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An Update from the UPMC Newborn Medicine Program

In This Issue

UPMC Children's Hospital of Pittsburgh is affiliated with the University of Pittsburgh School of Medicine and nationally ranked in nine clinical specialties by *U.S. News & World Report*.

UPMC CHILDREN'S HOSPITAL OF PITTSBURGH

Groundbreaking Research Seeks to Combat Arterial Thromboembolic Disease in Neonatal Cardiac Patients

For the last four years, **Thomas G. Diacovo, MD**, division chief of the UPMC Newborn Medicine Program, and director of Neonatal Cardiovascular Research, has led new studies to combat the development of acute thromboembolic events (ATE) in neonates who require surgical repair for complex congenital heart conditions.

Rates of thrombosis in post-operative neonatal cardiac patients, and in particular those requiring placement of a systemic to pulmonary artery shunt, are the highest of all pediatric patients treated in specialized centers. The current literature on the subject shows ranges of shunt thrombosis anywhere from 17 percent to 34 percent, with corresponding morbidity and mortality reflective of such high rates of blood clots. For Dr. Diacovo and his study companions, these rates of thromboembolic disease have been, and continue to be, completely unacceptable.

"There have been many anticoagulation agents developed for adults over many decades, going all the way back to the synthesis of aspirin in the mid-1800s, which have proven to be extremely successful in preventing clot formation in adults and saving lives. However, virtually none of these agents has ever been tested or confirmed in pediatric patients to understand their efficacy, safety, pharmacodynamics, and optimal dosage," says Dr. Diacovo.

Platelet function in neonates also has been understudied, and the availability and development of technologies to rapidly assess platelet response in pediatric patients to various agonists and antagonists has lagged in development.

However, Dr. Diacovo's research has begun to upend this suboptimal treatment paradigm with new findings, technological advances, and animal models that are now leading to important new clinical trials in human subjects.

Uncovering Responses to Platelet Agonists and Antagonists With Microfluidic Devices and a Novel In Vivo Mouse Model

In 2017 in the *Journal of the American College of Cardiology,* Dr. Diacovo and colleagues outlined their novel and groundbreaking process analyzing responses to single agents and combinations of platelet agonists and antagonists, and their findings of the efficacy and optimal usage of cangrelor on $P2Y_{12}$ receptor function in neonatal and pediatric CHD patients.[1]

Continued on Page 3

The NICU Family Advisory Board

Very few expectant parents ever anticipate that their child will need admission to the neonatal intensive care unit after birth. However, when a NICU transport and admission is required, it is very often a traumatic and frightening experience for the entire family. UPMC Children's operates a level IV NICU and routinely admits patients from up to four hours' distance, many of whom arrive via helicopter. The NICU at UPMC Children's is a bustling unit with more than 1,000 admissions each year, many for extended stays of several months.

To foster a continually evolving and improving patient and family experience for those who are in need of a NICU admission, the NICU Family Advisory Board (FAB) was created in 2014. Its creation was spearheaded by NICU Quality Improvement Program Manager and Family Experience Program Manager **Mary Jo MacPherson, BSN, RN, CBC**, as a means of providing evidence-based best practice patient experience for visiting families. In addition to her roles at UPMC Children's, Mrs. MacPherson also is the quality improvement manager for the Children's Hospitals Neonatal Collaborative (CHNC).

Entering its fifth year of operation, the FAB consists of a rotating mix of individuals that includes Mrs. MacPherson, two NICU floor nurses, and NICU alumni parents and grandparents, along with individuals from the surrounding Pittsburgh communities. The board meets monthly to discuss and provide firsthand perspectives on unit policies, and it helps guide the implementation of family-centered changes to procedures and practices. Every other month there are parent-to-parent events where board members or past NICU alumni will visit and interact with current families on the unit.

"These peer-to-peer support opportunities are incredibly helpful for families. They are able to visit with and interact with people who have gone through a similar experience with their child and come out the other side. If a family has been in the NICU for several months, they can begin to feel as though they will never be going home. Having the chance to interact with NICU "Alumni" families can be very beneficial emotionally," says Mrs. MacPherson.

Successes and Policy Changes Spurred by the FAB

Mrs. MacPherson indicates that since the FAB's founding, its members have been involved with helping shape or change approximately 17 different unit policies or equipment changes through the feedback process, and have offered more than 40 parent-to-parent events in the NICU for current inpatient families.

The projects have run the gamut from providing feedback when the NICU expanded from 33 to 55 beds in 2014, to parent involvement in a central line infection prevention and handwashing protocol. The FAB also has advised on various NICU policies, including allowing both parents to remain at their baby's bedside 24/7.

Mrs. MacPherson also points out what she sees as the FAB's most significant contribution to date: the change in parent sleeping policy at the bedside.

"It used to be the case that only one parent was allowed to sleep over in their baby's room. Usually it would be the mother, and the father had to leave and sleep elsewhere in the hospital. Within the first two months of the FAB's existence, they were instrumental in helping to get this policy changed to allow both parents to remain bedside at night if they wish," says Mrs. MacPherson.

Contributing to the QI Process

Quality improvement initiatives are a huge part of the day-to-day operation of virtually every NICU in the United States. At UPMC Children's, the FAB has taken an active part of several QI projects that have had tremendous success in improving clinical outcomes and other aspects of the NICU experience for patients, parents, and staff.

"Our Breastmilk = Medicine project in the NICU has increased the percentage of new moms breastfeeding at the time of discharge from 45 percent to 76 percent during its first month. In the more than five years since its inception, the average rate of mothers breast feeding at discharge has been maintained at 82 percent," says Mrs. MacPherson.

NICU Family Advisory Board Goals

- **Improve family-centered care through solicitation of feedback on new projects, policies, and procedures from NICU alumni parents.**
- **Provide parent-to-parent support for current NICU families from individuals with a previous NICU stay and discharge.**
- **Support quality improvement initiatives within the UPMC Children's NICU and promote the NICU's community presence and outreach work.**

The FAB also has been instrumental in another QI initiative called the Kangaroo-a-thon Project that sought to substantially increase the amount of skin-to-skin (STS) time between parents and their NICU babies.

"The FAB realized that sometimes fathers can be left out of the picture in everything that happens in the NICU, so they emphasized the importance of fathers in this aspect of parent-child interaction. It provides nothing but positive benefits. The more we can increase participation and the number of hours of STS, the better. Ideas from FAB members and their perspective that including fathers needed to be more of a priority has directly benefited many families," says Mrs. MacPherson.

An Instrument for Practice Change

Formation of a unit-based family advisory board has proven to be an effective tool for overcoming barriers to change. It has given the NICU an effective strategy for the provision of evidence-based, best-practice parent-to-parent emotional support, and it has been a key driver for implementation of transformational family-centered policy improvements that have shown significant impact on the overall patient experience in the UPMC Children's NICU.

Arterial Thromboembolic Disease in Neonatal Cardiac Patients *Continued from Page 1*

Using a novel mouse model created by the Diacovo lab while at Columbia University, and microfluidic devices by colleagues at the University of Pennsylvania capable of assessing clotting using 20-times less blood than in standard testing platforms (a significant advancement and desirous approach, particularly in neonates where blood draw amounts are limited for safety concerns), the researchers were able to not only show efficacy of the entire testing platform for determining platelet reactivity in these subject, but they were also able to show the in vivo efficacy of cangrelor setting the stage for the first trial in neonatal cardiac patients.

"A major success of our work during the first three years was our ability to go from our basic science studies to preclinical and then rapidly translate it into a phase 1 clinical trial that we are in the process of finishing," says Dr. Diacovo.

Predicting Response and Determining Functionality and Functional Changes

The types of studies Dr. Diacovo and colleagues are engaged in are providing the framework and foundation for a new paradigm of treatment determination to combat the scourge of arterial thrombo-embolic disease. By providing sound, evidence-based guidance and real-time analysis of platelet function in individuals, the most appropriate course of pharmacologic therapy to mitigate clot formation risk may be predicted.

"A large part of our research agenda from the outset has been to test these novel drugs in animal models in order to make better predictions of how these pharma-ceutical agents will actually work before introducing them into a child. Just looking at laboratory values has little bearing on actual function. This functionality is a crucial part of the equation we must work to understand," says Dr. Diacovo.

The existing methodologies and dearth of evidence to support treatments to combat arterial thromboembolic disease have relied mainly on extrapolation.

Preparations for a New Clinical Trial

While Dr. Diacovo and colleagues are still working to finish their first phase 1 trial, planning currently is underway for a second trial that will examine specific Xa inhibitory agents like apixaban. Dr. Diacovo's team is working to finish various ex vivo studies using their microfluidic devices and mouse modeling technologies to assess the differences between adults and neonates.

"Our preliminary work shows a vast difference between the two age groups, which you may understand intuitively, but because no one has been able to do these studies in the past we lack basic, concrete knowledge of how these agents work in the very young. Knowing what the true pharmacokinetics or pharmacodynamics are of these drugs in our neonatal patients, again, is the crux of our entire research endeavor," says Dr. Diacovo.

References and Further Reading

[1] Kaza EA, Egalka MC, Zhou H, Chen J, Evans D, Prats J, Li R, Diamond SL, Vincent JA, Bacha A, Diacovo TG. P2Y12 Receptor Function and Response to Cangrelor in Neonates With Cyanotic Congenital Heart Disease. *J Am Coll Cardiol.* 2017; 2(4): 465-476.

Neonatal and Pediatric Platelet Function and Pharmacology. NIH Project Number: 7R01HD081281-04. Principal Investigator: Thomas G. Diacovo, MD.

Continuity Care Faculty Program

All families and babies admitted to the NICU endure significant stress, time away from home, uncertainty about the future, and much more. Families of babies in the NICU who are inpatients for longer than three months deal with these and other issues much longer than most. Over extended periods of time, and because of the natural flow of staff changes and physician service periods (every two weeks at the UPMC Children's NICU), communications between families and providers also can become fragmented or inconsistent and can lead to stress and potential negative patient experiences.

Carrie Rubino, MSN, RN, CCRN

Diane Ankney, MSN, RN, NEA-BC

Beverly Brozanski, MD

In November 2018, at the suggestion of **Thomas Diacovo, MD**, chief of the UPMC Newborn Medicine Program, the UPMC Children's NICU developed and instituted a new program for any family/patient unit who need stays on the NICU for longer than three months.

Dubbed the Continuity Care Faculty Program, every long-term NICU patient is assigned one physician who oversees the entirety of their care, regardless of whether or not the physician is assigned to be attending for a given week.

Carrie Rubino, MSN, RN, CCRN, and **Diane Ankney, MSN, RN, NEA-BC**, unit directors of the UPMC Children's NICU, worked to implement the program and continue to oversee its elements. Ms. Rubino and Ms. Ankney work to identify the patients who are or will be in need of greater than 90-day-stays, and coordinate with the physician staff who will be assigned to the patients.

"Our physicians work together to determine who will be the best fit to oversee care for any particular patient, and we facilitate and help to coordinate all the necessary logistics. This includes holding a patient/family care conference at two-week intervals," says Ms. Ankney.

These have become vitally important for family members in a short period of time. The families have access to a consistent voice who oversees the care of their baby, and the family is included in all of the communications and major decisions or plans. The conferences and single point of communication from one dedicated physician have been able to break down communication barriers, enhance

communication with families, and enable a better understanding of family needs and the family's understanding of the care their child is receiving or will need in the future.

"In terms of patient volume, we have approximately three or four of these longer-term NICU stays at any given time. And we try to limit the number of continuity cases that each physician has at one time to just two," says Ms. Rubino.

Consistency of Communication Is Key to Family Satisfaction

The program was successful immediately upon implementation, ensuring communications to families from one team or physician to the next is seamless and consistent.

"Some of our patients are here for a long time — and oftentimes it is the families who know their babies best and can sense when something may be changing or an issue is arising. Valuing and respecting the parent's insights and opinions is something that we work diligently on so the family understands that we value their input," says **Beverly Brozanski, MD**, medical director of the NICU at UPMC Children's.

The EXIT Procedure:

Multidisciplinary Specialty Surgery for Complex Airway Anomaly in Neonatal Patients

Ex utero intrapartum treatment (EXIT) is a highly specialized, multidisciplinary surgical procedure used to deliver babies who have been diagnosed prenatally with various airway anomalies leading to airway compression or blockage, making a normal vaginal birth or traditional Caesarean section delivery unviable for the baby. Anomalies or conditions leading to airway compression for which the EXIT procedure may be needed include cervical teratomas, cystic hygromas, or a blockage of the airway from congenital high airway obstruction syndrome (CHAOS).

Diagnosing and treating some of rarest, most complex prenatal conditions amenable to in utero surgical intervention is a collaboration between the UPMC Newborn Medicine Program, the Fetal Diagnosis and Treatment Center, the Center for Innovative Fetal Intervention (CIFI), and the Center for Advanced Fetal Diagnostics (CAFD).

"Achieving good outcomes for these highly complex cases is not something every hospital or even academic medical center can accomplish. It takes a tremendous amount of resources, planning, procedural skill, and the technical expertise of dozens of individuals before, during, and after the surgery to perform this procedure safely and effectively," says **Kalyani Vats, MD**, assistant professor of pediatrics, a neonatologist with the UPMC Newborn Medicine Program, co-Director of the CAFD at UPMC Magee-Womens Hospital, and director of triage and antenatal consult services, also at UPMC Magee.

The ability to conduct EXIT procedures, and to conduct them safely and successfully, can be accomplished only by a multidisciplinary team of highly skilled, physicians, surgeons, and nurses operating in an environment with the necessary infrastructure and expertise to transform a potentially fatal neonatal emergency into a controlled situation.

UPMC is one such place with the ability to successfully navigate the complexities of the EXIT procedure, and it has been doing so for close to 15 years. The EXIT team at UPMC comprises experienced, highly skilled clinicians from multiple specialties and hospitals, including maternal-fetal medicine, maternal-fetal anesthesia, neonatology, pediatric surgery, otolaryngology, obstetrics, and nursing, along with an operating room that is specifically designed for performing fetal procedures. Clinicians at UPMC performed their first EXIT procedure in 2004, and have since conducted several EXIT and PRESTO (Presence of Extra Surgical Team at Operation) procedures (PRESTO is similar to EXIT, yet is a less extensive procedure). EXIT is a rare procedure; however, when it is called for it may be the only way to save the life of the baby.

The Center for Advanced Fetal Diagnostics

The CAFD is a multidisciplinary service primarily housed at UPMC Magee. This service provides comprehensive care to patients and their providers following the prenatal diagnosis of fetal anomalies.

Primary components of this service include prenatal ultrasound; genetics (including both genetic counseling and reproductive geneticist services); maternal-fetal medicine; neonatology; pediatric surgery. Additionally, the CAFD works closely and coordinates care with various pediatric subspecialties, that include cardiology, urology, neurology, neurosurgery, radiology, and others. The CAFD also works closely with the CIFI to provide comprehensive fetal surgery.

In a true multidisciplinary fashion, weekly meetings review CAFD patients and provide an opportunity for input from multiple specialties into the care of each patient. This coordination of care promotes seamless continuity from prenatal diagnosis and counseling through delivery and postnatal care.

EXIT Procedure Indications, Variations, and Best Practice Guidelines at UPMC

The most common indication for the EXIT procedure is a fetus with an airway compromised by a neck mass such as a cervical teratoma or lymphangioma, tracheal or laryngeal atresia (resulting in CHAOS), or severe micrognathia. The EXIT procedure allows time to secure the fetal airway by laryngoscopy, bronchoscopy, endotracheal intubation, or tracheostomy, depending upon the nature of the condition and the surgical preplanning and can have several variations (See Table 1 on Page 6).

EXIT-to-Airway turns an airway emergency into a controlled, planned procedure. The EXIT-to-ECMO strategy is useful in cases of severe pulmonary or cardiac malformations in which separation from

Continued on Page 6

The EXIT Procedure *Continued from Page 5*

uteroplacental circulation will lead to immediate instability in the newborn. In such cases, EXIT-to-ECMO strategy can be applied to secure the airway and insert venous and arterial cannulas for ECMO while on placental support. This approach avoids a possible period of hypoxia or acidosis during neonatal resuscitation.

Not all babies with airway obstructions will be candidates for the EXIT procedure. Some conditions may be able to be handled through alternative procedures or airway management protocols.

"Not every compromised airway calls for an EXIT procedure, nor does every mass in the neck. We look at all the signs and clues for the well-being of the fetus to determine airway function in advance. If it appears to be a life-threatening condition, then EXIT may be an option, but many other factors contribute to the final determination," says Dr. Vats.

Planning and Preparations for an EXIT Procedure

Virtually all cases of significant high airway obstruction are diagnosed prenatally via ultrasonography and confirmed by fetal magnetic resonance imaging (MRI) during the mother's pregnancy. Fetal MRI is an important aspect of the consultation and planning process for when an EXIT procedure may be a viable surgical option for both mother and baby.

Sufficient time is needed to assess both the mother and fetus, determine the extent of the airway anomaly, and uncover other issues that may be compromising the health or viability of the fetus. A plan for the nature of the EXIT procedure is needed. Also, alternate plans for care, should an EXIT procedure not be warranted, desired, or are considered safe. This process takes significant time and coordination between many clinical specialties, and then the family must be informed and counselled on all the options, risks, and unknowns that factor into such highly complex medical and surgical decisions.

"There are cases where we could perform an EXIT procedure, but other underlying issues may render securing the airway and ultimately repairing it moot. However, if the airway anomaly is the only major issue affecting the fetus, we can secure the airway through the EXIT procedure, and our ENT surgeons can continue to follow, evaluate, and reconstruct the airway later," says Dr. Vats.

Planning for an EXIT procedure typically begins early, usually at 24 to 25-weeks gestation. Planning includes diagnostics through the CAFD, consultations and case reviews with maternal-fetal medicine, ENT, neonatology, surgery, anesthesia, and any other specialties that may be needed based on the baby's underlying conditions.

Premature babies — especially those under 32-weeks gestation — are not good candidates for an EXIT procedure. The complications and contributing factors in a fetus at that gestation generally outweigh benefits of the EXIT procedure, according to Dr. Vats.

Table 1.
Variations of the EXIT Procedure and Their Indications

Procedure: EXIT-to-Airway

Indications:

- Cervical teratoma/lymphangioma
- Congenital high airway obstruction syndrome (CHAOS)
- Micrognathia (small chin)

Procedure: EXIT-to-Extra-Corporeal Membrane Oxygenation (ECMO)

Indications:

- Congenital diaphragmatic hernia (CDH)

Procedure: EXIT-to-Resection

Indications:

- Congenital pulmonary airway malformation of the lung (CPAM)
- Bronchopulmonary sequestrations (BPS)
- Mediastinal, cervical, or oral teratoma

"If the mother is fine, and the baby is fine, and no complications arise, we will expect to allow the pregnancy to continue for as long as possible so the fetus can grow and develop as much as possible, or until there is a change in status that warrants immediate intervention. The older and more mature the fetus is, when EXIT is performed, typically the better the outcomes will be. However, if we have an EXIT case that we are monitoring, the entire team must be on call and ready to go at a moment's notice should the mother arrive in premature labor. This aspect factors heavily into our planning process," says Dr. Vats.

A few days before the procedure is anticipated to occur, the entire team performs a walk-through of the procedure in a special operating room used for EXIT. Every element of the procedure is choreographed in advance, including where everyone will be positioned, and where equipment will be placed. Every specialty taking part in the procedure has a dedicated area for their needs in the operating suite.

"Because these procedures are so rare, they present an excellent teaching and observational opportunity for all levels of medical trainee and care providers. We direct a live feed of the procedure to another room set up specifically to view our EXIT cases, where residents, fellows, students, and others can observe, in real-time, the progression and details of the procedure," says Dr. Vats.

Surgical Details of EXIT at UPMC Magee and UPMC Children's

At a fundamental level, the EXIT procedure serves a simple function. By keeping the baby attached through the umbilical cord to the placenta to sustain perfusion and respiration, the EXIT procedure allows the team the time they need to deliver the baby via C-section, work to establish or secure an airway through whatever means are called for, and then separate baby from mother.

It is a simple concept, but one that requires some of the most thorough and complex planning to execute that is likely to be seen in a surgical procedure.

"Our colleagues in anesthesia and maternal-fetal medicine play a critical role in the success of this procedure. The mother must receive general anesthesia for the C-section. The deep anesthesia she receives is done to achieve and maintain a state of uterine relaxation to preserve uteroplacental circulation, and a special uterine stapling device is used to open the uterus to prevent bleeding," says Dr. Vats.

The team also must ensure that normal maternal blood pressure is maintained and that appropriate levels of fetal anesthesia are achieved without triggering cardiac depression. It is a delicate balance that must be struck, and the teams at UPMC have perfected their anesthesia protocols for the procedure.

Once the C-section is performed, the baby is then partially (the head and upper torso) delivered through the incision while remaining attached to the placenta through the umbilical cord. Anesthesia keeps the uterus soft and relaxed, which allows the placenta to continue to perform its function. The procedure preserves uteroplacental gas exchange so that the baby can continue to receive oxygen and nutrients from the mother while the team works to establish an airway that will permit the infant to breathe and obtain oxygen once he or she is fully delivered.

The baby is only partially delivered through the incision to naturally keep the baby warm without the need for other interventions to prevent hypothermia.

Potential risks to the EXIT procedure include intrauterine bleeding for the mother. For the baby, if endotracheal intubation fails, the surgical team will need to perform a tracheostomy to establish an airway before the procedure is completed and the baby whisked away to the NICU for follow-up care.

Once the baby's airway is established, and the delivery concludes, Dr. Vats and her neonatology team takes over and transfers the infant to the NICU where other procedures and care will take place. Further into the care plan, once the infant is stabilized in the UPMC Magee NICU, he or she is then transferred to the UPMC Children's NICU for the balance of their care and follow-up procedures based on their needs.

Postprocedural Care

After the delivery, the baby receives specialized care in the neonatal intensive care units of the UPMC Newborn Medicine Program, either at UPMC Magee or UPMC Children's. Babies who need help with respiration but do not require ECMO may be placed on a ventilator for respiratory support.

If called for as part of the surgical preplanning process, a pediatric surgeon also may perform additional procedure(s) to correct an underlying congenital anomaly that may be amenable to surgery.

Likewise, the mother will be monitored closely for hemorrhage, infection, or other postdelivery complications for an appropriate time period based on the specific nature of the case.

A debriefing session occurs upon conclusion of the procedure and before the team members depart. Team leaders from the various specialties involved in the case meet to briefly review the entire procedure and report their perspectives and opinions of how the entire case proceeded and any anticipated or unanticipated issues that arose. This initial debriefing is typically followed a few days later by another more detailed session where all team members, including nursing, participate to discuss the case. The entire EXIT team receives an update on how the mother and baby are progressing in their postoperative care, and the team also reviews the procedure notes and findings to identify, address, and collaboratively solve any issues that arose. The entire debriefing process is intended to inform and guide future cases, learning from any unique aspects that the cases provide and contributes to the evolution of best practices for these rare and complex deliveries.

EXIT Procedure — Key Team Members at UPMC

Stephen P. Emery, MD — Associate Professor and Director, Center for Innovative Fetal Intervention (CIFI) — UPMC Magee

Kalyani Vats, MD — Co-Director Center for Advanced Fetal Diagnostics (CAFD) — UPMC Magee

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Linda S. Dudas, RNC, MSN, CNL — Unit Director, Labor, Delivery, and Antepartum — UPMC Magee

Barb Eichhorn, RN, BSN — Nurse Coordinator, CAFD and CIFI — UPMC Magee

Douglas A. Potoka, MD, FACS, FAAP — Assistant Professor of Surgery, Division of Pediatric General and Thoracic Surgery — UPMC Children's

Clinical Trials in Neonatal Medicine: Shrinking the Ninety Percent Gap

Ninety percent of pharmaceutical agents that are used to treat or prevent various conditions in neonatal patients — medications that have been approved for similar usage in adult patients — have never actually been tested in neonates to determine their pharmacokinetics, pharmacodynamics, optimal dosing patterns, and other criteria.

Use of these agents in this patient population is largely driven by empirical evidence of how they work in adults and physician discretion based on the available clinical guidance or institutional protocols.

"The fact that most of the drugs we use in our neonatal patients have not undergone prior testing in this group is unsatisfactory at best," says **Thomas Diacovo, MD**, chief of the UPMC Newborn Medicine Program at UPMC Children's Hospital of Pittsburgh. "Yes, it is exceptionally difficult to conduct many of these studies. However, it is incumbent upon the field to do more and do better by our patients, regardless of the difficulty or barriers we face in building this badly needed evidence base."

Increasing the evidence base for the use of pharmaceutical agents in neonatal patients is a priority for Dr. Diacovo and his colleagues in the UPMC Newborn Medicine Program. The program is currently participating in ongoing multicenter investigations examining the efficacy of various medications in neonates.

In addition to the pharmaceutical clinical trials in progress, several new basic and translational investigations are examining aspects of necrotizing enterocolitis, immune and microbial development in the neonatal gastrointestinal tract, and a novel approach to using precision medicine in the diagnosis of genetic disorders in neonates.

Below are summaries of these promising new trials currently in progress that seek to improve the care of neonatal patients everywhere.

Cangrelor Use in Neonates

This investigator-initiated study being conducted at UPMC Children's and led by Dr. Diacovo, will assess the pharmacodynamics and pharmacokinetics of cangrelor used in neonatal patients who are at risk for thrombosis related to the use of pulmonary arterial shunting.

Dr. Diacovo and his study collaborators will seek to enroll up to 20 participants up to 28 days in age in this trial analyzing the safety and mechanistic properties of cangrelor in four discrete doses. The trial will start with a cohort of four subjects receiving the lowest dose and progress over time to additional cohorts of four — each receiving subsequently larger doses of the agent.

Apixaban and Heart Disease in Children

UPMC Children's is now participating in a multicenter, randomized study investigating the use of apixaban to prevent thromboembolism in pediatric patients with congenital heart disease or an acquired version of heart disease.

Sponsored by Bristol-Myers Squibb in collaboration with the Pediatric Heart Network and Pfizer, the study — titled "Safety and Pharmacokinetics of Apixaban Versus Vitamin K Antagonist or LMWH in Pediatric Subjects with Congenital or Acquired Heart Disease for Thromboembolism Prevention" — is a badly needed examination of how this antithrombotic functions in pediatric patients, and how it compares in usage and efficacy with low molecular weight warfarin (LMWH) or vitamin K antagonist (VKA).

Dr. Diacovo is serving as the site primary investigator for this study, and is collaborating internally with colleagues from the UPMC Heart Institute at UPMC Children's Hospital of Pittsburgh.

This apixaban study is being conducted in pediatric patients from age 3 months to 18 years. Various aspects of pharmacokinetics and safety will be examined, as well as outcomes related to bleeding events, fatal bleeding, and bleeding that requires some form of medical or surgical intervention to restore hemostasis.

Searching for High-Risk Markers for Necrotizing Enterocolitis

Liza Konnikova, MD, PhD, FAAP, assistant professor of pediatrics and developmental biology at UPMC Children's Hospital, is a physician-scientist who broadly investigates how neonatal mucosal immunity develops and its role in the pathogenesis of diseases, including necrotizing enterocolitis (NEC) and very-early-onset inflammatory bowel disease (VEOIBD).

NEC is the leading cause of death in preterm infants. Despite advances in neonatal care, the survival of infants with NEC remains low — less than 50 percent in many cases. In part, this is due to an inability to predict which infants are at risk for the development of NEC and the subsequent failure to utilize preventative strategies.

One of Dr. Konnikova's current studies seeks to understand Toll-like receptor (TLR) biomarkers in necrotizing enterocolitis and how to use these markers to identify premature neonates who are at high risk for developing NEC.

Dr. Konnikova's lab has identified that innate immune signaling via the Toll-like receptor 4 (TLR4) plays a key role in the development of NEC. Her team now is searching for novel biomarkers for NEC in a longitudinal cohort study of infants with NEC by assessing the TLR4 signaling capacity of these neonates, using combined in vitro and in silico approaches. In so doing, Dr. Konnikova and her team hope to advance the field by identifying newborns that are at risk for NEC development, thus creating a window for early prophylactic and interventional therapies.

Uncovering the Mysteries of Immune and Microbial Development in the GI Tract

The gastrointestinal (GI) tract is one of the body's largest immune organs. It is also host to 500 to 1,000 different bacterial species and as many as 10^{14} bacteria. The majority of these bacteria represent commensals that play an important role in the development and maintenance of the host immune system. The interplay between the immune cells and the commensal bacteria allows for host's immune system to respond to pathogenic bacteria while being tolerant of the commensal ones. However, how homeostasis is established and maintained in humans is very poorly understood.

Through translational studies of human tissue throughout gestation, as well as tissue from neonates and young children, Dr. Konnikova is working to decipher how homeostasis is established and maintained.

Dysregulation of the GI immune homeostasis leads to a number of diseases, such as necrotizing enterocolitis (NEC), very-early-onset inflammatory bowel disease (VEOIBD) and IBD. To facilitate studying mucosal immunity in health and diseases, Dr. Konnikova and colleagues have adapted mass cytometry (CyTOF) to perform deep immunophenotyping and functional analysis of immune cells at mucosal surfaces. These advances have allowed Dr. Konnikova to study immune dysregulation in various diseases such as NEC and VEOIBD.

The PreMOD2 Study

Toby D. Yanowitz, MD, MS, associate professor of pediatrics, obstetrics, gynecology, and productive sciences at UPMC Children's, serves as the site primary investigator for the PreMOD2 study. This study is investigating the benefits of delayed cord clamping (DCC) versus the use of umbilical cord milking (UCM) to mitigate bleeding in the brain in premature neonates and to prevent mortality. The trial is currently enrolling neonatal patients that are 30 to 32 + six weeks gestational age.

Dr. Yanowitz and the other study leaders are primarily interested in both short- and long-term outcomes of the use of UCM or DCC in those neonatal subjects delivered before 32-weeks gestation.

In this randomized study, patients will either receive UCM at the time of delivery (four times during a 15 to 20 second period) or DCC for a minimum of 60 seconds. The goal is to see if either method is better at preventing intraventricular hemorrhage or death in premature newborns.

Combatting HIE with EPO: The HEAL Trial

Hypoxic-ischemic encephalopathy (HIE) is a consequence of reduced blood flow and, ultimately, a reduced flow of oxygen to the brain that occurs close to the time of birth. Affecting approximately 12,000 babies each year in the United States, HIE has the potential to inflict devastating, permanent neurologic impairments. It leads to mortality in nearly 10 percent of cases, with higher rates attributable to more severe cases.

The usual therapy for HIE involves the use of hypothermia. The HEAL trial (High-dose Erythropoietin for Asphyxia and Encephalopathy) is a multicenter, randomized investigation of the efficacy of erythropoietin (EPO) that is being conducted to see if its use can improve outcomes when given in tandem with the use of hypothermia.

EPO acts both as a neuroprotective agent and as a growth factor in the brain. The study seeks to determine if EPO given in five doses of 1,000 units per kilogram, in combination with hypothermia, will reduce neurocognitive deficits and mortality in newborns.

Dr. Yanowitz is the site primary investigator for this trial at UPMC Children's.

Ceftobiprole Use in Neonates

Kathleen Schwabenbauer, MD, assistant professor of pediatrics and a neonatologist with the UPMC Newborn Medicine program, is the site primary investigator for a multicenter study designed to characterize the pharmacokinetics of ceftobiprole — a broad-spectrum antibiotic in the cephalosporin family that is used to treat a range of Gram-positive and Gram-negative bacterial pathogens.

The dynamics of the medication are being tested in neonates and infants who are up to three months of age but greater than or equal to 28 weeks gestation.

This open-label interventional study will evaluate the dynamics and safety of a single dose of ceftobiprole given to patients currently undergoing some form of systemic antibiotic treatment at a dose of 7.5 mg/kg body weight via a four-hour infusion.

Dr. Diacovo is serving as the co-primary investigator of this trial. ClinicalTrials.gov Identifier: NCT02527681.

Continued on Page 11

Bubble CPAP and Preterm Neonates: A Noninvasive Ventilation Approach to Quality Improvement — Six-Month Implementation Results Update

Preterm neonates — and particularly extremely preterm neonates who are less than 28-weeks gestational age — are at a high risk for developing bronchopulmonary dysplasia (BPD), which carries with it significant rates of morbidity and mortality. The use of mechanical ventilation for respiratory support, coupled with the use of pulmonary surfactants, increases these risks.

"In those neonates with a gestational age less than 28-weeks, the literature shows a nearly 40 percent rate of BPD. This has both short- and long-term complications for the patients and their families. With the implementation and use of bubble CPAP, a noninvasive, safe, and effective method of respiratory support for spontaneously breathing babies, we believe rates of BPD will be dramatically reduced, along with overall use of mechanical ventilation and other support measures that have been part of our existing standard of care," says **James Kiger, MD, MS**, medical director for Newborn Respiratory Care and Bubble CPAP implementation lead.

Implementation of the bubble CPAP protocol is not without its risks and challenges. Because the protocol entails its use in neonates up to 32-weeks gestational age (more or less time on the device is possible depending on the specific needs of the patient), there is the potential that it may be required to support infants for up to nine weeks.

"The changes needed to administer this protocol are fairly intensive and require strict adherence to the use and safety measures that we have put in place," says Dr. Kiger.

Vigilant monitoring of the positioning of the breathing apparatus and airway pressure is required to ensure the proper levels of positive pressure ventilation are delivered at all times.

Implementing the Protocol

Bubble CPAP protocol development began in February 2018. At that time, the implementation of a multidisciplinary committee was formed, consultations and training occurred with experts in the field from Columbia University in New York, and an extensive literature review of the established evidence of bubble CPAP use in preterm neonates was undertaken.

The protocol moved into active use in the NICUs at UPMC Children's and UPMC Magee-Womens Hospital on September 11, 2018, after all the necessary equipment, training, education, and protocol outcomes and practices were established and executed.

Outcomes and Benefits of the Protocol — Six-Month Metrics

The Bubble CPAP initiative in the UPMC Newborn Medicine Program is designed to provide a number of clinical benefits for preterm neonates. Achieving marked reductions in oxygen exposure, mechanical ventilation, morbidities associated with BPD, length of hospitalization, and the use of agents needed to treat the condition is paramount.

The administrative and cost-benefit potentials from the adoption of the bubble CPAP protocol includes reductions in the number of ventilator days and corresponding fleet size, secondary care costs associated with BPD (short- and long-term), and other financial benefits.

For the first six months of the Bubble CPAP initiative:

- ***Surfactant use*** *has declined by more than 50 percent.*

  Within just the first two weeks of the Bubble CPAP initiative, surfactant use dropped by more than 50 percent. That trend in decreases versus baseline statistics has continued.

- ***Unplanned extubations*** *have dropped considerably.*

  From September 2018 through January 2019, there were just five unplanned extubations. By comparison, in the five months preceding the use of bubble CPAP there were 12 unplanned extubations.

- *The total number of* ***ventilator days*** *has decreased even more dramatically.*

  Since the bubble CPAP protocol began in September 2018, the number of ventilator days has totaled 297 compared to 1,025 in the five months before implementation. That represents **a nearly three-fold decrease in ventilator days**.

Continued on Page 11

The Future of Bubble CPAP at UPMC

The UPMC Newborn Medicine Program will continue its use of bubble CPAP, and the protocol will eventually be implemented system-wide at all UPMC NICUs, even in Level II units for late- or mid-term infants.

Bubble CPAP Implementation Team

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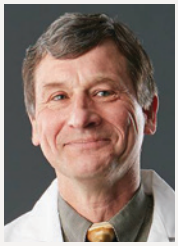
Clinical Trials in Neonatal Medicine *Continued from Page 9*

Genetics and Precision Medicine

Co-primary investigators Thomas Diacovo, MD, and **Jerry Vockley, MD, PhD**, chief of medical genetics at UPMC Children's,



currently are engaged in a collaborative effort between the UPMC Newborn Medicine Program, the Division of Medical Genetics at UPMC Children's Hospital of Pittsburgh, and the Institute for Precision Medicine (IPM) — a collaborative effort between the University of Pittsburgh and UPMC — to provide rapid genomic testing for NICU patients who present with rare and difficult-to-diagnose conditions that may have an underlying genetic cause.

UPMC Children's also is participating in a new national precision medicine clinical trial sponsored by the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health. This trial is studying the use of rapid, targeted, next-generation sequencing technology to diagnose underlying genetic causes for disease in high-risk neonates.

Led by researchers at Floating Hospital for Children at Tufts Medical Center, researchers at UPMC Children's will enroll neonates who may have a variety of genetic disorders, but whose diagnoses are unable to be determined through the use of standard testing. The new five-year study entails the conduction of whole-genome sequencing of the neonates, as well as a targeted examination of 1,722 genetic disorders known to afflict newborns.

The study will then compare the results between the targeted screening and the whole-genome sequencing to determine the viability of the targeted panel approach.

A First Graduation Ceremony

NICU patients and their families are a special group. The complexities of care needed to treat these medically fragile cases are difficult and emotionally demanding for both families and providers.

While the average NICU stay at UPMC Children's is approximately 14 days, there is a small subset of patients whose conditions and complexities of care requires substantially longer hospital stays. During these long days and weeks of working toward the best outcome possible, families endure what may be one of the most emotionally and physically demanding experiences they may ever have to face.

Bridget S. — Recent NICU graduate.

To celebrate the good outcomes of these extended NICU stays, in recent months the NICU staff at UPMC Children's instituted a graduation ceremony for all of its patients who have had admissions of 90 days or longer.

Upon discharge from the NICU, patients and families are presented with a diploma announcing their graduation, balloons, and a cap knitted by NICU volunteers. The traditional music played at graduation ceremonies — Pomp and Circumstance — is played as the family says their goodbyes to the NICU staff who have worked tirelessly to make this outcome possible.

An alert is sent out to staff via pickle phone when a discharge is happening so that anyone who is able to get away from their duties for a few minutes can join the event and wish the family well on their continuing journey and recovery at home.

UPMC | CHILDREN'S HOSPITAL OF PITTSBURGH

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About UPMC Children's Hospital of Pittsburgh

Regionally, nationally, and globally, UPMC Children's Hospital of Pittsburgh is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists. With generous community support, UPMC Children's Hospital has fulfilled this mission since its founding in 1890. UPMC Children's is recognized consistently for its clinical, research, educational, and advocacy-related accomplishments, including ranking 15th among children's hospitals and schools of medicine in funding for pediatric research provided by the National Institutes of Health (FY2018).