamat NA, Nelin TD, Eichenwald EC, Kirpalani H, Laughon MM, Jackson WM, Jensen EA, Gibbs KA, Lorch SA. **Loop diuretics in severe bronchopulmonary dysplasia: Cumulative use and associations with mortality and age at discharge**. *J Pediatr*. 2021;231:43-49.

EXCELLENCE IN ECMO

Our partnership with the extracorporeal membrane oxygenation (ECMO) team is extraordinary. For babies born in our Garbose Family Special Delivery Unit with high-risk physiology, we are in constant communication during labor and delivery, the postnatal transition, and the early postnatal hours to days. For babies delivered at outside hospitals with unexpected cardiopulmonary insufficiency, our ECMO team is ready to support any neonate 24/7.

Our ECMO Center Manager, James T. Connelly, BS, RRT-NPS, has been with the program since it opened in May 1990. Jim and his fellow core Clinical Specialists, Sue Williams, RNC, and Mike Regan, RN, make our program—which is one of the busiest in the nation—exceptional. Holly Hedrick, MD, serves as Surgical Director of CHOP's ECMO Center, and Natalie Rintoul, MD, is Medical Director of Neonatal ECMO.

The CHOP ECMO Center has completed more than 1 500 ECMO runs since it began, including a significant number in the Newborn/Infant Intensive Care Unit (42% of the center's overall volume). The center's first and 1000th patients were both treated for congenital diaphragmatic hernia.

The CHOP ECMO Center is designated a Platinum Level Center of Excellence by the Extracorporeal Life Support Organization (ELSO). The center's first Platinum Level award was bestowed from 2017-2020, and it was recently renewed for 2020-2023. This is the highest awarded honor from ELSO, and it is rarely achieved by ELSO member institutions, especially pediatric centers. ■

STUDY FINDS NO CHANGE IN PRETERM BIRTH OR STILLBIRTH IN PHILADELPHIA DURING PANDEMIC PERIOD

By Sara C. Handley, MD, MSCE, Attending Neonatologist

Despite early reports suggesting a decline in preterm births during the COVID-19 pandemic period, an analysis by our team and researchers at the Perelman School of Medicine at the University of Pennsylvania found no change in preterm births or stillbirths at 2 Philadelphia hospitals in the first 4 months of the pandemic. The findings, which were recently published in the *Journal of the American Medical Association*, resulted from the examination of an ongoing, racially diverse pregnancy cohort that assesses both spontaneous and medically indicated preterm birth.

The cohort, known as GeoBirth, includes more than 100 000 births at 2 Penn Medicine hospitals in Philadelphia since 2008. Each preterm birth, characterized as any birth occurring before 37 weeks' gestation, is manually classified by 2 independent, blinded reviewers as either a spontaneous preterm birth or a medically indicated preterm birth. The former includes preterm labor or early rupture of the membranes, and the latter includes conditions that necessitate an early delivery for the health of the mother or baby, such as preeclampsia or intrauterine growth restriction.

We analyzed 2 992 live births from March 2020 through the end of June 2020 and compared those births to 5 875 over the same 4-month period in 2018 and 2019. Making use of the robust GeoBirth data set, we compared rates of overall preterm birth, spontaneous preterm birth, medically indicated preterm birth, and stillbirth, defined as intrauterine demise after 20 weeks.

The data did not show any significant change in preterm or stillbirth rates during the COVID-19 pandemic. Even when breaking down the preterm birth data by spontaneous and medically indicated preterm births, we still did not detect differences between the pre-pandemic and pandemic period. These findings differ from European studies that have reported a decrease in preterm birth and increase in stillbirth during the first few months of the pandemic.

The GeoBirth cohort will allow us the opportunity to query how individual, societal, and environmental factors affect pregnant women and how those factors may be heightened by the varying effects of a pandemic. It is imperative that we have rigorous tools to study how these different factors may harm pregnant people and how the pandemic may exacerbate those factors so we can target appropriate strategies to improve the lives of women and their babies. ■

Reference:
Handley SC, et al. **Changes in preterm birth phenotypes and stillbirth at two Philadelphia hospitals during the SARS-CoV-2 pandemic from March-June 2020.** *JAMA.* 2021;325(1):87-89.

Azai'a, 4 months

CASE STUDY: AQUADEX PROVIDES RENAL SUPPORT AS BRIDGE TO PERITONEAL DIALYSIS

By Kristin J. McKenna, MD, MPH, Attending Neonatologist and Neonatal Director, Perinatal Nephrology Program

Baby B was born at 37 weeks and 4 days via vaginal delivery. He was found to be severely depressed with no spontaneous respiratory effort, requiring resuscitation in the delivery room, including intubation for respiratory failure and volume resuscitation for hypotension. APGARS assigned were low.

His initial NICU course was remarkable for:

- moderate to severe encephalopathy qualifying for therapeutic hypothermia
- hypoxemic respiratory failure requiring high-frequency ventilation and 100% oxygen
- persistent pulmonary hypertension requiring inhaled nitric oxide
- hypotension requiring fluid resuscitation and moderate inotrope support and concern for a possible abruption versus maternal-fetal hemorrhage given the baby's pale appearance
- anemia, requiring red blood cell transfusion shortly after birth

Transfer to our Harriet and Ronald Lassin Newborn/Infant Intensive Care Unit (N/IICU) was initiated within 24 hours of birth for potential need for extracorporeal membrane oxygenation (ECMO) support. After admission, Baby B's course evolved with coagulopathy requiring multiple blood products, concern for seizures requiring anti-epileptic therapy, evidence of multi-organ injury, and oliguric acute kidney injury (AKI) due to ischemic acute tubular necrosis. There was no evidence of infection.

The baby's degree of renal dysfunction, continued oliguria, and progressive fluid overload (>3 kg above birth weight), despite fluid restriction and trials of diuretic, prompted discussion by a multidisciplinary team as part of the N/IICU's Neonatal Renal Program to initiate ultrafiltration via Aquadex FlexFlow®. A femoral hemodialysis catheter was placed by the Interventional Radiology team and ultrafiltration was initiated on day of life 3. Aquadex was continued for a 10-day course. Initially, ultrafiltration was utilized to remove excess plasma water to help with fluid overload. For the latter part of the Aquadex course, modified hemofiltration was utilized to allow for fluid removal while correcting and stabilizing electrolyte imbalances. Improvement of Baby B's AKI with recovery of adequate urine production and improvement in renal function allowed for discontinuation of therapy.

Aquadex FlexFlow® (CHF Solutions) is FDA approved for slow continuous ultrafiltration in adults with diuretic resistant heart failure. The system has been used in the pediatric population given the smaller circuit volume of 33 mls and slower blood flow rates, both of which are better tolerated in small patients. This allows for use of smaller vascular catheters, a 6 Fr power PICC being the more commonly used device in the NICU population. Complications with this therapy include transient hemodynamic instability (although less than traditional hemodialysis approaches in small patients), clotting, catheter malfunction, and minor bleeding.

The Aquadex circuit can be used for ultrafiltration or modified continuous veno-venous hemofiltration (CVVH). This approach to renal replacement therapy (RRT) in the neonate allows for support of small infants with early renal insufficiency or renal failure who are not yet able to receive peritoneal dialysis (PD). Aquadex can provide renal support as a bridge to when the patient is able to transition to PD. Thus far, we have utilized this therapy at CHOP for AKI and congenital renal anomalies with renal insufficiency and/or renal failure in patients as premature as 29 weeks gestational age and as small as 1.3 kg.

Baby B continued to improve and wean support. His course was additionally complicated by ileal perforation on day of life 10 requiring exploratory laparotomy and ostomy creation, with subsequent ostomy take down on day of life 47. He was discharged home on day of life 56 on room air, tolerating full enteral ad lib feeds, with sodium bicarbonate as his only medication. His MRI was reassuring. Baby B continues to be followed by multiple subspecialists at CHOP, including Nephrology, Neurology, Surgery, and Neonatal Follow-up, as well as Early Intervention and Physical Therapy. ■