# NEONATOLOGY

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Each year, more than 800,000 newborns in the United States are diagnosed with neonatal jaundice.

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In 2004, the American Academy of Pediatrics published guidelines for the management of hyperbilirubinemia.<sup>3</sup> Since then, there have been only modest treatment advancements in jaundice. The current standard of care requires periods of isolation that can compromise the potential of the mother-infant bond.<sup>5</sup>

Mallinckrodt is committed to researching and advancing the understanding of neonatal jaundice.

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# The Neurodevelopmental Consequences of Congenital Heart Disease

Gil Wernovsky, MD, FACC, FAAP, Mary T. Donofrio, MD, FACC, FAAP, FASE, Melissa B. Jones, MSN, CPNP-AC, Jacqueline Sanz, PhD, ABPP-CN.

#### **Background:**

Children with complex congenital heart defects (cCHD) are now surviving neonatal and infant surgery with a frequency thought to be impossible only a generation ago. While advances in medicine and surgery have allowed the ability to "mend" children born with CHD, the increasing number of survivors has created a growing population of children in our primary and secondary school systems, and young adults entering the job force.

In the United States alone, over 35,000 infants are born each year with CHD, and more than a third of these infants have cCHD and will undergo "palliative" or "corrective" surgical interventions in the first year of life. It is estimated that there are more than one million adults now living in the USA with a variety of CHDs, which includes over 150,000 adults living with cCHD. Due to improved survival rates in the past two decades, there are larger numbers of schoolage children with increasingly complex forms of CHD. As survival rates have increased, additional attention has been directed toward understanding and treating the long-term challenges for these children and young adults, including behavioral problems, academic performance and mood disorders, all of which combine to affect health-related quality of life.

#### The "Neurodevelopmental Phenotype" in cCHD (see Table).

As a group, children and young adults with cCHD have a higher likelihood of academic, behavioral, social-emotional and motor coordination problems compared to children without CHD. While not all children with cCHD have these difficulties, the percentage of children with these challenges is significantly higher than in the general population. These problems are more prevalent in children with cCHD compared to less severe forms of CHD that do not require surgery, can be treated during catheterization, or do not require surgery until later childhood (see figure). Infancy

In infancy, problems that are more prevalent include feeding difficulties (perhaps in half of all children requiring heart surgery as neonates) and delays in reaching some important motor milestones such as rolling over, crawling or walking – opportunities for them to explore the environment. Although most neonates achieve full feedings by mouth shortly after discharge from the hospital, many require supplemental tube feedings into later infancy and beyond. While delays in motor skills are extremely common, most of the infant's milestones are delayed by only a few months or so. Following heart surgery in the neonate and infant, many heart centers now perform speech, occupational and physical therapy evaluations and treatment, as well as long term follow-up – as recommended by the American Heart Association and American Academy of Pediatrics.

#### Preschool

In preschool, there is a growing recognition of delays in certain elements of speech and language. To greatly oversimplify, speech and language can be broken down into two components: receptive language (the child hears and understands words), and expressive language (using words and sentences to communicate effectively). In many children with cCHD, receptive language is normal (e.g., if you say "point to the apple", the child will point to the apple). In contrast, children may have trouble with articulation (or coordinating the oral movement needed for forming words correctly), and with more complex expressive language. For example, a child may have trouble finding the right words (e.g., when you point to an apple and say, "what is that?", even though the child knows it's an apple), or as they get older, they may have trouble organizing sentences, staying on topic, or following the flow of a conversation. Importantly, recent work has suggested that up to 25% of children with cCHD have some form of hearing loss after surgery, which substantially impacts the development of language and academic skills; a formal hearing evaluation should be considered as part of the routine follow-up of these children.

In addition to delays in expressive language, some preschool children with cCHD (at least 25%) have ongoing difficulties with motor skills, including large motor delays (clumsiness), fine motor delays (problems with buttoning, zipping, cutting), and visual-motor delays (drawing). Visual-motor integration relates to the ability to coordinate thoughts and images into motor action. In preschool and school age children, handwriting represents a particular challenge: seeing handwriting on the board, knowing that it's a particular letter, and getting the hand to make the letter can be very frustrating to an otherwise bright child. In many

"Following heart surgery in the neonate and infant, many heart centers now perform speech, occupational and physical therapy evaluations and treatment, as well as long term follow-up – as recommended by the American Heart Association and American Academy of Pediatrics."

children, fine and gross motor skills improve by the time they enter school, though visual-motor problems remain prevalent.

By preschool age, problems with executive skills also begin to emerge. Executive function (EF) refers to a group of skills used to complete novel or complex tasks. In other words, these are not the "know how," but the "how you do it" skills, and become more important when we need to tackle something new or different – when we aren't on auto-pilot. Core components of EF include inhibition (being able to "put on the brakes" when needed), working memory (our mental chalkboard, where we keep track of



#### **Making Data Work For You**

Steve Spedale, MD, FAAP, is the director of neonatology for one of the country's largest women's hospitals. As an early adopter of electronic medical records in the NICU, Spedale recognized the need for improved technology not provided by the available EMRs. With that in mind, he began developing software add-ons independently to give him the tools he needed.

In 2011, Dr. Spedale realized his ideas could benefit other doctors and caregivers, so he built a development team to execute them. Together, they created PediNotes.

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and work with information "in our head"), and flexibility (being able to generate multiple solutions, change tactics when needed, and transition effectively between tasks/activities). These core skills allow us to initiate, plan, and organize our approach to tasks, and to regulate our emotions and behaviors across situations. For example, preschoolers with cCHD may have difficulty with tantrums, transitions, following classroom routines, or remaining flexible in social situations.

#### School-Age and Beyond:

As children with cCHD enter primary and secondary school in larger numbers, there is a growing recognition of a combination of challenges that may combine to cause academic and social problems. As we look more carefully at children with cCHD, there is a higher rate of diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), with estimates ranging between 25%-53% of children showing symptoms of the disorder, compared to 7-10% of the general population. The core features of ADHD include problems with attention, hyperactivity, and impulsivity, along with executive dysfunction. There are also higher rates of learning disabilities and academic problems in children with cCHD.

Early delays in language, visual and motor skills, processing speed, and self-regulation may interact over time to contribute to increased rates of ADHD and learning disorders, and problems in school more generally. Problems with EF are of particular interest, as they are one of the more commonly reported concerns in children, adolescents, and adults with cCHD (with studies consistently finding that more than half of children have concerns around some aspects of EF). EF is also known to strongly predict success in school (more so than "IQ" or early academic skills) and social relationships, and to strongly influence mental health and quality of life. That is, a child or teen with poorly developed EF may be bright and a strong reader, but struggle with tying together broader themes or "main ideas" when reading, or may have trouble effectively communicating while writing. They may master early math but have trouble with more complex math problem solving. They can struggle to complete work on time, procrastinate (since they have trouble knowing where to start), or forget to turn in completed work. This can lead to frustration as children, adolescents, and adults often fail to truly demonstrate otherwise strong skills in school or at work.

Finally, there are social-emotional challenges. Many children with cCHD have weaknesses with social skills and higher order language. There is an increased incidence of Autism, which is characterized by problems with social skills, communication, and flexibility. Problems with mood and anxiety are also common starting in school age, adolescence, and adulthood.

Despite these risks, there are many children with cCHD, even those with very complex medical histories, who do exceedingly well and do not seem to experience these challenges. It is important for us to investigate the "protective" factors from these individuals – in other words, what provides "resiliency" in the face of cCHD? In addition, there are many effective forms of intervention for ADHD, executive dysfunction, and learning disorders, and these can very much improve outcomes, especially when implemented early, though it should also be stated that it's never too late. Parents and providers should also work to identify and cultivate each child's strengths and talents, and to figure out how their child learns best.

Because of this, the AHA and AAP recognize the importance of regular neurodevelopmental evaluations in this high-risk sample, so that problems can be identified and managed early.

#### **Etiology:**

Although it is tempting to point at "one" feature as "the cause" of the above findings seen so commonly in cCHD, that would be a terrible oversimplification. The effects of cCHD on the developing brain of children are multiple, and cumulative over the early years of development.

Following conception, the closure of the neural tube and early brain development occurs at the same time that the heart forms, in the first trimester. In most cases, whatever causes CHD has "left its mark" on the heart by the end of the 8th week of gestation. In contrast, the brain continues to develop and mature throughout pregnancy (and beyond). Studies are accumulating demonstrating that the abnormal circulation caused by cCHD in the fetus is likely responsible for some of the abnormalities in brain growth and development present at birth. Clearly, "congenital heart disease" and "congenital brain disease" are co-linked variables in many children. Does the same factor or factors that cause CHD also cause brain abnormalities as well? Is the brain "wired" the same way in children with CHD compared to normal? How does the abnormal fetal circulation put an abnormal fetal brain at greater risk for other stressors? Early work in this area was limited to post-natal findings such as microcephaly and neonatal neurological examinations. Subsequent work utilizing fetal Doppler ultrasound revealed abnormalities in cerebral vascular pulsatility suggesting cerebral vasodilation and a decrease in cerebral vascular resistance in left heart obstructive lesions, with some suggesting an elevation in cerebral vascular resistance in right sided lesions. However, now that newer technologies such as magnetic resonance imaging (MRI) in the fetus and newborn have become more routinely available, it is has been noted that there is a mismatch of oxygen and likely substrate (glucose) delivery to the highly metabolically active brain of the developing fetus, particularly in the third trimester. Exciting developments in the understanding of placental development and altered placental function are on the horizon as well. The brain of many newborns with cCHD delivered at term appears 'immature'; several studies have shown that the brain of a full-term infant with cCHD has the complexity (or "maturity") of the brain of a 35-36 week gestation infant without cCHD. This has led to a paradigm shift over the past decade to encourage delivery as close to term (39-40 weeks) as possible, unless there are maternal or fetal reasons to recommend earlier delivery. Finally, genome-wide analyses and certain polymorphisms are being linked to both the prevalence of later school difficulties and cCHD, but also in the way the brain of the newborn responds to stressors such as cardiopulmonary bypass and postoperative care.

Importantly, many published studies exclude children with other known conditions which affect neurodevelopment, such as genetic syndromes, prematurity and additional congenital anomalies. Genetic syndromes and abnormalities on genetic screening, and/or additional congenital anomalies exist in up to 25% of neonates with cCHD. Finally, population studies of newborns with cCHD suggest a higher incidence of prematurity and "small for gestational age", possibly suggesting a role of

#### Table\*

Neurological, Developmental and Psychosocial Challenges Which Occur with Increased Frequency in Children, Adolescents and Young Adults Born with Critical Congenital Heart Disease

- Stroke
- Seizures
- Abnormal brain morphology and functional connectivity (MRI)
- Abnormal brain growth, cerebral atrophy (CT, MRI)
- CNS hemosiderin deposition (MRI)
- Oral-motor dysfunction
- Poor head control
- Delayed gross and fine motor milestones
- Apraxia of speech
- Clumsiness
- Problems with visual-spatial-motor integration
- Inattention and hyperactivity
- Cognitive impairment
- Impaired memory
- Difficulties with executive function
- Autism spectrum disorders
- Social awkwardness/Impaired social cognition
- Anxiety
- Depression
- Schizophrenia (associated with DiGeorge Syndrome)

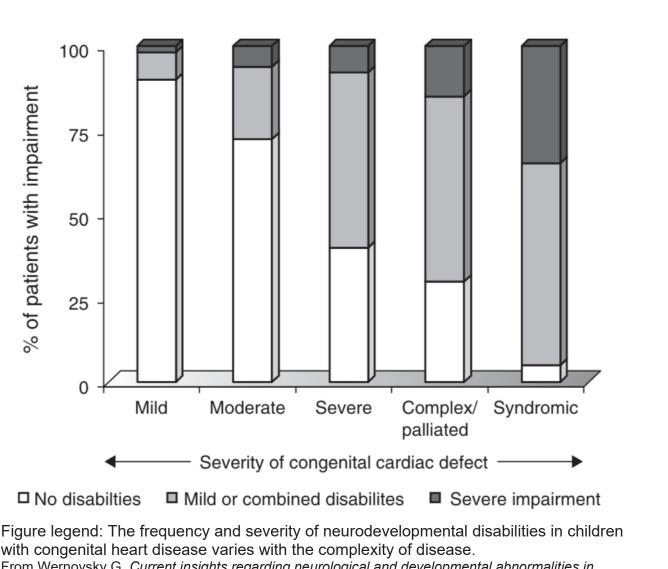
Legend: CNS= Central Nervous System; CT=Computerized Tomography; MRI=Magnetic Resonance Imaging

\*Modified (with permission) from Wernovsky G and Licht DJ: Neurodevelopmental Outcomes in Children With Congenital Heart Disease-What Can We Impact? Pediatric Critical Care Medicine 2016;17:S232-42

placental insufficiency. The placenta may be inherently abnormal and low fetal cardiac output and oxygen delivery to the placental circulation may be a factor, again suggesting an interaction between the type of cCHD and its effect on oxygen delivery and cardiac output to the fetal-placental axis.

For neonates with cCHD after birth, multiple factors occur nearly simultaneously that make it extremely difficult to separate out their relative contributions to long term outcomes. These factors include, but are not limited to, hypoxemia, low cardiac output, cardiopulmonary bypass, analgesic and anxiolytic medications, volatile anesthetic agents, paradoxical emboli (in children with right to left shunting), nutritional deficiencies, limited mobility and developmental stimulation in the early postoperative period, noise exposure, plastics and other toxins, prolonged mechanical ventilation and many more. In essentially all published studies, longer hospital length of stay (LOS) is related to worse longterm outcomes. It is highly likely that longer LOS represents a surrogate outcome variable for the additive and interactive causes mentioned above. Finally, the combined effects of a long stay in the intensive care unit and hospital on both the baby and the family, greatly increase the risk of acute- and post-traumatic stress disorder in parents (see below).

In past research, many long-term neurodevelopmental findings were attributed to cardiopulmonary bypass (CPB, particularly it's duration), pH management, deep hypothermic circulatory arrest, hematocrit, temperature, steroid use, modified ultrafiltration, and more. While these factors are certainly important to the brain and later development, recent work suggests that these effects are seen early in life but become minimal as the children develop. In the Boston Circulatory Arrest Study, the longest prospectively published study to date, deep hypothermic circulatory arrest (DCHA) was related to abnormal outcomes through age 4, both DHCA and low flow CPB were each related to different types of abnormalities at age 8, and by age 16, none of the measured CPB variables had a significant effect on outcomes. Importantly, in many studies, CPB and intraoperative management are responsible for less than ~5% of the variability of long-term developmental outcomes. Perhaps the most important factor in cardiac surgery and recovery is the technical success of the operation. An anatomically and physiologically successful operation leads to improved postoperative oxygen delivery and a shorter length of stay in the hospital; we believe that this is more important than how long it takes to accomplish the operation or factors related to CPB.



with congenital heart disease varies with the complexity of disease. From Wernovsky G. Current insights regarding neurological and developmental abnormalities in children and young adults with complex congenital cardiac disease. Cardiology in the Young 2006;16 Suppl 1:92-104. With permission

#### **Treatment:**

Thus far, research in the treatment of neurodevelopmental problems in patients with cCHD lags behind research in prevalence and etiology. For example, there is limited data at the current time to comment on the safety and efficacy of the psychotropic drugs (for example, stimulant medications for ADHD, anti-depressants, etc.) in children with cCHD, and this must be an individual decision with a child's cardiologist. Many of the medications currently available for children with structurally normal hearts slightly increase the risk of rhythm problems and high blood pressure; and some children with CHD may be at increased risk for rhythm disturbances when using these medications. It must be emphasized that no large study has determined the safety and efficacy of these drugs specifically in children with cCHD, or even if they work the same way as in children with structurally normal hearts. The decision to use medications to deal with behavioral issues or ADHD must be individualized to the child, balancing the unknown risks of these medications in children with CHD against the lifelong implications of academic and social difficulties. Close follow-up, planning and surveillance are warranted when beginning any new medication. Whether or not medication is used as a treatment tool, parents and families should be encouraged to seek out evidence-based therapies to treat speech-language and motor delays, executive dysfunction, and learning differences. Most often, it is the combination of medical and behavioral/therapeutic approaches that is most effective. Harnessing community resources, such as services and supports in the school system (e.g., individualized educational plans) is also critically important. Finally, one must address post-traumatic medical stress and family functioning, and evidence based therapy for mood or anxiety disorders. Most researchers agree that this is a central component to increasing effectiveness of other interventions.

Some studies are underway investigating whether increasing oxygen delivery to the brain and/or placenta of a fetus with cCHD can be safely accomplished through maternal administration. Also, there is growing evidence in studies across the globe that treatments geared toward decreasing maternal worry and improving parental mental health show significant promise in improving long term outcomes. These include prenatal counseling, pre- and post-operative support with clergy and palliative care teams, and increased contact with advanced practice nurses prior to and after hospital discharge.

#### **Future Directions:**

In our opinion, the outlook for children with cCHD remains quite optimistic. Many are now adults and are engineers, nurses, doctors, social workers, and teachers; many are parents themselves, and lead happy, productive lives. Nonetheless, there are ongoing challenges for those of us who care for these children to improve overall quality of life. It is important to emphasize that long-term prospective studies, and cross-sectional studies in older adults with CHD represent management strategies from the 1970's-2000's, and there is a suggestion that there is some improvement in many areas of functioning for children born more recently. This is likely due to the many important and simultaneous improvements in the last two decades—including more frequent prenatal diagnosis, research into the developing brain before and after surgery, a better understanding of anesthesia and cardiopulmonary bypass, improved post-operative care, and the benefits of structured follow-up programs. A number of additional factors will ultimately contribute to the academic success of our children, including genomics and a personalized medicine approach to surgery and perioperative care.

It has also been learned that - not surprisingly - the stress of having a child with cCHD on parents and families is prevalent, occasionally severe and long-lasting. Importantly, taking steps to improve parental mental health (mindfulness techniques, PTSD therapy, etc.) improve both the parents and the child's long-term outlook. As is said when you board an airplane: "Put your own mask on first before helping others". We cannot over-emphasize the importance of self-care — both physically and mentally — for families affected by a child with cCHD.

Finally, the best way to improve the outcomes for future

"Children with complex Congenital Heart Defects (cCHDs) are now surviving neonatal and infant surgery with a frequency thought to be impossible only a generation ago. While advances in Medicine and Surgery have allowed the ability to "mend" children born with CHD, the increasing number of survivors has created a growing population of children in our primary and secondary school systems, and young adults entering the job force."

generations is a continued and long-term partnership between

patients, parents, researchers, nurses, therapists, psychologists, physicians and many others. Advocacy by physicians, parents and patients at the government level for continued funding of research is crucial. We must continue to pursue the causes and treatment of heart disease in children, as well as the secondary effects on the brain and quality of life. Philanthropic contributions play a significant role in start-up funds for research as well. Finally, if families and children are willing, voluntary participation in clinical research studies remains the cornerstone of the process.

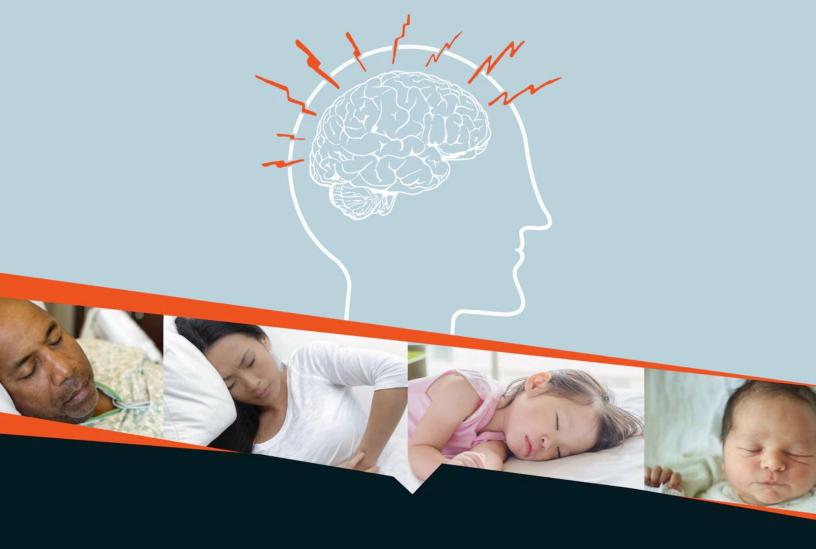
#### Summary of Current Findings, 2018:

- In the absence of an associated structural brain abnormality or genetic syndrome, cognitive function (IQ, intelligence) is typically within the normal range for most children with CHD
- Parental education, mental health and socioeconomic status are consistently the most strongly associated factors in the long-term outcomes for children with cCHD, rather than the specific type of CHD or its management. Of these, while the effects of low socio-economic status may be attenuated by participation in enrichment programs (e.g., early preschool, "headstart"), only parental mental health is truly modifiable.
- Early delays with language, motor, and visual motor skills are common in children with cCHD:
  - Problems with executive function which affects behavioral regulation and completion of complex tasks – are highly prevalent in cCHD, and may be the most important factor in long term success and healthrelated quality of life
  - There are higher rates of ADHD, Learning Disorders, and Autism in children with cCHD.
- Some identified risk factors for academic and behavioral difficulties include highly complex CHD requiring multiple procedures, a long hospital stay, and family PTSD. Healthrelated quality of life is also affected by the number of medications necessary and number of doctor visits per year.
- The association between abnormal fetal oxygen and substrate delivery, open heart surgery and postoperative care with later cognitive, language, or behavior difficulties continues to be an active area of investigation.

Given these findings, The American Heart Association and American Academy of Pediatrics have recommended regular neurodevelopmental evaluations, in infancy, school age, and adolescence, for children with cCHD. Included below is a list of recent selected interdisciplinary references related to the diagnosis and treatment of neurodevelopmental disabilities in children with cCHD.

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#### Case Study: A Misdiagnosis of an Unsuspected Diagnosis

Farhana Ali, MD, Gilbert I Martin, MD, Donald C Moores, MD

#### Abstract:

Gastroschisis is a common cause of neonatal intestinal evisceration. Fetal lacerations typically occur during cesarean section delivery. The patient reported here was born via an unsupervised vaginal home delivery, and presented with an intestinal evisceration through an inflicted abdominal laceration that was initially misdiagnosed as gastroschisis.

#### **Description:**

A five-hour old newborn was transferred to the Neonatal Intensive Care Unit (NICU) from another facility after resuscitation following a spontaneous vaginal birth at home. He was reportedly born in the shower to a primigravid mother who stated that she was unaware she was pregnant. Upon paramedic arrival to the home, the newborn was found to have exposed abdominal viscera, which was presumed secondary to gastroschisis (figure 1). The bowel was then covered in moist gauze and he was transported to a local hospital. At that facility, he was noted to have pink eviscerated bowel covered in moist gauze. The newborn was placed in a bowel bag, placed under a warmer, intubated to a conventional mechanical ventilator, and started on IV fluids. He was also noted to have dried blood on the anterior neck adjacent to a one centimeter open wound with jagged margins, for which the family had no reported explanation. The neck wound (figure 2) was explored, noted to be superficial, and was repaired with sutures, following which he was subsequently transferred to our NICU for ongoing management of presumed gastroschisis. Upon examination in the NICU, it was recognized that the bowel was eviscerated through an abdominal wall opening in the epigastrium, superior to the umbilical cord, and that the newborn actually had an abdominal wall laceration. He was taken emergently to the operating room for exploration of the penetrating trauma and evaluation for other internal injuries. There was a moderate amount of blood in the peritoneal cavity secondary to an omental bleed which was readily controlled. A subcapsular liver hematoma was noted to involve the right lobe, but no hepatic laceration was identified. There was no bowel or mesenteric injury identified, and the remaining organs were intact. Abdominal muscle, fascia, and skin layers were then closed with running sutures, and the neonate was returned to the NICU.



Figure 1 - Abdominal wall evisceration



Figure 2 – Neck Wound



Figure 3 - Gastroschisis

#### Discussion:

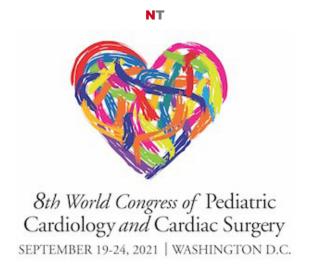
Gastroschisis (figure 3) is one of two major congenital anterior abdominal wall defects. Routine blood work in pregnancy may reveal an elevated alpha-fetoprotein, although the key modality for prenatal diagnosis is sonography. In gastroschisis, the defect is a small, full thickness cleft resulting in the herniation of abdominal wall viscera into the amniotic sac. The defect will be immediately adjacent to, and exclusively to the right of the umbilical cord. The eviscerated bowel lacks a covering sac and may be swollen and edematous, larger than the size of the abdominal wall defect itself. Exposed bowel will often appear matted, with a thickened fibrinous peel, attributed to the irritant effects of amniotic fluid. Gastroschisis can be easily differentiated on physical exam from its

congenital counterpart, the omphalocele. An omphalocele occurs as a central defect, emerging from the umbilicus, with an overlying membranous sac.2 Clearly, as in this case, gastroschisis must also be differentiated from rare non-congenital causes of bowel evisceration, such as an abdominal stab wound. In the suspicious setting of our patient, with his unconventional and unclear birth history, the presence of an unexplained neck wound, the incorrect anatomical presentation for a congenital wall defect and the evisceration of otherwise normal appearing bowel, non-accidental trauma must be considered. Evisceration of bowel should prompt immediate operative intervention, regardless of the etiology, but evisceration secondary to abdominal trauma is an indication for surgical exploration of the entire abdomen, given the risks for other intra-abdominal injuries and bleeding.<sup>3</sup> Gastroschisis, on the other hand utilizes a different surgical approach, and is more likely to be amenable to either primary reduction and closure, or to simple placement of a silo for the gradual reduction of viscera, culminating in fascial closure when the bowel can be fully reduced.4 In the absence of prenatal imaging and testing in our newborn, the clinical diagnosis based on physical examination was of key importance.

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#### **Letters to the Editor**

To the Editor (via email),

From: Lavery, Adrian <ALavery@llu.edu>

Subject: Letter to the Editor

Date: Thursday 6/14/2018 11:30 AM

Letter to the Editor,

As a neonatology fellowship program director, I am interested in the possibility of submission to your Journal the research manuscripts of fellows in training. Many are completing both basic science and clinical studies that I think might interest your editorial board. Would you consider animal studies and basic science manuscripts for review? Ideally their publications would result in a PubMed Identification number (PMID) to help with faculty promotion and tenure. Could you please comment regarding this issue. Lastly, what is the typical turnaround time for manuscript review and cost for publication in your Journal?

Adrian Lavery, MD, MPH
Associate Professor of Pediatrics
Director
Neonatal-Perinatal Medicine Fellowship Training Program
Loma Linda University

(via email)

Dear Dr. Lavery,

Thank you for your letter. Neonatology Today has been revamped over the course of the past few months. We encourage submission of clinical studies, basic research, and other academic topics as well case reports, especially from those in training. All submissions are peer reviewed.

PubMed is a free search engine used to access the MEDLINE database of references and abstracts medically related topics. The United States National Library of Medicine (NLM) at the National Institutes of Health (NIH) updates the database regularly. The database is part of the Entrez system of information retrieval. A PMID (PubMed identifier) is given to each PubMed record. PMIDs are assigned to letters to the editor, guidelines, opinion-editorial columns, and any material that the publisher includes in the journal. Although peer review manuscripts are assigned a PMID, a PMID does not guarantee that each submission is peer reviewed.

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suant to the best practice statement, NT makes Information about the methods of selecting articles available on our website as well as the journal itself, requires adherence to ethical guidelines, and asks for evidence that authors have disclosed financial conflicts of interest. Indexing usually begins following the current year and volume following approval. Once approved, publishers may also submit for volumes preceding the start date, if these are acceptable, these citations will also appear in PubMed.

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Sincerely,

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Mitchell Goldstein, MD
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# Presentations from National Perinatal Association 2018 Annual Conference on March 14-16, 2018 at Loma Linda University Children's Hospital

Erika Goyer, Family Advocate

The National Perinatal Association (NPA)is an interdisciplinary organization that strives to be a leading voice for perinatal care in the United States. Our diverse membership is comprised of healthcare providers, parents & caregivers, educators, and service providers, all driven by their desire to give voice to and support babies and families at risk across the country.

Members of the NPA write a regular peer-reviewed column in Neonatology Today.



Educate. Advocate. Integrate.

Last month. NPA's article focused on novel and innovative interventions for perinatal substance use and exposure that were presented as poster sessions at our 2018 conference. This month we focus on the presentations of evidence-based models of care.

For neonatal providers, few public health problems are as pressing and distressing as the crisis of perinatal substance use. As we see national rates of both licit and illicit substance use and dependence rise, we witness a corresponding crisis of infants exposed to substances in utero. Sometimes this exposure results in a constellation of symptoms that we describe as Neonatal Abstinence Syndrome (NAS) or Neonatal Opioid Withdrawal (NOW) and

these infants are often admitted to the Neonatal Intensive Care Unit (NICU) for observation, evaluation, and pharmacological treatment.

Because of our ability to intervene and relieve these symptoms with medications, much of our time and energy has understandably been focused on describing and assessing the immediate effects of substance exposure and withdrawal - using the Finnegan Neonatal Abstinence Score (FNAS) and other tools - and creating protocols for appropriate dosing and weaning of opioids. In time, the NICU became the customary place to care for these newborns and our care focused on the infants and their symptoms, usually in isolation from their parents. While much attention was given to scoring and medicating, little attention was paid to the mothers and families

"As we see national rates of both licit and illicit substance use and dependence rise, we witness a corresponding crisis of infants exposed to substances in utero."

Ironically, the creator of the Finnegan assessment, Dr. Loretta Finnegan, never intended for her scoring tool to be used in this way. She and others always knew that the primary intervention that best supported babies experiencing opioid withdrawal was the love and attention of their mothers. As a pioneer of family-centered, integrated care she champions preserving and promoting the mother-infant dyad and empowering mothers to be an integral part of their babies' treatment.

We were honored to have Dr. Finnegan as our keynote speaker, and she was chosen to give her perspective to open the National Perinatal Associations 2018 Annual Conference, Perinatal Substance Use: Evidence-Based Solutions and Support for the Family.

• See An Historical Perspective on Caring for Mothers with Substance Use Disorders and Babies with Neonatal Abstinence Syndrome, presented by Loretta Finnegan MD, LLD (HON.), SCD (HON.)

Over the course of three days, NPA's conference presenters shared a diverse range of evidence-based models of care. While the models differed considerably in setting and in the services provided, it was clear that in each case the pioneers of these programs carefully and conscientiously considered the responses that would be best suited to the talents and resources of their institutions and the unique needs of their communities. We were eager to share their work – and celebrate their successes at this national conference.

We hope that these innovative programs serve as inspiration for improving the care provided in your units.

 How to Reshape your Approach to Neonatal Opioid Withdrawal Syndrome (NOWs) presented by Adam Czynski, DO, FAAP

Women & Infants Hospital in Providence is the largest birthing hospital in Rhode Island with 9,100 births a year. After a thorough needs assessment, they developed a plan to centralize their care of NAS infants and create their Family Care Team model. A NAS Task Force was initiated, criteria for "Rooming In" were developed, and a plan for the ongoing education and support of the nursing staff was instituted. Women & Infant's first line of therapy for babies with NAS is non-pharmacologic, with clustered supportive care. Care is delivered with a team approach with parents included ev-



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ery step of the way. Family Care Rounds are integrated into the unit's routine. They are conducted in the Patient Room with entire team present. Families are responsible for updating the team about previous 24 hours of care. The baby's date of discharge and plan of care is discussed everyday as a family approaches their goal of going home together.

More information: Women & Infants Hospital of Rhode Island in Providence

 <u>Family-Centered NAS Care Program</u> presented by Lisa Grisham, NNP-BC and Maureen Kane, NNP-BC

At a time when lengthy hospitalizations were becoming the norm, Banner University Medical Center in Tucson, Arizona set the ambitious goal of "Home in Six Days" as a part of their Family Centered NAS Care Program. Their plan for family-centered, community-supported NAS treatment embraces the Eat, Sleep, Console model and prioritizes non-pharmacological interventions. Every effort is made to Identify mothers as early in their pregnancies as possible. If they choose to participate, mothers are connected



A collaborative of professional, clinical, community health, and family support organizations improving the lives of premature infants and their families through education and advocacy.



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- Access to RSV preventive treatment for all premature infants as indicated on the FDA label
- Clear, science-based nutrition guidelines for pregnant and breastfeeding mothers
- Safe, accurate medical devices and products designed for the special needs of NICU patients

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with the program's dedicated OB/GYN outpatient social worker. During neonatal consultations, a plan of care is developed and expectations are set. A carefully cultivated culture of acceptance and teamwork between the mothers and staff empowers parents to create solutions and helps alleviate guilt. Every effort is made to remove barriers to parenting and keep mother and baby together. Staff act as coaches and partners with the parent, showing them how to care for their infant if they develop symptoms of withdrawal and determining when pharmacological care is beneficial. Breastfeeding is actively supported and encouraged when mother is compliant with the Medication Assisted Treatment program and there are no other contraindications.

More information: Family Centered NAS Care Program

<u>Kaiser-Permanente Early Start Program: A Successful Perinatal Substance Abuse Intervention</u> presented by Andrea Green, PsyD and Amy Conway, MPH

Kaiser Permanente is a large, integrated managed care consortium based in Northern California that participated in 47,000 births in 2017. Their providers identified the need for assessment, education, and early intervention with pregnant patients experiencing the effects of substance use and misuse. The resulting Early Start Program has innovated perinatal care by integrating substance abuse specialists into Kaiser's prenatal clinic staff. This supports their ambitious efforts to conduct universal screening of pregnant patients. As part of routine care, a questionnaire of identified risks for problematic substance use is administered. If a need for intervention is confirmed with urine toxicology screening, patients can take advantage of ongoing counseling and case management visits that are linked with their routine prenatal care visits. The success of this innovative program is outlined in the article, "Substance Abuse Treatment Linked with Prenatal Visits Improve Perinatal Outcomes: A New Standard."

More information: Kaiser Permanente's Early Start

Magee-Women's Hospital of UPMC Pregnancy Recovery Program presented by Stephanie Bobby, BSN, RN, CARN

Magee-Women's Hospital in Pittsburgh, Pennsylvania can boast the impressive achievement of supporting more than 1,000 deliveries to women on Medication Assisted Treatment. Their comprehensive program of prenatal care, opioid agonist therapies (both methadone and buprenorphine), behavioral counseling, and community support is evidence of the promise of comprehensive, family-integrated care. Magee's Pregnancy Recovery Center staff has embraced the principles of relationship-based care that promotes patient engagement. Community outreach and relationship building is integral to their success. Their Community Based Care Management Team performs on-site assessments with new clients in their communities before making "warm hand-offs" to Pregnancy Recovery Program staff. This enables the care team to establish face-to-face contact with expectant parents within one day of referral. This model delivered Medication Assisted Treatment, behavioral counseling, and case management services to

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300+ patients in the programs first 12 months.

More information: <u>Pregnancy Recovery Center at Magee-Women's Hospital</u>

 Project Nurture: A Center of Excellence Model for Pregnant Women with Substance Use Disorders presented by Telia Anderson, PRC, CS (DONA) and Kasey Edwards, CRM, CADC

Project Nurture, a program of Health Share of Oregon, provides clients with comprehensive care and case management from early pregnancy to one year postpartum. Designed to address the unmet needs of mothers in Portland, Project Nurture delivers prenatal care, inpatient maternity care, and postpartum care for women who struggle with addictions. Their group-based interventions and services embrace a team-based approach that successfully integrates substance use treatment with maternity and pediatric care. Project Nurture locations offer Level 1 outpatient addiction treatment provided by certified alcohol and drug counselors (CADCs) as well as Medication Assisted Treatment (MAT) utilizing either methadone or buprenorphine. One key to the program's success is their commitment to providing peer-facilitated support. Project Nurture embraces the expertise of women who have personal experience with substance-exposed pregnancies. These "Experts by Experience" integrate their personal journeys with their professional training to bring a unique perspective. By blending their roles as Peer Recovery Mentors and doulas, "their presence has a powerful effect that helps the clinical team and the women they serve see themselves as both mothers and in recovery instead of one or the other."

More information: Project Nurture

• <u>The Mommies Program: An Integrated Model of Care</u> presented by Karen Palumbo, LCSW, LCDC

When the Texas Department of State Health Services prioritized efforts to arrest the rising rates of perinatal substance use and Neonatal Abstinence Syndrome (NAS), Texas providers needed timely solutions. Fortunately, the communities of San Antonio and Corpus Christi had already developed successful interventions. The Mommies Model is a region-specific, evidence-based program that effectively addresses the barriers to substance use treatment that pregnant women face. It outlines specific prenatal, intrapartum, and postpartum clinical pathways for women with Opioid Use Disorder (OUD) and standardizes care protocols. But one of the greatest achievements of the Mommies Model is that it has created a "cultural change" within Texas' healthcare system. Provider education and training has led to a more accepting and judgment-free environment for women seeking help with their Substance Use Disorders and improved access to care.

More information: <u>The Mommies Toolkit: Improving Outcomes for Families Impacted by Neonatal Abstinence Syndrome</u>

Members of the National Perinatal Association are committed to serving pregnant and parenting people who are substance dependent and their babies. We are grateful for the providers who support them.

While it is clear that the perinatal period presents unique risks for those who are substance dependent and their babies, it is also a time when there are unique opportunities for positive intervention. As clinicians, mental health, and community health care providers, it is imperative that we understand the nature of perinatal substance use disorders and provide interventions and care that preserve the parent-infant dyad, promote parenting potential, and support the baby's health and development." from the NPA Position Statement on Perinatal Substance Use, 2017

Please share NPA's resources on perinatal substance use and take the opportunity to get more involved in promoting interdisciplinary, collaborative perinatal care. <a href="www.nationalperinatal.org/">www.nationalperinatal.org/</a>
<a href="www.nationalperinatal.org/membership">www.nationalperinatal.org/membership</a>.

The author has no conflicts of interests to disclose.

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### **COURSE CONTENT INCLUDES:**



- HIE and Cooling
- IVH & White Matter Injuries and Management
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- Seizure Management
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- Palliative Care
- And More

# Registration & Agenda

https://tinyurl.com/neuronicu-sept

#### How Congress Can Help with Coverage Parity for Medically Necessary Foods and Treatment for Infants and Children

Alliance for Patient Access (AfPA) Government Affairs Team

The Alliance for Patient Access (allianceforpatientaccess.org), founded in 2006, is a national network of physicians dedicated to ensuring patient access to approved therapies and appropriate clinical care. AfPA accomplishes this mission by recruiting, training and mobilizing policy-minded physicians to be effective advocates for patient access.

(Apfed) there are twenty states that have passed laws to increase insurance coverage for medical foods. Apfed also notes that families in the Eosinophilic gastrointestinal diseases (EGIDs) patient community can pay as much as "\$1,200 or more out-of-pocket for a one-month supply of prescribed formula," as part of the patient's treatment regimen. The conditions and covered diseases contemplated in the federal legislation for coverage parity include: inflammatory bowel disease (e.g. Crohn's disease and ulcerative colitis), eosinophilic digestive disorders, food protein induced enterocolitis syndrome (FPIES), Immunoglobulin E and non-Immunoglobulin E-mediated food allergies, and malabsorption due to liver or pancreatic dysfunction, or short bowel syndrome.



As a parent, it is often hard to convince a toddler or child to try and eat a variety of fruits, vegetables, and proteins. Families are often faced with the additional challenge of monitoring and managing inherited metabolic disorders or digestive disorders diagnosed during infancy and childhood. Federal legislation to aid families in their access to "medically necessary foods" was introduced in Congress last year and continues to gather cosponsors as a means to help families combat their child's access to treatment for these conditions.

According to congressional findings listed in federal legislation introduced last year, medically necessary foods are not "uniformly reimbursed by health insurance," and therefore the financial burden falls to families for coverage of treatment to accommodate basic, life-sustaining needs, i.e. to keep their medically-challenged child nourished.

In May 2017, the Medical Nutrition Equity Act (S. 1194/H.R. 2587) was introduced with the intent to improve coverage, under Federal health programs (including Medicare, Medicaid, other specified federal health-care programs) and private health insurance, for foods and vitamins that are medically necessary for the management of certain digestive and metabolic disorders and conditions.

The legislation is bipartisan and the House and Senate bills are identical.

According to the American Partnership for Eosinophilic Disorders

"Cognitive development and physical growth failure are well-known consequences for those that have nutrient deficiencies or inadequate nutrition."

U.S. Senator Chuck Grassley (R-lowa), one of the original cosponsors of the Senate version of the bill, captured some of the conditions he hopes to impact and improve access to treatment for with the introduction of the legislation. His office noted in his support for the bill the example of Phenylketonuria (PKU), a rare inherited metabolic disorder, and mentioned further that "untreated, PKU can result in severe intellectual disability or even death." Because of the success of a federally-sponsored, newborn screening program, however, "PKU can be identified early, and treatment with special foods and medication can lead to a healthy life."

The solutions in the bill are also intended to make "clear that medical nutrition is as important to certain patients as prescription drugs or other medical treatment."

Healthcare Nutrition Council (HNC), an organization dedicated to raising awareness of malnutrition and the profound impact nutritional status has on overall health and treatment outcomes, notes that without access to medical nutrition, the results for infants, children, and adolescents can be dire. Cognitive development and physical growth failure are well-known consequences for those that have nutrient deficiencies or inadequate nutrition. Hospitalization and even death are likely outcomes though if treatment cannot be acquired.

In addition to patient protections through insurance coverage requirements, the Medical Nutrition Equity Act also accounts for preservation of the patient-physician relationship. The bill's provisions acknowledge that those medical foods and medically necessary treatments that are prescribed, ordered, and recommended by a qualified physician or health care provider, should justify coverage by health insurance plans. Parents and patients faced with these conditions trust their medical provider or pediatri-

cian to design a treatment plan based on the patient's interaction with the provider, the provider's medical expertise, and the provider's unique knowledge of the patient's medical history. Insurance companies that make coverage determinations do not experience this direct interaction with the patient requiring significant nutritional interventions.

Finally, the bill does not limit coverage to only foods and vitamins, but provides requirements for coverage of medical supplies and medical equipment (such as feeding tubes) that are a conduit to absorption of food and nutrients.

The American Academy of Pediatrics (AAP) has endorsed the legislation.1

1https://downloads.aap.org/DOFA/5-23-17%20Medical%20Nutrition%20Equity%20Act%20Support%20Letter%20Senate.pdf

NT

### 2017 BY THE NUMBERS







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### **Family Centered Care is** trendy, but are providers really meeting parents needs in the NICU?

#### **Consider the following:**

Surveys show hospital support groups are being widely underutilized by parents.





And only 10% of NICUs surveyed connect parents with non-hospital support.

**Graham's Foundation**, the global support organization for parents going through the journey of prematurity, set out to find the missing piece that would ensure all parents have real access to the support they need.

See what they found by emailing info@grahamsfoundation.org to request a free copy of the 2017 whitepaper, "Reaching Preemie Parents Today" (Heather McKinnis, Director, Preemie Parent Mentor Program, Graham's Foundation).

You may be surprised to see what NICUs are doing right and where their efforts are clearly falling short.

Graham's Foundation empowers parents of premature babies through support, advocacy and research to improve outcomes for their preemies and themselves.



Visit www.GrahamsFoundation.org to learn more.

#### Are You in the Field of Congenital, Pediatric or Structural Cardiology?

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#### **Medical News, Products & Information**

Compiled and Reviewed by Mitchell Goldstein, MD Editor in Chief

Springer Nature Announces Search for New Editor-in-Chief of the Journal of Perinatology (Previously posted in NT May, 2018)

An international search for a new Editor-In-Chief is under way.

Editor-in-Chief

Journal of Perinatology

The official journal of the Section on Neonatal-Perinatal Medicine, American Academy of Pediatrics, and of the National Perinatal Association of the United States

Springer Nature, together with the Section on Neonatal-Perinatal Medicine, American Academy of Pediatrics and the National Perinatal Association of the United States, announce an exciting opportunity for an exceptional candidate to serve as Editor-in-Chief of the Journal of Perinatology (JPER).

The Journal of Perinatology provides all members of the perinatal/neonatal healthcare team with original information pertinent to improving maternal/fetal and neonatal care, embracing the full scope of the specialty, including clinical, professional, political, administrative and educational aspects. The Journal also explores legal and ethical issues, neonatal technology and product development.

Candidates should have a Ph.D., M.D., or equivalent degree, and a comprehensive knowledge and understanding of the field of perinatal and neonatal healthcare. In addition, candidates should have a distinguished research and publication record, high standing among peers, and prior experience in peer-review activities related to the publication of research in the field of perinatology.

Responsibilities include timely review of manuscripts under consideration by the journal, closely collaborating with the Publisher to appoint Section Editors and the Editorial Board, and commissioning submissions in areas of interest and scope. The Editorin-Chief will work routinely with the Publisher, the Section on Neonatal-Perinatal Medicine, American Academy of Pediatrics and the National Perinatal Association of the United States, on journal development with the goal of raising the journal's impact

and advancing the field of perinatology.

A full description of the responsibilities involved is appended to this announcement. The appointment will be a five-year term, and a small editorial stipend is included.

Interested candidates should submit their curriculum vitae, statement of interest, and a vision statement for the journal to Nickie Roake, Publishing Manager of JPER, at nickie.roake@nature.com.

Deadline for applications: 31st July 2018

Duties and responsibilities of the Editor-in-Chief

The Editor-in-Chief is responsible for driving the strategic direction of the journal in collaboration with the Editorial Board and Springer Nature, and with input from the Section on Neonatal-Perinatal Medicine, American Academy of Pediatrics and the National Perinatal Association of the United States. He/she is the figurehead of the journal and is responsible for raising the journal's profile within the community, and ensuring that content published meets the editorial strategy and policies of the journal, as stated in the journal's aim and scope.

The Editor-in-Chief is responsible for the content of the journal, normally making all final decisions (i.e., accept, revise, or reject) regarding the disposition of manuscripts. In addition, the Editor-in-Chief has the following responsibilities:

- To work with the Publisher and editorial team to develop improved ways to optimized the content, quality and speed of publishing of high quality articles. This includes:
  - i. Soliciting content and encouraging potential authors,
  - ii. Commissioning Review papers and Editorials, and
  - iii. Coordinating/commissioning themed special issues.
- To continually seek to improve the journal's standing among perinatal/neonatal journals via maintaining and increasing the impact factor.
- To recruit an international and diverse expert panel of Section Editors and Editorial Board members.
- To ensure that all Section Editors are properly trained to perform their duties, and to monitor their performance (including acceptance rate and manuscript handling times).
- To perform initial evaluation of submitted manuscripts to ensure that they are properly within the scope of the journal

The National Urea Cycle Disorders Foundation

The NUCDF is a non-profit organization dedicated to the identification, treatment and cure of urea cycle disorders. NUCDF is a nationally-recognized resource of information and education for families and healthcare professionals.

www.nucdf.org | Phone: (626) 578-0833

and meet minimum requirements for a research paper, and to reject outright swiftly those which do not merit external review.

- To monitor the progress of manuscripts to ensure timely processing with help from the Editorial Assistant.
- To ensure that the review process is carried out with fairness and integrity. In particular, to ensure that procedures for exposing and managing conflicts-of-interest or misconduct are in place and adhered to.
- Chair an annual Editorial Board meeting, in collaboration with the Springer Nature JPER Publishing Manager.
- To manage the annual publication target/ page budget as set by Springer Nature.
- To promote the journal among the community of authors in order to maintain a pipeline of quality submissions.

NT

University Hospitals
Rainbow Babies &
Children's Hospital
study finds Vitamin D
supplement
decreases wheezing
for black
preterm infants

Prematurity associated wheezing is higher in African American infants.

Newswise — CLEVELAND – African American infants born prematurely are at higher risk for recurrent wheezing. This condition can cause the baby discomfort

and is a risk factor for developing asthma later in life. There are no widely-accepted therapies to prevent prematurity-associated wheezing.

In a first-of-its-kind study published in the Journal of the American Medical Association (JAMA), an University Hospitals Rainbow Babies & Children's Hospital (UH Rainbow) physician researcher found black preterm infants experienced a significant decrease in recurrent wheezing with sustained supplementation of vitamin D. Among infants born at 28-36 weeks gestation, a daily dose of vitamin D through six months of age decreased recurrent wheezing by more than 10 percent.

Prior to conducting the study, it was unclear which vitamin D supplementation strategy would be superior. According to the study's principal investigator, Anna Maria Hibbs, MD, MSCE, FAAP, Eliza Henry Barnes Chair in Neonatology at UH Rainbow, continuing vitamin D supplementation with 400IU/day until 6 months of age corrected for prematurity may decrease their chance of recurrent wheezing.

"Parents need to know African American preterm infants are at high risk of wheezing in infancy," says Dr. Hibbs, who is also associate professor of pediatrics at Case Western Reserve University School of Medicine. "I hope this study can highlight the burden of wheezing illness experienced by premature babies and the importance of targeting interventions that can lessen this burden."

The randomized clinical trial included 300 black infants born preterm between January 2013 and January 2016 at four sites in the United States. Infants were enrolled in the study prior to discharge from the neonatal intensive care unit or newborn nursery, and received open-label multivitamin until they were consuming 200 IU per day of cholecalciferol or vitamin D from formula or fortifiers added to breastmilk. Once they were receiving at least 200 IU/day from their diet, they received either 400 IU

of vitamin D per day or placebo until six months of age, adjusted for prematurity. In both groups, exclusively breast-fed infants were provided with a multivitamin containing 400 IU/day. One-hundred fifty three infants received the daily dose of vitamin D, and 147 were randomized in the placebo group.

Among the 300 study participants, 277 completed the trial. Recurrent wheezing was experienced by 31.1 percent of infants in the sustained vitamin D supplementation group, and 41.8 percent of infants in the diet-limited supplementation group. Both strategies were similar in terms of bone health. The study, funded by the National Heart, Lung and Blood Institute and the Office of Dietary Supplements, enrolled infants at UH Rainbow, MetroHealth, Medical University of South Carolina, and Montefiore Medical Center.

"Vitamin D is an attractive treatment option because it is easy to administer, and is relatively inexpensive. Parents can be in control of this intervention," says Dr. Hibbs. "Further research is needed to identify and optimize interventions that can reduce the wheezing burden, and help us understand any health benefits that may continue as the infants grow up."

NT

American Academy of Pediatrics, Section on Advances in Therapeutics and Technology Membership Drive

American Academy of Pediatrics (AAP), Section on Advances in Therapeutics and



The Brett Tashman Foundation (a 501(c)3 not for profit charity) gives 100% of monies raised from its annual golf tournament to the nation's most esteemed doctors researching **Desmoplastic Small Round Cell Tumor** (DSRCT).

June 30, 2018 at Sierra Lakes Country Club in Fontana, CA.

Please check for more information: http://TheBrettTashmanFoundation.org

Technology (SOATT) announces a membership drive

The American Academy of Pediatrics' Section on Advances in Therapeutics and Technology (SOATT) invites you to join our ranks! SOATT creates a unique community of pediatric professionals who share a passion for optimizing the discovery, development and approval of high quality, evidence-based medical and surgical breakthroughs that will improve the health of children. You will receive many important benefits:

- Connect with other AAP members who share your interests in improving effective drug therapies and devices in children.
- Receive the SOATT newsletter containing AAP and Section news.
- Access the Section's Website and Collaboration page – with current happenings and opportunities to get involved.
- Network with other pediatricians, pharmacists, and other health care providers to be stronger advocates for children.
- Invitation for special programming by the Section at the AAP's National Conference.
- Access to and ability to submit research abstracts related to advancing child health through innovations in pediatric drugs, devices, research, clinical trials and information technology; abstracts are published in Pediatrics.

AAP members can join SOATT for free. To activate your SOATT membership as an AAP member, please complete a short application at http://membership.aap.org/Application/AddSectionChapterCouncil.

The Section also accepts affiliate members (those holding masters or doctoral degrees or the equivalent in pharmacy or other health science concentrations that contribute toward the discovery and

advancement of pediatrics and who do not otherwise qualify for membership in the AAP). Membership application for affiliates: http://shop.aap.org/aap-membership/ then click on "Other Allied Health Providers" at the bottom of the page.

Thank you for all that you do on behalf of children. If you have any questions, please feel free to contact:

Mitchell Goldstein, MD, FAAP, Section Chairperson, MGoldstein@llu.edu and

Christopher Rizzo, MD, FAAP, Membership Chairperson, crizzo624@gmail.com

NT

#### Impaired Fetal Environment Linked to Lower Survival After Heart Surgery in Newborns

CHOP Researchers: Impact May Last Years after Initial Surgery

Newswise — Philadelphia, May 30, 2018 – Children who undergo surgery for congenital heart disease have lower survival rates by three years of age if there are specific problems during fetal development, such as hypertension in the mother or the newborn being born preterm or small for gestational age. These problems are considered markers of an impaired maternal-fetal environment (MFE).

"We already knew that an impaired maternal-fetal environment correlates with neonatal mortality and morbidity in children who don't have heart disease," said study leader J. William Gaynor, MD, a pediatric cardiologist at Children's Hospital of Philadelphia (CHOP). "In this study, we investigated the impact of those impairments on child outcomes after infant heart surgery."

Gaynor and colleagues published their study online Feb. 13 in the European Journal of Cardio-Thoracic Surgery.

The researchers performed a retrospective analysis of 135 newborns with congenital heart disease (CHD) from a larger study of neurodevelopment outcomes after infant cardiac surgery. Two thirds of the cohort of 135 infants had transposition of the great arteries or hypoplastic left heart syndrome (HLHS). The study team defined an impaired MFE as involving pre-eclampsia in the mother, being small for gestational age, or being born preterm. Pre-eclampsia entails gestational hypertension, plus either protein in the urine or injury to the liver or kidney.

In the study cohort, 28 of the 135 newborns, or 21 percent, experienced an impaired MFE. Those infants had longer hospital stays after surgery than the infants without an impaired MFE. Hospital mortality was similar for both groups, but survival at 36 months of age was significantly lower for children with an impaired MFE (68 percent vs. 96 percent). Within the subgroup of patients with HLHS, survival was also lower among those with an impaired MFE.

"Evidence is mounting that the MFE and the placenta are abnormal in many fetuses with CHD, with adverse effects on early development," said Gaynor. Impaired neonatal growth, in turn, may predict worse surgical outcomes. In addition, he added, there is increasing recognition that CHD in a fetus is associated with the mother's health as well.

The researchers noted that the impact of an impaired MFE may extend for years after the initial surgery—here, up to age three. Further studies, said Gaynor, should investigate the mechanisms driving MFE in fetuses with CHD, and on potential strategies to improve the MFE.

CHOP is particularly well positioned to pursue research into the maternal-fetal environment, because the hospital houses the Center for Fetal Diagnosis and Treatment (CFDT), one of the world's largest and most comprehensive fetal therapy centers, and the Fetal Heart Program, a dedicated team of physicians, nurses and imaging specialists focused

#### **CALL FOR EDITORIAL**

NEONATOLOGY TODAY is interested in publishing articles from Neonatologists, Fellows, and NNPs on case studies, research results, hospital news, meeting announcements, etc. Please submit your manuscript to: Articles@Neonate.biz We will reply promptly.

on fetal cardiovascular conditions. The CFDT also includes the Garbose Family Special Delivery Unit, the first obstetrical delivery unit in a pediatric hospital dedicated to the care and delivery of high-risk fetuses with complex anomalies requiring medical or surgical interventions and care immediately after birth.

Mark P. Johnson, MD, a co-author of the current study and Director of Obstetrical Services in the CFDT, said, "An impaired MFE may result in functional immaturity and abnormal development of multiple organ systems, including the heart. Whether this abnormal development raises the risk of higher infant mortality after heart surgery is a question that merits further investigation."

James William Gaynor et al, "The impact of the maternal-foetal environment on outcomes of surgery for congenital heart disease in neonates," European Journal of Cardio-Thoracic Surgery, online Feb. 13, 2018. http://doi.org/10.1093/ejcts/ezy015

NT

#### NeoMed 100 mL Syringe Now Characterized for Use in the Medfusion® v6 3500 Enteral Ready Pump

Higher volume delivery system now available

Woodstock, GA – NeoMed is pleased to announce it has added the 100 mL syringe to its portfolio of characterized syringes for use in the Medfusion v6 3500 Enteral Ready Pump. NeoMed's 100 mL syringe and the Medfusion Enteral Ready Pump are designed to serve as a single solution for the higher volume nutrition delivery needs of NICU and PICU patients.

With the addition of the newly characterized 100 mL syringe, NeoMed now offers 65 syringe configurations in sizes ranging from 6 mL to 100 mL for use in the Medfusion Enteral Ready Pump. The 100 mL syringe has significantly lower priming volume compared to giving sets used with bags and may help reduce the

number of syringes needed to administer a single large volume feed. Furthermore, the 100 mL features an off-center tip, solid polypropylene plunger, and hands-free tip cap, designed to help maximize nutrition delivery while enhancing aseptic technique.

NeoMed has partnered with Smiths Medical to provide an enteral ready pump. Once installed, the NeoMed Enteral Library can be used for both Legacy and NeoConnect® syringes. This enteral pump solution adheres to The Joint Commission's recommendation, which states, "Use distinctly different pumps for IV applications" and "Do not use IV tubing or pumps for enteral feeding." Orange and purple faceplate options are available to color coordinate with NeoMed's Enteral Safety System, offering visual distinction from common parenteral or IV lines.

Vice President of Business Development, Marc Waldman, stated, "Optimal nutrition delivery always remains at the forefront of our product design. It is our hope that the 100 mL syringe will replace costly feeding bags that may not deliver maximum macronutrients, micronutrients, and lipids to the patients that need them most."

Vice President of Engineering and Product Development, Ben Davis, said, "We are so pleased to now offer the largest enteral syringe that is available for use with Medfusion pumps. Previously, 60 mL was the largest volume that could be administered on a Medfusion pump using a single syringe. Now, a volume of up to 100 mL can be administered with a single syringe on the same pump. This supports improved patient outcomes and eases workflow for the clinicians providing care to these patients."

For ordering information, contact your NeoMed regional account manager, visit www.neomedinc.com, or call 888-876-2225.

About NeoMed, Inc.

Founded in 2007, NeoMed develops innovative enteral collection and delivery products supporting the specialized feeding and medication dosing needs of the low birth weight, neonatal, and pediatric patients. With 148 successful ENFit transitions representing over 15 million administered feed and medication doses, NeoMed is committed to improve patient outcomes through product designs that meet safety, clinical, and regulatory guidelines while supporting cost-containment objectives.

Disclosure: NeoMed has provided support to NT in exchange for placement of this news item.

NΤ

# "Baby Steps to Home, Second Edition" Released

The National Association of Neonatal Nurses (NANN) is proud to announce a new edition of Baby Steps to Home, now available at http://www.babystepstohome.

First launched in 2014 and funded by a grant from the Preemie Healthcare Coalition, Baby Steps to Home was created as a free resource for NICU providers and parents, standardizing the discharge pathway and education given to parents during their NICU journey. This pathway and education about their baby's condition helps to prepare parents to take their baby home.

The design of the pathway begins on admission, with incremental topics to be covered as the baby's care progresses, so that parents are better prepared to take their baby home. In each step, nurses and providers will find evidenced-based PDFs for their own information, so that messaging to parents is more standardized. These are accompanied by easyto-understand, documents that can be edited with each unit's logo and then printed and handed to parents during or following a discussion. The parent-focused content discusses common issues and diagnoses parents may encounter while their baby is in the NICU, suggests questions to ask their baby's provider, and provides practical information and tips parents will need now and after discharge.

The new edition offers revisions to 85% of the handouts and the addition of 19 new provider and parent handouts, including:

- Newborn screening and critical congenital heart defects screening
- Postpartum depression
- · 6 new diagnoses, including Neona-

- tal Abstinence Syndrome and Microcephaly
- 6 new medications
- New section on procedures
- Updated and expanded resources section

This 2018 edition was edited by Rebecca South, BSN, RNC-NIC, a NICU nurse at Texas Health Resources Plano in Plano, Texas and Suzanne Staebler, DNP, NNP-BC, FAANP, FAAN, a Clinical Professor at the Nell Hodgson Woodruff School of Nursing at Emory University.

#### NΤ

# Leading organizations in prenatal screening and diagnosis issue new consensus statement on genome sequencing

Joint statement on "The use of diagnostic genome-wide sequencing for fetal diagnosis."

January 9, 2018, Washington DC - Prenatal screening and testing has changed dramatically since the 1970's. The introduction of ultrasound technology and the more recent completion of DNA sequencing of the human genome have led to tremendous advances in prenatal diagnosis. With the availability of genomic sequencing, much more detailed genetic information related to the fetus can now be uncovered. As DNA technologies are developed and applied to prenatal testing, unique challenges and questions arise about their applicability to various populations. In response, three national organizations issued a joint position statement today entitled, "The use of diagnostic genomewide sequencing for fetal diagnosis."

The joint position statement was published today online in Prenatal Diagnosis and was issued jointly by the International Society for Prenatal Diagnosis (ISPD), the Perinatal Quality Foundation (PQF), and the Society for Maternal-Fetal Medicine (SMFM).

The more comprehensive information that

is available with sequencing can improve the ability to uncover the cause of birth defects, but the practice is not without challenges and complexities that need to be considered. Outlined in greater detail in the newly released position statement, the consensus opinion for when the genome-wide testing should be considered are summarized:

- DNA sequencing is beginning to be used for the evaluation of fetuses with suspected genetic disorders for whom standard chromosomal testing has already been performed and is uninformative. In some cases, sequencing may be offered concurrently with standard testing when expert genetic opinion determines that is unlikely to identify a cause for the presenting fetal phenotype.
- Routine use of genome-wide sequencing as a diagnostic test is not currently recommended due to insufficient validation data and knowledge about the benefits and pitfalls.
- Testing is currently best done in trios (both parents and the fetus). Parents require genetic experts to provide pre- and post-test counseling and for result disclosure; many specific counseling points are recommended as minimal for the informed consent process and to enhance the patient/ parent understanding.
- 4. The indications that might warrant consideration of prenatal genomic testing include: a fetus with ultrasound-identified anomalies that might suggest a genetic etiology, but the standard genetic testing has not identified the cause; cases in which expert genetic consensus suggests a high likelihood of a genetic etiology; couples with a previous affected fetus, stillbirth or child with no genetic diagnosis and the identification of a recurrent pattern of anomalies in a new pregnancy.
- A list of laboratory recommendations for consistent test quality, DNA variant interpretation, and return of results to parents are listed in the new position statement.

"In an effort initiated by the Position Statement Committee of ISPD, representatives from the three organizations, ISPD, PQF and SMFM, recognized the importance of

a shared, consistent message to health-care providers about the application of new technologies to prenatal and perinatal care," said Ignatia Van den Veyver, MD, a maternal-fetal medicine specialist, ISPD President and co-author of the position statement. "This resulted in a productive, collaborative effort to develop this joint position statement. We envision this as the beginning of similar future collaborations that will benefit prenatal care providers and patients in the current rapidly evolving genomic era."

#### About ISPD

The International Society for Prenatal Diagnosis (ISPD) was founded in 1996 to address the need to advance the medical practice and science of prenatal diagnosis and therapy by bringing together a global multidisciplinary group of medical and scientific professionals with interests and expertise in a diverse array of clinical and research aspects of prenatal diagnosis and fetal care. While ISPD focuses on all areas relevant to this field, the Society has a unique focus on and expertise in reproductive and prenatal genetic screening and how this aspect of care integrates with other disciplines of prenatal diagnosis. ISPD's vision is that evidence-based practice and culturally sensitive preconception and prenatal screening, diagnostics and therapy shall be available to all families. ISPD hosts an annual conference dedicated to discussing the latest in the field. For more information, please visit http://www. ispdhome.org.

#### About PQF

The Perinatal Quality Foundation is an independent non-profit foundation incorporated in 2004. The mission of the Perinatal Quality Foundation is to improve the quality of obstetrical medical services by providing state of the art educational programs, and evidence-based, statistically valid monitoring systems to evaluate current practices and facilitate the transition of emerging technologies into clinical care. The strength of the PQF is its ability to bring together experts and leaders devoted to maternal and fetal health to reflect on, select, and implement programs to facilitate quality perinatal patient care.

#### About SMFM

The Society for Maternal-Fetal Medicine (est. 1977) is a non-profit membership organization representing the interests of obstetricians/gynecologists who have additional formal education in maternal-fetal medicine. The Society is devoted to reducing highrisk pregnancy complications by providing continuing education to its more than 2,000 members on the latest pregnancy assessment and treatment methods. It also serves as an advocate for improving public policy and expanding research funding and opportunities for maternal-fetal medicine. SMFM hosts an annual scientific meeting in which new ideas and research in the area of maternal-fetal medicine are unveiled and discussed. For more information, visit http://www.smfm.org.

NT

## BRETT TASHMAN FOUNDATION

Making DSRCT History

#### The 3rd Annual Brett Tashman Foundation Golf Tournament

June 30, 2018 Sierra Lakes Golf Club Fontana, California

### HURRY AND RESERVE YOUR SPOT TODAY FOR OUR ANNUAL GOLF TOURNAMENT. REGISTRATION CLOSES SOON!

The tournament will take place Saturday, June 30, 2018 at Sierra Lakes Golf Club in Fontana, California,

beginning promptly with a shotgun at 7:30 a.m. Golf, including lunch and a gift bag with wonderful gifts from donors such as a Cancun stay (pay only taxes & registration fee), is reasonably priced at \$150. If you are not a golfer, please join us for the luncheon starting at 1 p.m for \$60. The luncheon includes a gift bag and full access to our silent auction and raffle. A sampling of some of the many hotels to bid on: Beverly Hills Marriott, The Phoenician, Snowbird Resort, and the Inn at Playa del Rey. Also get ready to bid on one of a kind items, Southwest Airlines, sports tickets including UCLA, golf equipment, foursomes at the Terranea and Porter Valley, amusement parks, sports memorabilia, fun activities, and numerous restaurants.



Who will be the winning bidder of this luxurious 4-night all-inclusive destination?

- There will also be great on-course contests, including a hole in one prize of a Chevy Malibu sponsored by Rotolo Chevrolet.
- We are adding monetary sponsors' logos to our website as they come in:
   http://thebretttashmanfoundation.org/join-us/event-sponsors/

   If you would like to join us as a sponsor, please check
   thebretttashmanfoundation.org
   or email Dr. Lauren Tashman at tash5@aol.com.
   You may also call 909.981.1530 for additional information.
- All proceeds support The Brett Tashman Foundation's efforts in funding research to find a cure for Desmoplastic Small Round Cell Tumor (DSRCT), a deadly cancer.

#### **Purchase Tickets**

We look forward to seeing you on June 30th! With Gratitude,

The Brett Tashman Foundation



# FROM THE NATIONAL PERINATAL INFORMATION CENTER: Adverse Outcome Index, Updated 2017

Janet H. Muri. MBA and Susan Mann. MD

Ms. Muri has been with the National Perinatal Information Center since 1986 and it's President since 2007. Ms. Muri oversees all collection, processing and analysis of clinical and financial data submitted by NPIC member hospitals and other state, federal and private data sources related to contract work. She is the principal on many of the NPIC contracts including the Defense Health Agency Perinatal Performance Information Project, the Georgia Regional Perinatal Care Network project and the Alliance for Innovation in Maternal Health (AIM).

Dr. Mann is a practicing Obstetrician/Gynecologist at Beth Israel Deaconess Medical Center for the past 30 years. She is Director of Team Training and Simulation for the Obstetrics and Gynecology Department. Dr. Mann is a researcher in Quality Improvement in Obstetrics and Gynecology, Multidisciplinary Teamwork, and Healthcare system engineering. She has created the QualBridge Institute to help institutions identify opportunities for improvement and assist in the creation of solutions including strengthening communication and improving teamwork between providers of care

The National Perinatal Information Center (NPIC) is driven by data, collaboration and research to strengthen, connect and empower our shared purpose of improving patient care.

For over 30 years, NPIC has worked with hospitals, public and private entities, patient safety organizations, insurers and researchers to collect and interpret the data that drives better outcomes for mothers and newborns.

**Background:** The Adverse Outcome Index (AOI) is a set of three composite measures designed to measure the volume and magnitude of ten adverse events that may occur during the delivery process and potentially expose a perinatal team to malpractice liability. The events were selected by the original developers, because they were deemed definable, and possibly modifiable, through improved team training and communication.

In 2001, a panel of experts from the American College of Obstetrics and Gynecology (ACOG), the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN), The Society for Obstetric Anesthesia and Perinatology (SOAP), the Armed Forces Institute of Pathology (AFIP), the US Navy Bureau of Medicine and Surgery (BUMed), the Office of the Surgeon General - US Army, TRICARE Management Activity (the US military health system), and participants from the hospitals selected for a team training study co-sponsored by the Department of Defense, the Risk Management Foundation of the Harvard Medical Institutions, and the Beth Israel Deaconess Medical Center Obstetrics/Gynecology Foundation selected the 10 measures (6 maternal and 4 neonatal) from a larger panel of events. Through a rigorous consensus process, each event was assigned an appropriate "weight" reflecting the relative degree of severity of the event. For example, "maternal death" has the highest severity weight (750), perineal laceration the lowest (5). The sum of the weights of all other events is equal to the severity weight for maternal death.

The 10 adverse events with assigned weights are:

In-hospital Maternal Death	750
In-hospital Neonatal Death ≥ 2500 grams and ≥ 37 Weeks Gestation	400
Uterine Rupture During Labor	100
Maternal Intensive Care	65
Birth Trauma	60
Unanticipated Operative Procedure	40
Admission to NICU of Neonate Birthweight ≥ 2500 grams and ≥ 37 Weeks Gestational Age for > 1 Day	35
APGAR 5 < 7	25
Maternal Blood Transfusion	20
4th Degree Perineal Laceration	5

In 2005, NPIC worked with the original developers of the AOI to translate the previously manually collected data variables into an algorithm that could be applied to the administrative data set thereby expediting the calculation of the AOI on historic data for baseline rates, during a team training/QI initiative and during the post-monitoring period to sustain improvement.

Unlike most outcome measures that only reflect mother or baby, the AOI profiles the delivery dyad and the three composite measures each reflect a different way for hospital quality leaders to think about adverse events.

**THE ADVERSE OUTCOME INDEX (AOI):** The number of patients with one or more identified adverse events, divided by the total number of deliveries.

THE WEIGHTED ADVERSE OUTCOME SCORE (WAOS): The total weights of all the adverse events, divided by the total number of deliveries.

**THE SEVERITY INDEX (SI):** The total weights of all the adverse events, divided by the number of patients with an adverse event. (Note: each delivery is only counted once, but each event is counted.)

**2017 Update:** The introduction of ICD-10 coding in October 2015 required a review of the entire AOI algorithm in order to ensure all complications and co-morbidities were being captured and certain "Present on Admission" complications were not incorrectly attributed to the L&D team.

Each measure was updated to ensure alignment with code changes; some measures underwent more notable changes so as to align with quality improvement initiatives in Maternal Child Health, and feedback from the field regarding opportunities to make the AOI more responsive to variations in case mix across hospital populations.

NPIC worked extensively with Susan Mann, MD, one of the original AOI developers, to refine and update the algorithm to Version  $^4$   $^{\circ}$ 

#### Highlights of those changes on the maternal side include:

Maternal Intensive Care (formerly Maternal Admission to the ICU): Numerator cases reflect mother with a CDC defined Severe Maternal Morbidity (SMM) code. Denominator cases are delivered women excluding those with a placental disorder or with a SMM and Present on Admission (POA) code.

Unanticipated Operative Procedure: Added denominator exclusions of placental disorders, cervical cancers and hysterectomy with ICU admission.

Maternal Blood Transfusions: Updated code list to align with SMM blood transfusion code list.

4<sup>th</sup> Degree Perineal Laceration (formerly 3<sup>rd</sup> or 4<sup>th</sup> Degree perineal Laceration): Removed 3<sup>rd</sup> degree perineal lacerations.

#### For the newborn, the changes included:

In-hospital Neonatal Death  $\geq$  2500 grams and  $\geq$  37 Weeks Gestation: Changed from death within 7 days to death within 28 days and updated the excluded congenital anomalies list to mirror those excluded from NQF #716 Unexpected Complications in Term Newborns, formerly known as Unexpected Newborn Complication (UNC).

(month, year etc.). None of the weights assigned to an event were changed but the shift away from the proportion of lower weighted events (lacerations) and possibly picking up more inborn deaths (the second highest weighted) item, likely explains the increase in range and rate in the WAOS.

The Severity Index (SI) reflects the degree of severity of adverse events within the cohort of cases with an event. The SI increase between V3.0 and V4.0 is likely driven by the same changes mentioned in the WAOS compounded by the fact that there are fewer cases in the denominator with the removal of 3<sup>rd</sup> degree lacerations, not offset by increases in other categories.

Future Opportunities: The AOI composite of metrics have been used for years by NPIC members but also in our work with AHRQ, Premier, Defense Health Agency, Maryland Patient Safety Initiative etc. and by individual hospitals nationwide who want a simple, straightforward algorithm that can be run against the administrative data set and requires no manual abstraction.

V4.0 improves on some of the previously voiced critiques of the AOI and provides alignment with a number of the other nationally

	V3.0	V4.0
Adverse Outcome Index (AOI)		
Range	.026086	.016088
Comparative Rate	.053	.042
Target	.036	.024
Weighted Adverse Outcome Score (WAOS)*		
Range	.54 - 2.38	.59 - 3.25
Comparative Rate	1.42	1.54
_ Target	.87	.88
Severity Index (SI)		
Range	20.34 - 34.11	31.25 - 47.16
Comparative Rate	26.52	36.56
Target	23.96	36.13

Birth Trauma: Numerator cases align with the UNC definition of Severe Birth Trauma.

Admission to NICU of Neonate Birthweight  $\geq$  2500 grams and  $\geq$  37 Weeks Gestational Age for > 1 Day: Denominator aligns with UNC congenital anomaly exclusions as well as inborns affected by maternal drug and alcohol use.

APGAR 5 < 7: Denominator aligns with UNC congenital anomaly exclusions as well as inborns affected by maternal drug and alcohol use.

The above table displays the impact on the range, rates and target as a result of updating the AOI from V3.0 to V4.0 (Version 2.0 only reflected minor coding updates). The Target rate reflects the rate for the top quartile of NPIC members contracting for the quarterly AOI Reports.

The AOI Comparative and Target rates reflect the number of cases with an adverse event. The drop from V3.0 - V4.0 would be expected with the elimination of  $3^{\rm rd}$  degree lacerations offset perhaps by a small increase with the capture of neonatal in-hospital deaths within 7 to 28 days.

The Weighted Adverse Outcome Score (WAOS) is the sum of the event weights divided by the number of deliveries for the quarter

accepted perinatal metrics. There are still opportunities remaining, including robust case mix alignment by hospital level of care and modification for rural or critical access hospitals. A previously applied predictive model showed promise when applied to a limited cohort of hospitals; testing on a larger, longitudinal data set may unlock the key to proactively preventing/mitigating serious adverse events.

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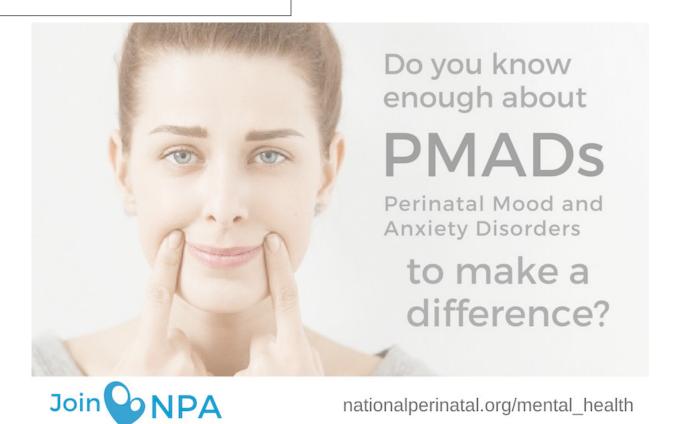
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# Abstracts from the Advances in Therapeutics and Technology Meeting on April 2-6, 2018 in Snowbird, Utah

Donald Null, MD, Mitchell Goldstein, MD, Arun Pramanick, MD, and Steven Derdack, DO

The 35th Annual Advances in Care Conference – Advances in Therapeutics and Technology: Critical Care of Neonates, Children, and Adults (formerly: High-Frequency Ventilation of Infants, Children & Adults) will present high quality education and networking opportunities to healthcare professionals who provide care for critically ill neonatal, pediatric, and adult patients with a focus on advances in therapeutics and technologies. Along with featured speakers, the conference includes abstract presentations on research on advances in these areas.

Every year abstracts for presentation at its annual meeting. Accepted abstracts are also published in Neonatology Today. The conference agenda can be found on the next page.

#### 2018 Awards

#### Jack Haven Emerson Award for MD or PhD research

Neonatal Abstinence Syndrome: A Family Centered Approach in a Community Hospital Authors: Lisa Z. Klein DNP, CNS, RNC-OB, RNC-LRN, CCRP, Bridget Buckaloo MSN, RN, Nancy Forsyth NNP, Theresa Crowson, RNC-OB, Ann Regacho BSW. Women's and Children's Services, Beebe Healthcare, Lewes DE

#### Applied and Basic Research

The Use of Weighted Blankets in the Care of Infants with Neonatal Abstinence Syndrome. Virginia Summe, RN; Margaret Eichel MSN, RN, RNC-NIC; Rachel Baker, PhD, RN, CPN TriHealth: Good Samaritan Hospital, Cincinnati, OH

#### ATT2018-1

Adjunct use of Mechanical Ventilation and Veno-venous ECLS in a Model of Prolonged Field Care and Ground and High-Altitude Evacuation

Brendan M. Beely, RRT1; Teryn R. Roberts, MS1; Vitali Karaliou, MD1; Daniel S. Wendorff1, George S. Harea1; Kyle N. Sieck1; Teryn R. Roberts, MS1; Jae H. Choi, PhD, DVSc1; Leopoldo C. Cancio, MD2; Valerie G. Sams, MD3; Andriy I. Batchinsky, MD1 1The Geneva Foundation, Tacoma, WA; 2United States Army Institute of Surgical Research, JBSA Ft. Sam Houston, TX; 3San Antonio Military Medical Center, JBSA Ft. Sam Houston, TX

Introduction: Realities of the multidomain battlefield of the future dictate the need for new life saving interventions able to support life functions during extended care in place and during prolonged field care (PFC) and aeromedical evacuation. Extracorporeal life support (ECLS) is a potential treatment of choice for PFC as it can provide cardiovascular and pulmonary function, and stabilize patients during various stages of aeromedical evacuation. We previously showed that adjunct use of mechanical ventilation (MV) and a small ECLS system permits reductions in injurious ventilator settings and sustains animals with ARDS due to smoke inhalation and burns for over 72 hours. Here, we analyzed MV as an adjunct therapy to ECLS in a model of combat relevant ARDS due to bilateral pulmonary contusion, intracavitary hemorrhage, resuscitation in a 48-hour ground and high-altitude evacuation model.

We hypothesized that veno-venous ECLS permits reductions in mechanical ventilation during aeromedical evacuation.

Methods: Female Yorkshire swine (54.2±1.2 kg, n=15) were anesthetized and surgically prepared for study. On Day 1 animals received MV at 10 mL/kg (Draeger V500, Draeger Medical, Lubeck, Germany) and ECLS via a 23Fr. bi-caval Avalon catheter placed in the right jugular vein and connected to the Cardiohelp (Getinge GmbH, Rastatt, Germany) ECLS system. Once ECLS was initiated, MV support was reduced proportionally to maintain normoxia and normocarbia. Next, animals underwent ground transportation to the adjacent building and high-altitude chamber using the MERK (Smeed Technologies, Cumming GA) equipment platform. Next, in uninjured state the animals underwent a 3-hour flight at 5k, 8k, and 30k ft. followed by ground transport back to our animal ICU where the animals were maintained overnight. On Day 2, after discontinuation of heparin, animals received bilateral pulmonary contusion using a modified captive-bolt stunner (Model ML, Karl Schermer, Omaha, NE). Next the transport and flight were repeated as in Day 1. For all phases of travel, MV was provided either by the SAVeII (n=11; Automedx, Coppell, TX) or the EMV+731 (n=4, Zoll Medical, Chalmsford, MA). Data are means ± SEM

	Day 1				Day 2		
	BL	Post ECLS	Evacuation	30K	Post Injury	Evacuation	30K
ECLS Blood Flow	N/A	1.05±0.07	1.28±0.04†	1.29±0.12	1.47±0.17	1.86±0.06	1.88±0.01
RR	15.2±0.6	9.27±0.64*	9.94±0.21*	10.36±0.8*	15.47±2.17	11.3±0.24*	11.0±0.76*
$V_{E}$	8.16±0.26	4.30±0.44*	5.04±0.2*	5.13±0.66*	4.86±0.74	4.47±0.16	4.38±0.56
V <sub>T</sub> /Kg	10.01±0.01	7.70±0.32*	7.65±0.17*†	8.26±0.47*	6.55±0.67	6.13±0.16	6.11±0.48
PFR	398±14	358±17	353±10†	263±66	269±43	174±10*	61±8*
Art pH	7.47±0.01	7.55±0.02	7.55±0.01†	7.60±0.04	7.44±0.02	7.39±0.01	7.41±0.04

Table 1 – Selected means±SEM from animals supported with reduced MV as adjunct to ECLS, \* significant difference compared to BL (day 1) or PI (day 2); † significant difference between days; p<0.05.

Results: Data are shown in Table 1.

Conclusion: VV-ECLS permitted a reduction in minute ventilation and sustained cardiovascular and pulmonary support during PFC and evacuation of animals with combat relevant trauma.

#### ATT2018-2

Pulmonary interstitial emphysema in premature infants: old enemy of new generation

Authors: Bhatt P, Kibe R, Barton L, Ramanathan R, Biniwale M PURPOSE OF THE STUDY:

Pulmonary interstitial emphysema (PIE) is a severe complication of mechanical ventilation in preterm infants that may lead to air leakage and/or bronchopulmonary dysplasia (BPD). We compared the characteristics of premature infants developing PIE at two time frames block 1 (2001-2008) and block 2 (2009-2016). We also compared the risk associated with infants developing PIE with infants of similar gestation.

#### METHODS:

This was a retrospective cohort study from 2001 to 2016 at a level 3 neonatal intensive care unit. The infants in block 1 were compared to block 2 to assess changes in characteristics of developing PIE in two time periods. Infants in block 2 were then compared to infants of similar gestational ages without PIE to find risks associated with PIE. Stepwise logistic regression analysis performed using IBM SPSS version 24 software.

#### **RESULTS:**

A total of 77 patients developed PIE during the last 16 years. Incidence of PIE was comparable in both blocks with 44 (9.7%) developing in block 1 compared to 33

(10.3%) in block 2. Infants with block 2 had lower mean gestational age (24.5 wk vs 25.4 wk; p < 0.020) as well as birth weight

#### 35th Annual Conference

# Advances in Therapeutics and Technology: Care of Critically Ill Neonates, Children, and Adults The Cliff Lodge and Spa in Snowbird, UT

April 3, 2018

Time	Title	Speaker
3:00pm- 5:00pm	Pre-registration Cliff Lodge Meeting Room	
	Abstract Presentations: Moderated by Arun Pramanik, MD	
5:00pm	Opening Remarks	Arun Pramanik, MD
5:20pm	Continuous Infusion of IGF-1 Protein Complex for 3 Days Does Not Harm the Lung of Mechanically Ventilated Preterm Lambs	M J Dahl et al Univ. of Utah
5:40pm	Structural Development of the Brain of Former Preterm Lambs with Behavioral Defecits	K Albertine et al Univ. of Utah
6:00pm	<b>Special Lecture</b> Respiratory Syncytial Virus Update 2018: Still a Threat.	Mitchell Goldstein, MD
7:00pm	Conclusion	

#### 35th Annual Conference Advances in Therapeutics and Technology: Care of Critically Ill Neonates, Children, and Adults April 4, 2018

Wednesday Morning Session

Time	Title	Speaker		
7:00am-	Continental Breakfast			
8:00am	Vendors: Magpie Room			
	Registration: Cliff Ballroom			
	Presentations: Moderated by Stephen Derdak, DO			
8:00am	The International Children's Advisory Network: A Novel Approach to Youth and Family Engagement	Charles Thompson		
8:30am	Stabilizing Minute Ventilation Using a Fixed Servo Pressure in High-Frequency Jet  Ventilation	J Goldstein Brown University		
8:45am	Determination of Optimal Endotracheal Tube Tip Depth from the Gum in Neonates by X-ray and Ultrasound	D. Kurepa et al Cohen Children's Medical Center NY		
9:00am	Special Panel Discussion What is/should be the Role of Industry (representatives) in the Hospital and/or Your Practice	Colleen Kraft, MD., FAAP President AAP plus selected others		
10:15am	Break			
10:45am	The Use of Mini Bronchial Alveolar Lavage (Mini-BAL) as Part of a Neonatal Antibiotic Stewardship Program	T Iannetta et al Mott Children's Hospital Ann Arbor MI		
11:05am	Special Lecture Antibiotic Stewardship	Arun Pramanik MD		
12:05pm	Break			

#### 35<sup>th</sup> Annual Conference Advances in Therapeutics and Technology: Care of Critically Ill Neonates, Children, and Adults April 4, 2018

Wednesday Evening Session

Time	Title	Speaker		
Light Refreshments/Vendors  Magpie Room				
	Presentations: Moderated by Donald Null, MD			
5:00pm	<b>Special Lecture</b> New Priorities in Combat Casualty Care.	Michael Davis MD Director Combat Casualty Care Research Program		
	Introduction of a round table on prolonged field care and aeromedical evacuation.	Andriy Batchinsky MD		
6:00pm	Special Lecture  Lung Growth and Development Early in Life	Robert S. Tepper, MD		
7:00pm	Conclusion			

#### 35<sup>th</sup> Annual Conference Advances in Therapeutics and Technology: Care of Critically Ill Neonates, Children, and Adults April 5, 2018

Thursday Morning Session

Time	Title	Speaker
7:00am-	Continental Breakfast/Vendors	
8:00am	Magpie Room	
	Presentations: Moderated by Mitchell Goldstein, MD	
8:00am	Point of Care Ultrasound in Diagnosis, Treatment and Follow-up of Neonatal Peripheral Intravenous Extravasation Injuries	D Kurepa Cohen Children's Medical Center NY
8:15am	Special Lecture Use of pulse oximeter to screen Critical Congenital Heart Disease	Mitchell Goldstein MD
9:15am	Workshop #1	
10:05am	Break Refreshments/Vendors: Magpie Room	
10:35am	Workshop #2	
11:15am	Workshop #3	
12:05pm	Break	

#### 35th Annual Conference Advances in Therapeutics and Technology: Care of Critically Ill Neonates, Children, and Adults

April 5, 2018 Thursday Evening Session

Time	Title	Speaker		
4:00pm- 5:00pm	Light Refreshments/Vendors  Magpie Room			
	Presentations: Moderated by Donald Null, MD			
5:00pm	The Lighter Side of High Frequency Venmtilation: Fluid and Pressure Mechanics with Heliox	A Pulak et al Loma Linda Univ Children's Hospital CA		
5:15pm	Ambient Noise Production by High-Frequency Neonatal Ventilators	J Goldstein et al Brown University RI		
5:30pm	Neonatal Neuroimaging after Repair of Congenital Diaphragmatic Hernia Predicts Two- Year Neurodevelopmental Outcome	J Gunn PhD et al Royal Children's Hospital Melbourne Australia		
5:45pm	Pulmonary Interstitial Emphysema in Premature Infants: Old Enemy of New Generation	P Bhatt et al LAC+USC Medical Center/Children's Hospital, LA CA		
6:00pm	Presentation of the 25th Annual Jimmy Schulz Award			
6:05pm	Presentation of the 20th Annual Jack Emerson Award	l		
6:10pm	Special Lecture 21 <sup>th</sup> Robert deLemos Memorial Lecture Management of Pulmonary Hypertension in Infants and Children Beyond the Neonatal Period	Steven Abman, MD		
7:10pm	Conclusion			



# Advances in Therapeutics and Technology: Critical Care of Neonates, Children, and Adults

Formerly: High-Frequency Ventilation of Infants, Children & Adults

#### 35<sup>th</sup> Annual Conference Advances in Therapeutics and Technology: Care of Critically Ill Neonates, Children, and Adults April 6, 2018

Friday Morning Session

Time	Title	Speaker				
7:00am-						
8:00am	8:00am Magpie Room					
Presentations: Moderator Andriy Batchinsky MD Special session: Round table: Prolonged field care and aeromedical Evacuation						
8:00am	Extracorporeal life support as a platform intervention in prolonged field care	Andriy Batchinsky MD				
8:10am	A Novel Training Platform for Life-Saving Interventions During Prolonged Field Care	D S Wendorff Geneva Foundation				
8:25am	New Approaches to Anticoagulation Management; Changes in ECLS Outcome in a Single Center	Philip Spinella MD Geneva Foundation				
8:50am	Special Lecture Disturbances of Coagulation during Extracorporeal Life Support	Andre Cap. MD, PhD				
9:35am	Prolonged Field Care through the Lens of Norwegian Special Forces	CDR Geir Strandenes				
10:15am	Break					
10:35am	Adjunct use of Mechanical Ventilation and Veno-venous ECLS in a Model of Prolonged Field Care and Ground and High-Altitude Evacuation	B M Beely et al Geneva Foundation				
10:50am	Effects of Temperature Correction on main Arterial Blood Gas Valuesin a Combat Relevant Model of Lung Injury Treated with Therapeutic Hypothermia	Andriy Batchinsky MD				
11:00am	Special Lecture Strategies to Achieve a Successful Quality Improvement Initiative	Jeffrey Gould, MD				
12:00pm	Break	1				

#### 35<sup>th</sup> Annual Conference Advances in Therapeutics and Technology: Care of Critically Ill Neonates, Children, and Adults April 6, 2018 Friday Evening Session

Time	Title Speake					
4:00pm-						
5:00pm	Magpie Room					
	Presentations: Moderated by Arun Pramanik, MD					
5:00pm	SPECIAL LECTURE	James B Fink PhD, RRT, FCCP				
	Role and Delivery of Aerosol Therapy in Pulmonary	No CE offered				
	Critical Care					
6:00pm	Special Presentation Sequelae of Preterm Lung Disease in Adolescents and Adults	Stephen Derdak DO				
7:00pm	Why is HFVP so Successful and Where is it Going	G. Sarduci				
7:10pm	Conclusion					

# 35th Annual Conference Advances in Therapeutics and Technology: Care of Critically Ill Neonates, Children, and Adults April 7, 2018 Saturday Morning Session

Time	Title	Speaker					
7:00am-8:00am	Continental Breakfast/Vendors Magpie Room						
	Presentations: Moderated by Arun Pramanik, MD						
8:00am	Preterm Birth and 3 Days of Mechanical Ventilation Appear to Reduce Capillary Surface Density in Brain White Matter of Lambs	L. Pettit et al Univ of Utah					
8:15am	Histone Deacetylase Inhibitor Analog, M4PTB, Improves Alveolarization in the Lung of Mechanically Ventilated Preterm Lambs	MJ Dahl et al Univ of Utah					
8:30am	Using Orange Juice for IV Fluid Resuscitation, is Normal Saline the Best Choice for Volume Replacement?	M Goldstein et al					
	The Effects on Humidity When the Temperature Probe is not Placed Proximal to the Patient Wye	J Wright					
8:45am	Pop-Off Pressure is Dependent on Maintenance of Flow	M Goldstein et al Loma Linda Children's Hospital					
9:00am							
9:15am	Break						
9:30am	Special Lecture Noninvasive/Less Invasive Ventilation and Appropriate Patient Selection	Donald Null MD					
10:30am	Conference Summary an Closing Remarks	Donald Null, MD					
10:45am	Thank you!						



(629 g vs 762 g; p < 0.003). All the neonatal morbidities including survival were similar in both groups. All the infants in second block were less than 28 weeks gestation, which were then compared to infants without PIE. Logistic regression controlling for gestational age revealed most important factor was need for invasive ventilation at 24 hours (p < 0.029). More infants with PIE needed increased duration of invasive ventilation (p<0.001) and developed BPD (P < 0.034). Other gestational age adjusted neonatal morbidities and mortality were not significantly different. CONCLUSION:

Infants with lower gestational age and weight are still at risk for developing PIE. The risk factors for PIE in preterm infants was invasive ventilation at 24 hours. Main consequence is prolonged invasive ventilation leading to BPD.

#### ATT2018-3

IHistone deacetylase inhibitor analog, M4PTB, improves alveolarization in the lung of mechanically ventilated preterm lambs. Dahl, M J.1; Wang, Z M.1; Null, D2; Yoder, B A.1; deCaestecker, M3; Hukriede, Neil A.4; Albertine, KH1. 1. Pediatrics, University of Utah, Salt Lake City, UT, United States. 2. Pediatrics, UC Davis, Davis, CA, United States. 3. Medicine, Vanderbilt University, Nashville, TN, United States. 4. Developmental Biology, University of Pittsburgh, Pittsburgh, PA, United States.

Background: Neonatal chronic lung disease (CLD) is characterized by alveolar simplification and altered expression of genes associated with mesenchymal thinning and vascular formation. Both characteristics are associated with histone (H) 3 hypoacetylation and DNA hypermethylation in lung tissue. Our previous studies using chronically ventilated preterm lambs treated with histone deacetylase inhibitors (HDACi) valproic acid or trichostatin A showed that preserving histone acetylation improves alveolar formation and rectifies gene expression in the lung. However, valproic acid and trichostatin A have toxic and teratogenic potential. We recently reported that the histone deacetylase inhibitor analog, M4PTB, improved respiratory gas exchange parameters in mechanically ventilated lambs.

Objective: We hypothesized that an HDACi analog that enhances recovery after acute kidney injury without toxic or teratogenic effects in zebrafish larvae and mice, and improves respiratory gas exchange parameters in preterm lambs, will improve alveolarization in chronically ventilated preterm lambs.

Design/Methods: Preterm lambs (~131d gestation; term is ~150d), treated with antenatal steroids and postnatal surfactant and caffeine citrate, were managed by mechanical ventilation (MV). Six preterm lambs were treated once daily with M4PTB (100 mg/Kg, dissolved in olive oil, added to ewe's colostrum that was fed enterally). Six other preterm lambs were similarly fed but without added M4PTB. Respiratory gas exchange was assessed continuously. At the end of 3d, alveolarization was quantified by morphometry and stereology, using systematic uniform random sampling.

Results: Targets of oxygenation (PaO2 of 60-90 mmHg) and ventilation (PaCO2 of 45-60 mmHg) were maintained daily with lower fractional inspired O2 and peak inspiratory pressure among the preterm lambs treated with MV+M4PTB relative to MV alone. No evidence of toxicity was detected. Radial alveolar count (RAC)

Alveolar morphometry and stereology			
Lamb group	RAC (#)	Vv sc (%)	
MV+M4PTB	6.2±1.0*	4.9±2.0*	
MV	4.1±0.2	2.3±1.0	
Mean±SD; n=6; unpaired t-test; *p<0.05			

and secondary septal volume density (Vv sc) were significantly larger (p<0.05; table) among the preterm lambs treated with MV+M4PTB relative to MV alone.

Conclusion(s): These results suggest that the HDACi analog, M4PTB, prevents alveolar simplification, similar to the HDACi valproic acid or trichostatin A, in preterm lambs that are supported by MV for 3d. No evidence of toxicity was detected in the MV+M4PTB group. Thus, M4PTB leads to better alveolar formation and, as we showed previously, better respiratory gas exchange.

#### ATT2018-4

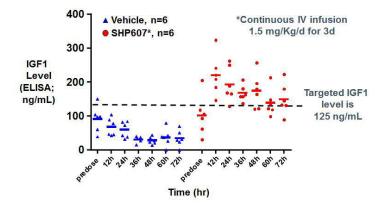
Continuous infusion of IGF1 protein complex for 3 days does not harm the lung or brain of mechanically ventilated preterm lambs. Dahl, M J.1; Zhou, Z2; Keefe, Dennis2; Barton, Norman2; Chung, J-K2; Ward, Robert M.1; Albertine, KH1. 1. Pediatrics, University of Utah, Salt Lake City, UT, United States.2. Shire Pharmaceuticals, Lexington, MA, United States.

Background: Insulin-like growth factor 1 (IGF1) plasma protein levels are low in preterm infants. Previous studies indicate that low IGF1 plasma levels are associated with evolving neonatal chronic lung disease and its comorbidities, including brain injury, in preterm infants.

Objective: We recently reported (EPAS2017:1549.5) that plasma IGF1 protein levels were low (~100 ng/mL) in normal unventilated fetal lambs at ~128d gestation (similar to triangles at "predose" in the figure; ~28w human equivalent) and increased ~2-fold postnatally (~220 ng/mL) in normal unventilated term lambs at ~150d postnatal age (not shown; ~6y human equivalent). We also showed that plasma IGF1 protein level declined in ventilated preterm lambs, regardless of ventilation mode (similar to triangles at 12-72h in the figure). Whether repletion of plasma level of IGF1 protein will be harmful or perhaps improve lung and brain outcomes is not known.

Design/Methods: We measured plasma IGF1 protein level by ELISA (Mediagnost; Reutlinger, GER). Two groups of preterm lambs (n=6) supported by invasive mechanical ventilation for 3d had SHP607 (IGF1/BP3 complex; optimized dose of 1.5 mg/Kg/d) or vehicle (saline) continuously infused intravenously. Respiratory gases were kept in acceptable physiological range, as was plasma glucose. Lung tissue and brain tissue were collected at the end of 3d.

Results: SHP607-treated preterm lambs had elevated plasma IGF1 level (circles results in the figure) that gradually approached the target of ~125 ng/mL (dashed line in the figure). Physiologically, although no statistical differences were detected, some apparent distinctions were apparent. FiO2 and PIP required to maintain physiological oxygenation and ventilation targets were somewhat lower in the SHP607-treated group vs vehicle-treated group. So, too, systemic hemodynamic pressures were somewhat lower and more stable in the SHP607-treated group vs vehicle-treated group. Molecularly, mRNA and protein abundance of apoptotic,



proliferation, or vascular growth molecules in lung or brain were not altered by SHP607 vs vehicle. Structurally, alveolar formation and capillary surface density in the lung, and gray/white matter ratio and capillary surface density in the brain were not altered by SHP607 vs vehicle.

Conclusion(s): Continuous infusion of SHP607 for 3d did not harm preterm lambs or injure their lungs or brain. Longer infusion periods will be necessary to identify outcomes of exogenous IGF complex infusion.

#### ATT2018-5

Developing Aerosols for Critical Care: Infants to adults James B. Fink PhD

Aerogen Pharma Corp., 1660 S. Amphlett Blvd, Suite 360, San Mateo, CA, USA 94402

Summary: Medical aerosols are commonly prescribed for treatment of critically ill patients requiring ventilator support, both on and off the ventilator. To date, no medications have been specifically approved for administration to mechanically ventilated patients. The efficacy of these aerosols are limited by factors such as artificial airways, mechanical ventilatory support, administration of high flow oxygen, respiratory parameters and severity of disease. Aerosol drug approvals (and drug labels) are based on clinical trials conducted with moderately ill patients at home. Both in vitro and in vivo studies reveal that standard jet nebulizer delivery during mechanical ventilation provide lung delivery less of 2 – 3% of dose in adults (< 1% with infants), compared to the 10 - 12 % achieved with devices used in approval trials. In the ICU, patients often require different aerosol delivery devices and delivery strategies (dose volumes and frequencies) than those on their label to achieve desired therapeutic outcomes. With advancements of methods delivery to the lungs > 40% of nominal doses can be delivered to adults and infants lungs during mechanical ventilation. Therapeutic administration of aerosol to the lungs with both low and high flow nasal oxygen have resulted in up to 30% lung dose. These levels of pulmonary drug delivery efficiency should be sufficient to support drug/device development for both intubated and non-intubated adults and infants. These new methods and their implications will be reviewed.

Introduction: The era of modern positive pressure mechanical ventilation began with the Polio pandemics in the 1950s. These ventilators commonly incorporated a pneumatic jet nebulizer, which were used to administer a range of medical aerosols. In 1985, MacIntrye compared distribution of radiolabeled aerosol and lung deposition from a small volume jet nebulizer to intubated mechanically ventilated patients (3%), and spontaneously breathing volunteers (12%).1 This 4 fold difference in lung delivery was the first evidence that standard doses of drug formulations approved for delivery via jet nebulizer to spontaneously breathing ambulatory patients with mild to moderate respiratory disease, may not be sufficient for treatment of mechanically ventilated patients with more severe disease. In 1990, Fuller and Dolovich confirmed low nebulizer deposition in mechanically ventilated subjects, but showed 3–4 fold greater delivery with pMDIs. 2

In the realm of infants, a comparison of radiolabeled aerosol with jet nebulizer and pMDI in 1 – 4 kg infants with bronchopulmonary dysplasia (BPD), during spontaneously breathing and mechanical ventilation.3 In contrast with adults, lung dose was similar (<1 %) between devices and type of breathing. This low deposition frac-

tion is associated with a higher dose/kg than adults at greater delivery fraction, however such low delivery efficiency and relatively high standard deviation may account for the lack of any medical aerosol approved for low gestational and term infants.

Aerosol Drug Delivery for intubated patients

Use of metered dose inhalers, soft mist inhalers, ultrasonic and vibrating mesh nebulisers have been associated with higher aerosol delivery efficiency during CMV than standard jet nebulizers. Ari et al (2010) reported that placement of aerosol generator in the inspiratory limb proximal to a simulated adult resulted in similar inhaled doses for pMDI, USN and VMN (17%) all greater than Jet nebuliser (< 4%). Device placement plays an important role during CMV, resulting in deposition ranging from 4 – 28%. Breath synchronization has been associated with increased inhaled dose vs continuous nebulizer, increasing inhaled dose to greater than 50% in adults.4 In a nonhuman primate model of low birth weight (1 kg) infant mechanical ventilation, Dubus et al (2005), administered radiolabeled aerosol with VMN and JN, reporting a >20 fold greater efficiency with VMN (15%) than JN (0.5%).5

Aerosols to Non-intubated Patients

Critically ill patients have special needs pre and post mechanical ventilation. High respiratory rates, low inspiratory times, high inspiratory flow with low tidal volumes can challenge use of standard aerosol options.

Common strategy is to use standard jet nebulizer via mouthpiece or mask. Dugernier and colleagues reported lung deposition of



Vibrating-mesh nebulizer

	VN-C	JN	p-value
Both lungs (from SPECT-CTanalysis)	34.1 ± 6.0	5.2 ± 1.1	<0.00
Both lungs (from planar analysis)	32.6 ± 10.1	$4.9 \pm 1.0$	0.001
Right lung	$17.9 \pm 2.8$	$2.7 \pm 0.7$	< 0.00
Let lung	$16.3 \pm 3.4$	$2.5 \pm 0.5$	< 0.00
Right/Left lung ratio	$1.12 \pm 0.18$	$1.07 \pm 0.23$	0.159
3D Penetration index			
Right lung	$0.48 \pm 0.19$	$0.48 \pm 0.21$	0.982
Left lung	$0.40 \pm 0.20$	$0.41 \pm 0.17$	0.798
Tracheal area	$5.0 \pm 4.3$	$0.3 \pm 0.4$	0.035
Extrapulmonary fraction			
Oropharyngeal	$4.6 \pm 1.5$	$0.6 \pm 0.2$	0.001
Stomach	$14.5 \pm 6.2$	$1.6 \pm 1.5$	0.001
Lost fraction			
Chamber/Tube + MP	26.6 (21.9-27)	2.0 (1.3-3.2)	0.028
Expiratory filters	$12.3 \pm 4.3$	$21.2 \pm 3.0$	0.028
Nebulizer retention	2.4 (2. 3-2.4)	62.8 (60.5-68.8)	0.008
Pulmonary/extrapulm. deposition ratio	1.93 ± 1.12	3.05 ± 1.92	0.032

4.9 to 5.2% with JN and 32 – 34% with vibrating mesh nebulizer (VN) with valved chamber.6

Figure 1 - Illustration of vibrating-mesh nebulizer with valved reservoir (above) standard jet nebulizer (below) used to administer radiolabeled aerosol to 6 healthy volunteers in crossover design. Imaging outcome of aerosol deposition expressed as percent nominal dose.

Oxygen is commonly administered by nasal cannula to patients, with higher flows used to meet the patients inspiratory flows.

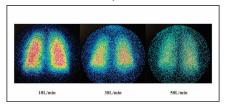
Administration of aerosol via mouthpiece during oxygen administration can reduce lung dose. It would be attractive to administer aerosol with the oxygen. B Bhaysham and colleagues (2008) reported 8 – 28% inhaled dose from a mesh nebulizer administered with humidified oxygen at 3 L/min through a range of nasal cannula sizes. In a phase 1 trial, a system for nasal administration of radiolabeled 7% hypertonic saline aerosol (MMAD< 3 $\mu$ m) reported 40 ± 3% of emitted dose deposited in the lung of adults with 6±3% nasal deposition (Navratil ISAM 2013). Lung deposition was similar to that achieved with mouthpiece administration using a Pari LC Sprint.



The National Perinatal Association (NPA) is an interdisciplinary organization that gives voice to the needs of parents, babies and families and all those interested in their health and wellbeing. Within NPA, parents and professionals work together to create positive change in perinatal care through education, parent programs, professional guidelines and events.

www.nationalperinatal.org

With increasing oxygen and breathing parameters change, the efficiency of standard aerosol options are reduced. It is increasingly

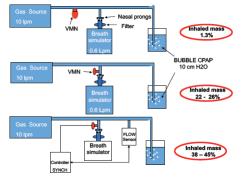


common to administer high flow nasal oxygen (10 - 50 L/min) to hypoxic/dyspneic patients. In vitro and in vivo reports characterize inverse relationships between oxygen flow and inhaled aerosol.,

Figure 2 - Images of aerosol deposition to the lung via high flow nasal oxygen at 10, 30 and 50 L/min representing 1.8%, 3.76% and 2.23%, respectively. 7

#### Nasal aerosol delivery to infant

Infants are obligate nose breathers until 6-9 months, so nasal route for aerosol administration is the preferred route. Placement of the aerosol generator is critical for delivery efficiency. Based on in vitro testing, inhaled dose can range from 1-45% with preterm infants. In the example below continuous aerosol is diluted in the gas flow going to and past the infant. Placement between gas flow and infant increases inhale dose by an order of magnitude, and synchronizing aerosol generation with inspiration results in an



additional 2 fold increase of inhaled dose. Generation of aerosol particles between  $1-3~\mu m$  reduces impactive losses in the delivery system and upper airways, optimizing lung delivery.

Figure 3 - In vitro model of aerosol delivery during nCPAP with vibrating mesh nebulizer operating continuously in the flow from gas source(top) between gas flow and nasal prongs (middle) and synchronization of aerosol with inspiration (bottom) 8

#### Clinical and Commercial implications

The practice of administering inhaled aerosols to intubated during mechanical ventilation and post extubation should be considered "off label use", even with drugs previously approved for inhalation. Label studies for most drugs now approved for inhalation were based on treatment of not very sick adult or larger pediatric subjects at home. Effective administration to the intubated patient often requires a modification in device configuration, dose, and frequency. In addition, a variety of drugs not approved for inhalation have been administered to critically ill patients such antiinfectives, antivirals, prostanoids, anticoagulants, diuretics, surfactants and PFCs. The absence of definitive clinical trials leaves the prescribing clinician at risk with insufficient guidance on indiciation, dose, frequency and optimal method of administration representing a current unmet need for future drug device development. Consequently, there exists an unmet medical need for inhaled medications in intubated and mechanically ventilated infants and adults. As we develop consistent, repeatable and effective methods and technologies for delivering aerosols to critically ill infants and adults, the development of drug/device products for administration to these patients is finally feasible.

Clinical safety and efficacy studies in intubated mechanically ventilated and critically ill patients may be somewhat shorter and less complicated than trials for asthma and COPD drugs for chronic

ongoing use. The typical ventilator patient averages 5 days of CMV, with > 90% of patients off the ventilator after 11 days of mechanical ventilation. Consequently, time of treatment for ventilated target populations would typically be less than 2 weeks, vs 6 months for COPD or asthma trials. In addition, medications are administered by trained professionals at the bedside, reducing issues of adherence and proper technique so common with take home studies, and all ventilated patients are closely monitored, often in the ICU. Shorter trials administered in more controlled conditions can substantially reduce cost and time of product development.

#### Conclusion

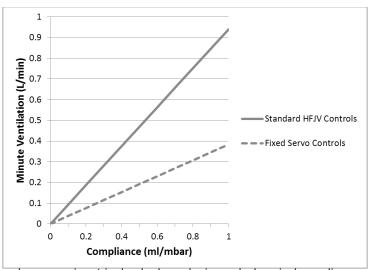
With 20 million patients intubated each year in the US alone, there clearly is unmet medical need to develop drugs and devices for treating these sickest of patients, many with pulmonary related pathologies.

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#### ATT2018-6

Title: Stabilizing Minute Ventilation using a Fixed Servo Pressure in High-Frequency Jet Ventilation

Authors: Justin R. Goldstein, MD; Martin Keszler, MD Institution: Department of Pediatrics, Warren Alpert Medical School at Brown University, Women and Infants Hospital of Rhode Island Background: High-frequency Jet Ventilation (HFJV) is a commonly used form of ventilation for NICU patients. While newer models of conventional ventilators and high-frequency oscillators offer volume-targeted modalities, the Jet ventilator was designed to servo-regulate the amount of gas delivered into the endotracheal tube to maintain a set peak airway pressure, thus mimicking pressure-controlled ventilation. Conventional volume-targeted ventilation stabilizes minute ventilation as lung compliance varies. This reduces drastic fluctuations in blood carbon dioxide levels and decreases incidence of pneumothorax, intraventricular hem-



orrhage, periventricular leukomalacia and chronic lung disease when compared to pressure-controlled modes.

Objective: We performed a bench study to test the hypothesis that operating the Bunnell Life Pulse Jet Ventilator with a fixed servo pressure results in more stable minute ventilation during large changes in lung compliance when compared to the standard HFJV pressure controls.

Methods: A miniature plethysmograph chamber was designed and tested for its ability to measure HFJV minute ventilation and adjust lung compliance within the chamber. Utilizing an excised rat lung, compliance was adjusted while pressure settings were held constant to determine the effect on minute ventilation. Testing was performed using standard jet pressure controls (PIP and PEEP) and fixed-servo pressure controls. Data were analyzed using random intercept mixed models with point estimates and 95% confidence intervals reported.

Results: Ventilators were tested at 4 different control settings for both standard and fixed-servo modes. Three trials were performed at each setting. Standard HFJV pressure controls result in an increase in minute ventilation of 0.94 L/min (0.87, 1.01) for every 1 ml/mbar increase in compliance. Fixed-servo controls increase minute ventilation by 0.38 L/min (0.34, 0.43) per 1 ml/mbar increase in compliance. Fixed-servo controls reduce fluctuations in minute ventilation by 55.6% (47.1%, 64.0%).

Conclusions: When operating the HFJV with a fixed servo pressure, minute ventilation is significantly more stable than standard pressure controls. This study shows that utilizing the HFJV in this fashion would keep minute ventilation relatively stable despite large changes in lung compliance, thus reducing adverse complications of CO2 fluctuations.

#### ATT2018-7

Title: Ambient Noise Production by High-Frequency Neonatal Ventilators

Authors: Justin R. Goldstein, MD; Alyse M. Laliberte, MPH; Martin Keszler, MD

Institution: Department of Pediatrics, Warren Alpert Medical School at Brown University, Women and Infants Hospital of Rhode Island Background: Noise has detrimental effects on clinical stability and neuro-developmental outcomes in neonates. Newborn infants show a physiologic response to sound starting at 23-25 weeks of gestation, which can affect their stability during a long NICU course. Current recommendations are for ambient noise levels in the NICU to not exceed 45 decibels (dB), as it can induce apnea, bradycardia, blood pressure fluctuations and oxygen desaturations. In addition, newborns exposed to loud noise can develop hearing impairment with subsequent speech delay and intraventricular hemorrhage with resulting neurologic impairment.

Noise also has a potentiating effect on ototoxic medications. High frequency ventilators (HFV) are one of the loudest noise exposures in the NICU. New generations of HFV devices including the Dräger VN 500 and Bunnell Life Pulse model 204 jet ventilator may be quieter (in addition to other benefits).

Objective: To quantify and compare the noise created by four high frequency ventilators over a range of clinically appropriate settings. Our hypothesis was that the new generation of HFV devices are quieter than the Sensormedics 3100A and the Bunnell Life Pulse Jet Ventilator models 203.

Methods: Four high frequency neonatal ventilators (Dräger VN 500, Sensormedics 3100A & Bunnell Life Pulse Jet Ventilator models 203 and 204) were set to a range of settings and attached to a neonatal test lung. The ventilators were placed at equal distances from an open warmer and a high-fidelity decibel meter (EXTECH 407780A) was placed on the warmer. Steady-state sound levels were recorded over a range of ventilator settings. For the oscillators (Dräger and Sensormedics), adjustments were made to frequency (Hz), mean airway pressure (MAP) and amplitude ( $\Delta$ P). For the jet ventilators, adjustments were made to frequency, positive end expiratory pressure (PEEP) and peak inspiratory pressure (PIP). Data were analyzed by t-tests, ANOVA and regression models.

Results: The Dräger ventilator was overall the quietest, with average sound levels of  $49.8 \pm 0.49$  dB across all settings. The average noise from the Sensormedics was  $53.6 \pm 2.01$  dB, for Bunnell Model 203 was  $54.1 \pm 1.09$  dB and for Bunnell Model 204 was  $53.7 \pm 1.45$  dB. Adjustments made to frequency/rate and MAP/PEEP had minimal effect on noise level, while increasing amplitude/PIP resulted in significantly more noise by all ventilators. At all tested settings, the Sensormedics and Bunnell ventilators were louder than the Dräger, and the difference became greater as amplitude/PIP increased. The Model 204 jet ventilator was not quieter than the Model 203, with much of the noise coming from the humidification cartridge.

Conclusions: The Dräger VN 500 in high-frequency mode produces significantly less noise that both the Sensormedics and Bunnell ventilators. These data suggest that using the Dräger VN 500 in HFOV mode may reduce the potential for adverse outcomes created by ventilator noise.

#### ATT2018-8

Using Orange Juice for IV Fluid Resuscitation, is Normal Saline the Best Choice for Volume Replacement?

Mitchell Goldstein MD, Munaf Kadri MD, Elba Fayard MD, Richard Peverini MD. Division of Neonatology, Department of Pediatrics, Loma Linda University Children's Hospital, Loma Linda, CA

Background: Neonates who are resuscitated in the delivery room are often identified as poorly perfused and hypotensive. In the not so distant past, the use of colloid or crystalloid was debated. Several years ago, Sodium bicarbonate was abandoned as a therapy that was applicable to neonatal care. In fact, the use of bicarbonate was noted to be associated with needless morbidity and potentially mortality as a worthless therapy. Normal saline alone was advocated as primary therapy for hypoperfused and hypotensive neonates.

Hypothesis: We asked if Normal Saline is the ideal resuscitation fluid.

Materials and Methods: A number of different solutions were compared: Normal Saline, ½ Normal Saline, Sodium Bicarbonate, Sterile Water, D10W, and Orange Juice. We evaluated dextrose content, osmolality, pH, Sodium and Potassium content as well as other potential side effects associated with each individual solution.

Results: The results are presented in the following table below:

	Sugar Content	Osmolality	pН	Sodium	Potas- sium	Other Effects
Normal Saline	0	308 mOsm/L	4.5-7.0 (4.3-4.5 mea- sured)	15.4 meq/dL	0	Acidemia
½ Normal Saline	0	154 mOsm/L	4.5-7.0	7.7 meq/ dL	0	Hypo- osmolar
Sodium Bicar- bonate	0	1000 mOsm/L	7.0-8.5	50 meq/ dL	0	Potential to cross CSF. Hyperos- molar
Sterile Water	0	0	5.0-7.0	0	0	Hypo- osmolar
Ringer's Lactate	0	278 mOsm/L	5.0-7.0	13.1 meq/dL	0.5 meq/ dL	Lactate metabolized to Bicarb
D10W	10 g/dL	500 mOsm/L	4.3	0	0	hyperglyce- mia
Orange Juice (unprocessed)	10 g/dL	482-612 mOsm/L	4.35	0	5.3 meq/ dL	Vitamin C, Citrate buffer

Anaesth Intensive Care. 2000 Jun;28(3):287-92.

http://www.jstor.org/stable/40588223

https://www.medicines.org.uk

Discussion: The use of alternative solutions for volume resuscitation has application for emergent situations and battlefield deployment. Indeed, during the Second World War, coconut water was used when plasma was not readily available. Citrated products have been used for decades for the purpose of blood preservation. Orange Juice appears to have properties that may be desirable for volume resuscitation. Sterility issues notwithstanding, promotion of normal saline as the best solution for resuscitation and/or replacement may miss the mark.

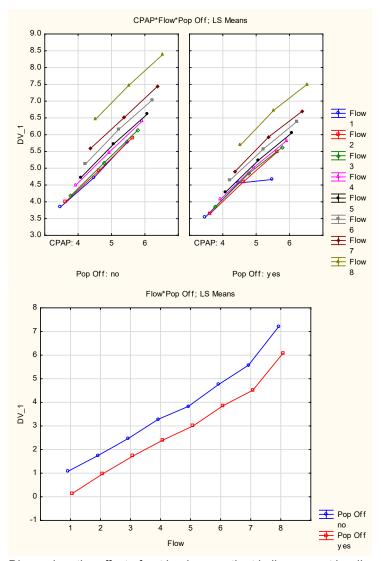
Rop-Off Pressure is Dependent on Maintenance of Flow. Mitchell Goldstein MD, Carter Tong, RRT, Shelley Haug MD, Farha Vora MD, Munaf Kadri MD, Ricardo Peverini MD, Elba Fayard MD.

Loma Linda University Children's Hospital. Loma Linda, California

Background: the use of nasal continuous positive airway pressure (CPAP) has long been a stable of neonatal and pediatric ventilation. Bubble CPAP is created by submersing the expiratory limb of the pressure tubing in a water column submersed to the desired water pressure. Studies evaluating the effectiveness of varied ventilation paradigms have demonstrated the superiority of bubble CPAP over that which had been supplied by a ventilator (i.e., standard CPAP). The Babi plus comes with a pressure pop off that is designed to limit bubble CPAP to its applicable range. Hypothesis: we asked if the pressure pop off on the Babi Plus was necessary for the application of the CPAP and the effect of removing the pop off.

Materials and methods: According to established use, wall flow was connected in line to the Babi plus. To simulate actual use and to eliminate the effect of water vapor inline, the heater was kept inline but not turned on. A pneumotachograph (Validyne) was connected inline to the Babi plus device. Measures of flow and pressure were obtained at settings of 4,5, and 6 cm H2O. Flow was varied from 1 to 8 lpm in increments of 1 lpm. ANOVA was used to analyze the flow and pressure data.

Results: Inter and intra rata differences were significant (p<0.01). Increasing flow and pressure both gave rise to increased propagated flow through the Babi plus apparatus. Please see figures below.



Discussion: the effect of not having a patient in line cannot be discounted. Patient effort may provide additional pressure and flow at various times during the ventilatory process. Flow and pressure increments appeared to be predictable from the increases in flow and pressure. The effect of not having a pressure pop off inline produced a discernible but consistent shift at all tested flows and pressures.

Conclusion: The Babi Plus provides a consistent interface that may be tweaked further according to individual patient needs. Clinical trials must be done to establish the utility of the pop off valve in providing a different ventilation milieu.

ATT2018-10 Quality Improvement Initiative Jeffrey B Gould, MD Stanford University

This presentation is based on an analysis of the factors that were found to be important to the success of perinatal quality improvement collaboratives sponsored by CPQCC and CMQCC over the last 20 years. Attention will be given to topic selection, strategic planning, and project management. The presentation will stress the role of value in the creation and conduct of a successful quality improvement initiative and the importance of attending to the social aspects required for successfully changing behavior as well as the role of data in motivating and guiding a successful quality improvement initiative.

#### ATT2018-11

Neonatal Neuroimaging after Repair of Congenital Diaphragmatic Hernia Predicts Two-Year Neurodevelopmental Outcome

Julia K Gunn PhD, Alice Burnett PhD, Margaret Moran PhD, Rodney W Hunt PhD

The Royal Children's Hospital, The University of Melbourne and the Murdoch Children's Research Institute

Background: Neurodevelopmental impairment is well described amongst survivors of congenital diaphragmatic hernia (CDH). Follow-up of CDH patients is recommended but is resource intensive. Neonatal neuroimaging holds promise as a biomarker of brain injury and may identify children at highest risk of impairment.

Aim: To determine whether routine use of post-operative neonatal cerebral magnetic resonance imaging (MRI) in infants with CDH could detect later neurodevelopment.

Method: From 2003 to 2014, 140 infants underwent surgery for CDH, of whom 85% survived to discharge. Routine neurodevelopmental follow-up occurred in 84 children (80% of eligible) of whom 83 had neuroimaging, including cranial ultrasound (CUS) (81), MRI (57) and CT (1). Non-sedated MRI scans were undertaken following surgery and reported by 2 neonatologists using a standardised scoring system to identify parenchymal injury or haemorrhage, myelination, cortical folding, ventricular dilatation and subarachnoid spaces. CUS were defined as normal or abnormal according to clinical report. Neurodevelopmental assessment was performed at 2 (48), 5 (26) and 8 years (27). Brain imaging scores in the newborn period corrected for gestational age at the time of the scan were correlated with outcome measures at each age, adjusting for known clinical confounders. The RCH Human Research Ethics Committee approved the study.

Results: Findings considered to be of clinical significance were identified on CUS of 10 (12%) infants and MRI of 16 (28%) infants respectively. Mean scores were in the normal range for all domains assessed at 2, 5 and 8 years. Rates of language delay and verbal IQ more than 1 standard deviation below the expected mean were 23% of 2 year olds and 25% of 8 year olds.

Accounting for clinical confounders, mean cognitive scores were lower in 2-year-olds with white matter injury on MRI (p=0.03) and mean motor scores were lower in 2-year-olds with myelination (p=0.01) or cortical folding delay (p=0.01). Cortical folding delay was associated with a motor score <85 (p=0.02). A CUS with clinically significant abnormalities was associated with lower scores in all domains and an increased risk of a cognitive or motor score <85. Whilst associations were identified between MRI findings and 5 and 8 year old neurodevelopmental assessments, these were no longer significant when adjusting for known clinical confounders.

Conclusion: Both CUS and MRI were able to independently identify children at increased risk of neurodevelopment at 2 years of age but less reliable in determining an association with later neurodevelopmental outcomes.

#### ATT2018-11

The use of Mini Bronchial Alveolar Lavage (Mini-BAL) as Part of a Neonatal Antibiotic Stewardship Program.

Tony Iannetta, RRT, George E Mitri, RRT, Teresa J Keppler, RRT, Robert E Schumacher, MD, Mohammad A Attar, MD

Michigan Medicine C.S. Mott Children's Hospital, Department of Pediatrics and Communicable Diseases.

Introduction: The University of Michigan Neonatal intensive care unit(NICU) is a 52 Bed Level 4 ICU. Data from a national database revealed that our NICU's antibiotic use rate (antibiotic days/1000 NICU days) were twice that of peer institutions. The continued use of antibiotics in the face of "negative cultures" was identified as a principal drive of this behavior. 17% of the "culture negative" but treated patients were treated for pneumonia. An additional number of patients were treated on the basis of tracheal aspirate findings, the reliability of which can often be questioned.

We hypothesized that, compared to our practice of obtaining proximal tracheal aspirate samples, the use of a blind protected Mini-BAL to obtain distal pulmonary fluid specimens would be safe and provide reliable results with fewer patients being treated (negative lavage findings) and better targeting of antibiotic choice in those with positive cultures. This report describes the technique and pilot results in a group of neonatal patients with suspected VAP.

Methods: Criteria for Mini-BAL used was: 1. At risk population (>2 weeks of age, receiving mechanical ventilation for >2 days, radiologic signs c/w VAP, clinical signs of worsening gas exchange and other selected clinical signs of infection. Initial safety concerns limited patients to those with FiO2 <60% and receiving only conventional mechanical ventilation. Prior to the start of the procedure patient's condition was optimized by increasing sedation and oxygenation, patients were then suctioned to remove any secretion in and around the endotracheal tube(ETT). Sterile technique is used during this procedure; the BAL Cath was inserted into the ETT through the suction port on the "Y" Ballard suction adapter. When the inner catheter is at the desired location, 2 - 5ml of normal saline is added as needed followed by 1ml of air. Aspiration of the lavage sample is done, and the specimen is sent to the lab for processing. (Video)Safety was monitored by SpO2 and continuous vital sign monitoring.

Results: Between June 25th 2017 and December 2nd of 2017 a total of 27 Mini- BAL procedures were done on 19 patients. A satisfactory specimen was obtained in 100% of procedures. 22/27 specimens had evidence of inflammation (PMS) on gram stain. Sixteen specimens yielded positive cultures. 14/16 yielded a single organism. All organisms identified were considered pathogenic. No adverse events were recorded.

Conclusions: Mini-BAL appears to be technically feasible, safe, and shows promise as a useful test in guiding appropriate treatment of ICU patients. The results produced have characteristics of BAL procedure from a larger sample. The mini-BAL is being developed as part of an NICU-unit wide antibiotic stewardship program. Preliminary results suggest efficacy in reducing antibiotic use.

#### ATT 2018-12

What should/is the Role of Industry in your Practice?

Colleen Kraft, MD, Donald Null, MD, Mitchell Goldstein (Moderator) American Academy of Pediatrics

Advancements in child health technology and therapeutics occur as a result of partnership and collaboration between pediatricians and industry. The intellectual resources and expertise necessary to inform innovative products for children are present across academic institutions, businesses, non-profit organizations and foundations. The American Academy of Pediatrics is the organization under which our researchers, practitioners, and entrepreneurial pediatricians can meet for these discussions. The opportunity is to hold substantive conversations regarding product development, the evidence base for product efficacy, and applicable solutions for children. Shared values of honesty, transparency, and integrity should govern these interactions. Financial risk becomes reality for industry that invests in therapeutics and technology for children; the right product development and subsequent use for children becomes a win-win for child health. Concerns about conflict of interest, as valid as they are, have the unintended consequence of preventing our child health experts from meaningful engagement with industry that invests in moving child health therapy forward.

Engagement of the AAP members with industry, keeping conflict of interest in mind, should result in collective impact initiatives that leverage shared values and advance aligned goals. Discourse should occur as an ongoing dialogue, including product intent, clinical trials, review of the evidence base, application to the Food and Drug Administration for indicated use in the pediatric population, and post-market surveillance. Pediatric resident education regarding ethical and functional interaction with industry should occur

beyond "no interaction" for professionalism purposes. Our trainees and early career pediatricians can practice these interactions with industry with reflective debrief with a mentor, fostering ethical and substantive conversations and awareness of pitfalls that can occur. ATT2018-13

Preterm birth and 3 days of mechanical ventilation appear to reduce capillary surface density in brain white matter of

Null, D2; Pettit, L1; Rebentisch, A1; Dawson, E1; Wang, Z M.1; Hicks, R1; Dahl, M J.1; Yoder, B A.1; Albertine, KH1

1. Pediatrics, University of Utah, Salt Lake City, UT, United States. Pediatrics, UC Davis, Davis, CA, United States.

Background: Prolonged mechanical ventilation (MV) of premature infants leads to evolving neonatal chronic lung disease. Frequently, the brain is injured as well. Our previous studies, using preterm lambs, indicate that MV from 3d to 21d shifts balance to more apoptosis and less proliferation of neurons, immature and mature oligodendrocytes, and astrocytes.

Objective: Our previous results suggest that prolonged MV may disrupt the presence of different cell types in brain tissue of pretrerm lambs. We hypothesized that MV will alter presence of neuronal progenitor cells and capillaries in the immature brain.

Design/Methods: Preterm lambs, treated with antenatal steroids and postnatal surfactant, were managed by MV or high-frequency nasal ventilation (HFNV) for 3d (n=4/group). We use HFNV as the positive gold-standard for alveolar formation in the lung. At the end of 3d, cortical brain tissue from the temporal lobe was fixed. We used immunohistochemistry to localize doublecortin (DCX)-positive neuronal progenitor cells and p-glycoprotein-positive capillaries in gray matter and white matter. Negative staining controls were used. We used stereology to quantify surface density of each cell type, using systematic, uniform, random sampling.

Results: Results are summarized in the table. For gray matter, no differences were detected for either surface density of DCX (Sv DCX)-positive neuronal progenitor cells (cm-1) or capillaries (Sv cap; cm-1) between PT 3d MV versus HFNV groups. In white matter, Sv DCX-positive neuronal progenitor cells also were not different between the two respiratory support modes. In contrast, Sv cap was significantly lower for the PT 3d MV group compared to the PT 3d HFNV group (p<0.05).

Conclusion(s): These results suggest that preterm birth and 3d of MV may have their initial effects on capillary growth in white matter

Stereology of brain tissue of preterm lambs				
Lamb group	Gray matter		White matter	
	Sv DCX	Sv cap	SC DCX	Sv cap
PT 3d MV	287±15	102±7	70±28	67±8
PT 3d HFNV 258±20 115±10 113±33				96±7*
Mean±SD; n=6; *p<0.05 by unpaired t-test				

compared to 3d of HFNV. Neuronal progenitor cells do not appear to be affected at the early time point of 3d of continuous respiratory support. Analyses are ongoing to quantify nestin-positive neural stem cells in the same groups of preterm lambs, as well as other preterm lamb groups that were supported for 21d by MV or HFNV. HL110002

#### ATT 2018-13

Context-Responsive Anticoagulation is Associated with Reduced Complications and Transfusion in Neonatal and Pediatric ECMO Philip Spinella, MD

Geneva Foundation

Objective: Determine the impact of a comprehensive context-responsive anticoagulation and transfusion guideline on the frequency and severity of bleeding and thrombotic complications as well as blood product utilization during extracorporeal membrane oxygenation (ECMO).

Design: Single center, observational pre- and post-implementation cohort study.

Setting: Academic pediatric hospital.

Patients: Patients in the PICU, CICU, and NICU receiving ECMO support.

Interventions: Program-wide implementation of a context-responsive anticoagulation and transfusion guideline.

Measurements: Pre-implementation subjects consisted of all patients receiving ECMO between January 1 and December 31, 2012 and underwent retrospective chart review. Post-implementation subjects consisted of all ECMO patients between September 1, 2013 and December 31, 2014 and underwent prospective data collection. For both cohorts, data collection included standard demographics, ECMO technical specifications, non-ECMO therapies, coagulation parameters, and blood product administration. Additionally, a novel grading scale was used to define hemorrhagic complications (major, intermediate, and minor) and major thromboembolic complications.

Main Results: 76 ECMO patients were identified: 31 during the preimplementation period and 45 in the post-implementation period. Overall observed mortality was 33%, with no difference between periods. Compared to pre-implementation, the post-implementation group experienced fewer major hemorrhagic and major thrombotic complications, fewer severe hemorrhagic complications, and received a lesser RBC transfusion volume.

Conclusions: Use of a context-responsive anticoagulation and transfusion guideline was associated with a reduction in hemorrhagic and thrombotic complications and RBC transfusion requirements. Further evaluation of guideline content, compliance, performance and sustainability is needed, as well as of impact on other clinically relevant outcomes.

#### ATT 2018-14

A Novel Training Platform for Life-Saving Interventions During Prolonged Field Care

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1 The Geneva Foundation, Tacoma, WA, 2 Morsani College of Medicine, University of South Florida, Tampa, FL, 3 Baltimore Shock Trauma Hospital, Baltimore, MD, 4 U.S. Army Institute of Surgical



The National Perinatal Association (NPA) is an interdisciplinary organization that gives voice to the needs of parents, babies and families and all those interested in their health and wellbeing. Within NPA, parents and professionals work together to create positive change in perinatal care through education, parent programs, professional guidelines and events.

www.nationalperinatal.org

Research, JBSA Ft. Sam Houston, TX, 5 University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, 6 San Antonio Military Medical Center, San Antonio, TX

Background: Historically, the U.S. and its allies have been able to establish air and sea superiority. This has enabled medical evacuation to follow the current "Golden Hour" doctrine: get patients from the point of injury to the nearest medical facility within an hour of injury. Under this doctrine, casualties are stabilized by the first responder, whether a medic providing paramedical-level care or a Soldier providing simple first aid. Future warfare will demand a different approach: "Prolonged Field Care" (PFC), requiring casualties to be stabilized and maintained for up to 72 hours at or near the point of injury, with limited resources and capabilities, before evacuation. We have established a training platform centered around a 72-hour model of combat relevant injury in swine.

Methods: We determined the most important surgical interventions for stabilization were: definitive airway management, establishing vascular access for potential therapies (including larger than 18 Fr cannulation), and insertion of chest tubes for tension pneumothorax. In addition, we evaluated emerging technologies and techniques that are becoming part of a combat surgeon's toolbox, including resuscitative endovascular balloon occlusion of the aorta (REBOA) and more extensive use of extracorporeal life support (ECLS) devices including full extracorporeal membrane oxygenation (ECMO) for gas exchange or cardiac bypass in the case of arrest (eCPR) and continuous renal replacement therapy (CRRT) for massive organ dysfunction. Additionally, we trained the use of point of care testing devices for evaluation of patient status including analysis of blood gas results to make ventilator adjustments, and ultrasound to evaluate levels of fluid edema in the lungs. Using our training platform, non-medical personnel have trained under the supervision of a general surgeon on these procedures, as well as learning basic skills to maintain a stabilized patient for up to 72 hours after a combat-relevant injury. All animal work has been conducted under IACUC approved protocols in compliance with the Animal Welfare Act, the implementing Animal Welfare Regulations, and the principles of the Guide for the Care and Use of Laboratory Animals. Results: Using a crawl-walk-run strategy, personnel first observed, then assisted, a trained surgeon on procedures before performing themselves. For tracheostomy, personnel training in the technique observed upwards of 30 successful tracheostomies of varying complexity. Non-medical personnel have now performed 5 tracheostomies without adverse event, 2 of which were performed with no medical provider physically present, using telemedical assistance. Non-physician personnel have successfully inserted dual-lumen ECLS cannulas with no complications three times, twice under supervision once via telemedicine. Personnel continue to train in the use of ultrasound for percutaneous vascular access in both stable

gas results.

Conclusions: In the future multi-domain battlefield, the ability to perform lifesaving interventions in the field will be the difference between life and death for combat casualties. Specifically, those casualties who will have their evacuation delayed will require greater stabilization than is currently practiced in the field, and may require up to 72 hours of PFC. Adding simplified emergency techniques to the combat medics' toolkit will help bridge the gap between point of injury first aid and advanced medical care. Training to stabilize and maintain an animal following a combat relevant trauma for up to 72 hours can give non-medical providers the ability to perform under stressful PFC conditions. Wet labs utilizing animal training models will be a crucial part of any training program.

and non-heart beating condition. Lung ultrasound has been performed 140 times to evaluate animals for lung edema. Non-medical personnel have made countless ventilator changes based on blood

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#### **Featured Upcoming Conference**

36<sup>th</sup> Annual Conference - Advances in Therapeutics and Technology March 26-30, 2019

The Cliff Lodge and Spa in Snowbird, UT USA Registration:

http://paclac.org/advances-in-care-conference/

#### **Conference Description:**

Educational and networking opportunities for healthcare professionals who provide care for pediatric patients including those in critical care environments with a focus on advances in therapeutics and technologies. Includes featured speakers, workshops and abstract presentations on research on advances in these areas.

#### **Continuing Education Credit Provided by:**

Perinatal Advisory Council: Leadership, Advocacy, And Consultation. Physician, nursing, and respiratory continuing education credit will be provided.

#### **Special Panel Discussion:**

Avoiding the Conflict, Working to Develop Better Relations with Industry. Colleen Kraft, MD, President, AAP with Don Null, MD and Mitchell Goldstein, MD

#### Agenda:

- Rashmin Savant MD BPD New Concepts in Pathogenesis and Prevention
- Cynthia Blanco MD Metabolic Disturbances of Prematurity When How and Who to Treat
- Sinjo Hirose MD Fetal Surgery
- Arun Pramanick, MD. Game Changers in Neonatal-Perinatal Medicine- A View Through a Retroscope
- Don Null Persistent Pulmonary Hypertension in the Preterm Newborn Etiologies and Cardiopulmonary Management
- Marty Keszler, MD New Modalities in High Frequency Ventilation
- Mitchell Goldstein, MD. Rediscovering the Denominator
- 9. Steve Derdak, DO. Pediatric Origins of Adult Disease



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# The Genetics Corner: A Consultation for Metopic Craniosynostosis and Skeletal Anomalies

Subhadra (Subha) Ramanathan, MSc, MS and Robin Clark, MD Case History:

An 8 week old Hispanic female was seen for an initial genetic assessment in the Craniofacial Team. She presented with trigonocephaly and possible metopic craniosynostosis, fixed flexion of both elbows at 90 degrees, talipes varus, and hypoplastic great toes with hypoplastic/absent nails. Her 23-year old primigravida mother was the primary historian but her Spanish-speaking maternal grandmother and an interpreter were also present.

The baby was born through meconium-stained amniotic fluid at 40 weeks gestation by C-section, for failure to progress, at a community hospital. Birth weight was normal: 7 lbs 6 oz. Congenital anomalies were noted at birth. Head US and echocardiogram were normal. Renal US showed mild pelviectasis of both kidneys. No other testing was performed. She failed her newborn hearing screening test in both ears but was discharged home with her mother. The referral documentation did not note any maternal health problems in the pregnancy.

The mother reported to the genetic counselor that she had a seizure disorder with onset in her teens that was treated with zonisamide (Zonegram TM, 800 mg BID) throughout the pregnancy. Hypothyroidism was treated with levothyroxine prior to the

Figure 1: Hypoplastic great toes with absent distal phalanges and nails.

pregnancy. She restarted levothyroxine at 17 weeks' gestation. She was counseled that neither of those medications poses a significant teratogenic risk.

As the visit was concluding, the maternal grandmother mentioned, through the interpreter, that the mother had been treated for "Valley Fever" (coccidioidomycosis due to *Coccidioides immitis*) during the pregnancy. Subsequently, the mother acknowledged that she had contracted disseminated coccidioidomycosis with meningitis in her teens and had been treated with fluconazole (Diflucan TM, 100 mg QID) since then. She reported taking the medication during the pregnancy until 17 weeks' gestation. She recalled being counseled about the risks of fetal fluconazole exposure when she had been prescribed the medication as a teen. She had not been using contraception. At a follow-up appointment with the clinical geneticist, the mother modified the history stating that she had discontinued fluconazole for about a week when the pregnancy was first detected at 4 weeks, and then resumed taking the medication at half the prescribed dose of her own volition.

Physical examination of the baby revealed brachycephaly, frontal bossing, a metopic ridge, small dysplastic ears and diastasis of periorbicularis oris muscle (deep groove in the midline between philtral ridges). She had patent choanae with air flow through both nares. She had tapered fingers with narrow, hyperconvex nails,



Figure 2: Dysmorphic features with trigonocephaly, metopic ridging, bilateral epicanthal folds, short nose, diastasis of periorbicularis oris muscle



Figure 3: Fixed flexion of elbows at 90 degrees.

accessory palmar and flexion creases on the hands, bilateral talipes varus and absent distal phalanges of the great toes with absent nails bilaterally. She had fixed flexion at the elbows suggesting radiohumeral synostosis. Her genitalia were normal. Radiographs were ordered.

#### Consultant's report

This child has fluconazole embryopathy. In 1992, Lee, et al. first reported that high dose fluconazole exposure in the first trimester causes a pattern of congenital anomalies in humans. Several infants with fluconazole embryopathy have been reported since then (Aleck and Bartley, 1997; Pursley, et al., 1996; Lopez-Rangel and Van Allen, 2005). Recognizable features include craniosynostosis, dysmorphic facial features (epicanthal folds, hypertelorism, low nasal bridge with a short nose), dysplastic ears, cleft palate, cardiac defects, skeletal anomalies including hypoplastic great toes with deficient distal phalanges and absent nails.

Fluconazole is widely used for the treatment of a range of candidal and cryptococcal fungal diseases. It penetrates the CSF and is routinely used for fungal infections of the central nervous system. The teratogenic effects of fluconazole appear to be highly dependent on the dose, duration of exposure and timing of exposure relative to conception. The FDA lists fluconazole as a Category D drug in pregnancy for all indications except the treatment of vaginal candidiasis. The critical period for teratogenesis appears to be prior to 14 weeks' gestation. Exposure to high dose fluconazole after 14 weeks' gestation has not been reported to cause fetal anomalies. Five cohort studies on single or low-dose fluconazole exposure (e.g. 150 mg single dose for vaginal candidiasis) during pregnancy did not identify an increased risk for congenital malformations, whereas reports of fluconazole teratogenicity document prolonged exposure over several months to high doses (400-1200 mg/day) (Firth et al., 2014). A few studies suggest that exposure to low dose fluconazole may cause a slight increased risk for oral clefts, cardiac anomalies and spontaneous abortion.

Fluconazole embryopathy shares many features with Antley-Bixler syndrome (ABS), an autosomal recessive multiple craniosynostosis and congenital anomaly syndrome. The two conditions have a similar phenotype because they affect the same enzymatic pathway. Fluconazole inhibits the fungal cytochrome P450-dependent lanosterol 14-α-demethylase enzyme (CYP51), and the synthesis of ergosterol, an essential component of the fungal cell membrane. In humans, cytochrome P450 oxidoreductase (POR) transfers electrons to all microsomal cytochrome P450 (CYP) enzymes, including CYP51A1, an essential enzyme for the synthesis of cholesterol and cell membranes and a precursor of steroid hormones and bile acids (Cassina M et al., 2017). Pathogenic variants (mutations) that reduce the activity of the human cytochrome P450 oxidoreductase gene, POR, cause Antley Bixler syndrome with genital anomalies and disordered steroidogenesis (MIM# 201750). By reducing the efficacy of this enzymatic pathway, early fluconazole use in pregnancy creates a "phenocopy" of ABS.

Our patient's mother is now taking 400 mg of fluconazole per day. She expressed a desire to have more children in the near future. She was counseled extensively about the importance of planning every future pregnancy and working with her health care provider to change to an alternative medication, such as amphotericin B, prior to conception and at least through the first trimester of any future pregnancy because of the risks for congenital anomalies associated with fluconazole exposure.

#### **Practical Applications:**

- 1. Whenever possible, personally review the prenatal and pregnancy history in detail, face-to-face and in private. Try not to rely solely on the history in the medical record. Resist the urge to copy and paste. The history of prenatal fluconazole exposure, which was the key to this diagnosis, was not recorded in the neonatal hospital discharge summary. A mother who feels guilty about her medication exposure may not be forthcoming about her use of a teratogenic agent.
- 2. Be curious, be receptive and ask follow up questions. In this case, had we asked about the nature of her seizures, we might have elicited the history of *C. immitis* meningitis and fluconazole therapy earlier in the interview.
- 3. Consider the "phenocopy". Some environmental agents can mimic recognizable genetic disorders.

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The Brett Tashman Foundation (a 501(c)3 not for profit charity) gives 100% of monies raised from its annual golf tournament to the nation's most esteemed doctors researching **Desmoplastic Small Round Cell Tumor** (DSRCT).

June 30, 2018 at Sierra Lakes Country Club in Fontana, CA.

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The authors have no conflicts of interests to disclose.

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# How to Care for a Baby with NAS



### Use the Right Words

I was exposed to substances in utero. I am not an addict. And my mother may or may not have a Substance Use Disorder (SUD).



#### Treat Us as a Dyad

Mothers and babies need each other. Help my mom and me bond. Whenever possible, provide my care alongside her and teach her how to meet my needs.



#### Support Rooming-In

Babies like me do best in a calm, quiet, dimly-lit room where we can be close to our caregivers.



#### Promote Kangaroo Care

Skin-to-skin care helps me stabilize and self-regulate. It helps relieve the autonomic symptoms associated with withdrawal and promotes bonding.



### Try Non-Pharmacological Care

Help me self-soothe. Swaddle me snugly in a flexed position that reminds me of the womb. Offer me a pacifier to suck on. Protect my sleep by "clustering" my care.



### **Support Breastfeeding**

Breast milk is important to my gastrointestinal heath and breast feeding is recommended when moms are HIV-negative and receiving medically-supervised care. Help my mother reach her pumping and breastfeeding goals.



#### **Treat My Symptoms**

If I am experiencing withdrawal symptoms that make it hard for me to eat, sleep, and be soothed, create a care plan to help me wean comfortably.

Learn more about Neonatal Abstinence Syndrome at www.nationalperinatal.org

#### THE VALUE OF HUMAN MILK ACCESS FOR PREMATURE INFANTS



Protecting Access for Premature Infants through Age Two

The National Coalition for Infant Health is a collaborative of more than 150 professional, clinical, community health, and family support organizations focused on improving the lives of premature infants through age two and their families. NCfIH's mission is to promote lifelong clinical, health, education, and supportive services needed by premature infants and their families. NCfIH prioritizes safety of this vulnerable population and access to approved therapies.

#### Dear Colleagues,

Babies thrive on a diet of human milk, as peer-reviewed research in recent decades has demonstrated. Moreover, breastfeeding and human milk have proven to reduce respiratory complications, gastrointestinal infections, sudden infant death syndrome, and a number of other serious morbidities. In cases where mothers cannot breastfeed or produce sufficient breastmilk, bottle-fed milk from the mother or other human donors offers comparable benefits.

The most vulnerable infants, those born prematurely with a birth weight less than or equal to 1,250 grams, have a particular need for a human milk diet. Research examining its exclusive use has established an unmistakable dose response relationship between human milk diets and the discharge rates of pre-term infants. A diet of human milk reduces the number of total parenteral nutrition (intravenous feeding) days, incidences of sepsis, the frequency of surgery and mortality rates in pre-term infants.

# How Does a Human Milk Diet Affect NEC?

With the help of a human milkbased diet fortified with human milk-based fortifier:

- NEC incidences are reduced by 77%
- For every 8 infants treated, one case of NEC is prevented

Yet, despite these clear benefits, families may face limited options due to lack of insurance coverage for human milk and human milk-based fortifiers, and other access challenges.

#### MILK AS MEDICINE

Human milk has proven particularly effective in reducing a baby's risk of necrotizing enterocolitis (NEC), a condition in which the intestinal tissue dies, with associated abdominal distention, temperature instability and shock. NEC occurs most often in premature or sick babies and is often life threatening. Treatment may require invasive surgeries and can have lifelong consequences.

Overall, evidence shows a correlation between an exclusive human milk diet and lower mortality and morbidity as compared to a bovine or cow-based diet. In essence, human milk isn't merely nutrition—it's medicine. An increasing number of healthcare professionals and hospitals now share this view.

Relying on a full regimen of human milk, especially when compared with total parenteral nutrition typically covered by insurance, provides tangible economic benefits. Reductions in the instances of NEC alone reduce costs by \$7,508 per infant and cut expected costs of surgical NEC by \$10,785 per infant. These savings pose significant long-term cost implications.

Nevertheless, existing informed consent procedure defies current data by requiring a mother to consent to an exclusive human milk diet for her baby. Scientific consensus, on the other hand, supports that hospitals should obtain informed consent from parents opting for a non-human milk diet.

#### QUALITY AND SAFETY IN THE IDEAL HUMAN MILK DIET

Pre-term infants benefit from an exclusive human milk-based diet. The mother's own milk is usually the best option, and programs now exist to foster a hospital environment that encourages breastfeeding. One such program is the Baby-Friendly Hospital Initiative, an accreditation program for maternity facilities that encourages an optimal environment for appropriate infant feeding and mother-baby bonding. The program promotes quality and the maintenance of the milk supply in accredited institutions.

However, mother's milk alone is rarely enough for delicate preterm infants. In fact, 72% of very pre-term mothers are simply unable to provide the necessary calories, nutrients and quantity of milk. Donor human milk, donor human milk with human-derived fortifier, and human milk cream appropriately supplement the diet in such cases. A multi-step process protects infants by assuring the quality and safety of donor milk.

Moreover, similar to the plasma industry, there is an inherent risk to not adequately screening and processing human milk products. DNA verification and blood product level testing is imperative. There is also the need for clinically evaluating human milk products in the same way that pharmaceutical or other biologic products are studied.

#### **BARRIERS TO ACCESS**

Despite the proven benefits of human milk and the increased availability of donor human milk, pre-term infants and their families often struggle to overcome significant barriers to access—if they are even made aware of options to provide the best possible nutrition for the child.

Barrier #1: Access to Hospital-Grade Breast Pumps

Hospital-grade pumps for mothers at home facilitate the human milk diet, optimizing pre-term infant health. The personal pumps mothers often receive under their insurance coverage simply do not meet the quality of hospital pumps. The consequence of health plans that fail to provide hospital grade pumps is typically return hospitalizations for failure to thrive and other nutritional-related complications.

The Affordable Care Act has not solved this problem. In fact, it has made it worse in some cases because no minimum specifications exist for the breast pumps provided through insurance. Virtually any pump meets the law's standards. As a result, re-

# Human Milk Quality & Safety: Best Practices

- 1. Preliminary screening of individuals wishing to donate.
- 2. DNA fingerprinting using polymerase chain reaction on donor milk. Results must align with the final product to eliminate the possibility of donors adulterating or diluting their milk with cow's milk.
- 3. Milk tested for bacterial contamination just like any blood product.
- 4. Nutritional analysis guarantees a minimum of 20 kilocalories per ounce.
- 5. Final nutritional content held to same standard as prescription drugs.
- 6. Truth in manufacturing. Full disclosure should be provided regarding the effect of various technological modifications of breast milk including homogenization and pasteurization that may impact the nutritional value of the milk.

quirements for coverage are a patchwork of policies with few guidelines and no quality assurance.

Barrier #2: Insurance and Medicaid Coverage for Donor Milk

Donor milk represents a critical bridge if a mother has a delayed or inadequate supply of her own breastmilk. Establishing more donor milk banks in close proximity to hospitals is critical, especially because so few hospitals have the ability to provide this life-saving resource within their own facility.

Donor milk's cost and availability can bar access, but for every dollar spent on donor milk, \$11 in medical costs can be saved. Many unsanctioned donor milk networks have evolved, especially in the age of social media. This practice severely undermines quality and safety. Supplies procured online may not have been screened, processed or evaluated sufficiently. Appropriate donor milk coverage policies can free mothers from having to resort to potentially dangerous black market sources because of cost considerations.

An increasing number of insurance companies are paying for donor milk, or at least part of the cost (such as the fortifier). Yet the number covering donor human milk in full is far from ideal. Insurers more often pay for donor milk under specific conditions, but



Protecting Access for Premature Infants through Age Two

A collaborative of professional, clinical, community health, and family support organizations improving the lives of premature infants and their families through education and advocacy.



# The National Coalition for Infant Health advocates for:

- Access to an exclusive human milk diet for premature infants
- Increased emotional support resources for parents and caregivers suffering from PTSD/PPD
- Access to RSV preventive treatment for all premature infants as indicated on the FDA label
- Clear, science-based nutrition guidelines for pregnant and breastfeeding mothers
- Safe, accurate medical devices and products designed for the special needs of NICU patients

www.infanthealth.org

standards vary, causing confusion among preemie parents who are already emotionally drained. The Medicaid statute does not address lactation services, so as with breast pump coverage, the level of donor human milk coverage varies widely by state, further complicating stressful situations.

Barrier #3: Lack of Adequate Safety Nets for Medicaid Recipients

Low-income families are often unprepared to handle the arrival of a premature child, a situation exacerbated by disparity. Hospitals can empower these parents by supplying data and helping them understand how an exclusive human milk-based diet benefits their baby.

Even with education, however, parents sometimes simply cannot provide the preferred diet due to holes in Medicaid coverage. This occurs at fundamental levels such as a mother's transportation to the NICU or accommodations for overnight care in order to properly breastfeed her baby. Other children at home may also need attention, introducing prohibitive child care costs.

Moreover, low-income families seldom have benefits such as paid time off or maternity leave. The cost of a human milk diet can be quite expensive, impacting household finances even more severely because of lost income.

#### CONCLUSIONS

Data indisputably shows that an exclusive human milk based diet improves premature babies' health and survival, especially in avoiding complications like NEC. Public policy should reflect those benefits, but the Affordable Care Act and Medicaid statute do not address them in any meaningful way. Moreover, inconsistencies in coverage can confuse patients.

Specific barriers for mothers of premature infants include access to hospital-grade breast pumps, health plan coverage for donor human milk, and consistent, adequate Medicaid coverage that facilitates breastfeeding and supports a human milk diet.

The existing informed consent procedure also fails to reflect the value of a human milk diet. Mothers must currently opt in to an exclusive human milk diet, but few understand its importance. A more scientifically informed consent procedure would require mothers to opt out of an exclusive human milk diet for their babies.

In recognizing the importance of premature infants' health, policy-makers can work together to ensure access to a human milk diet. Optimal nutrition for infants not only saves lives and improves the quality of life but also can benefit the entire healthcare system and reduce costs over the long term.

Sincerely,

mmmmill.

Mitchell Goldstein, MD Medical Director National Coalition for Infant Health

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The author has identified no conflicts of interest.

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#### **National Coalition for Infant Health Values (SANE)**

**Safety.** Premature infants are born vulnerable. Products, treatments and related public policies should prioritize these fragile infants' safety.

**Access**. Budget-driven health care policies should not preclude premature infants' access to preventative or necessary therapies.

**Nutrition.** Proper nutrition and full access to health care keep premature infants healthy after discharge from the NICU.

**Equality.** Prematurity and related vulnerabilities disproportionately impact minority and economically disadvantaged families. Restrictions on care and treatment should not worsen inherent disparities.

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## Monthly Clinical Pearls: "Times Have Changed! Or Have They?"

Joseph R. Hageman, MD

In 1981 when I was a neonatal fellow in the Children's Memorial Hospital (Northwestern University) program, Sheila Hebein, a Mom of a child with Down syndrome, came to Evanston Hospital one morning and was putting together a slide presentation for new parents of a newborn with Down syndrome for the National Association for Down Syndrome (NADS.org). She needed someone to play the father of the newborn with Down syndrome. I volunteered after being up all night on call in the NICU at Prentice Women's Hospital to play the Dad so I would "look the part". At that time, she was the Executive Director of the National Association for Down Syndrome (NADS). I really felt privileged to be able to help "get the word out" to help educate parents and medical professionals about Down syndrome and working to change the mind-set and to maximize the intellectual and social potential of these children. This was a relatively new effort, as when I was in medical school a few years earlier, I learned that children with Down syndrome generally had IQs of around 40 and most were "institutionalized".

After the presentation was finished, through the years I would have an occasional medical student say "Hey, weren't you in...." and I felt like a movie star.

How we approach the counseling of our patients' parents starts in collaboration with the obstetricians and maternal fetal medicine specialists and genetic counselors after a syndrome is identified prenatally (1-3). The quad screen is a maternal blood test used to predict the risk for Down syndrome, Trisomy 18 and open neural tube defects:

- It measures maternal serum levels of alpha-fetoprotein (produced by the fetus), human chorionic gonadotropin (hCGwithin placenta), unconjugated estriol (uE3-fetus and placenta) and inhibin A (placenta and early on by the corpus luteum)
- Performed typically between 15 and 19 weeks' gestation
- Detection rate is 60-75% for Down syndrome and Trisomy 18 and >90% for open neural tube defects
- Patterns and associated conditions:
  - Elevated hCG and Inhibin A with decreased alphafetoprotein and decreased estriol: Increased risk for Down syndrome
  - All markers decreased: Increased risk for Trisomy 18 (3)

If the results are strongly suggestive of Down syndrome, further evaluation including an ultrasound (redundant nuchal skin) and chromosome analysis is performed. There is a newer prenatal screening test available now which is the cell free fetal DNA test which actually looks at genetic material from the baby in the mother's blood

If the diagnosis of Down syndrome is confirmed, a counseling discussion is convened and options are discussed. I sent a draft of this blog to Ann Garcia, who is the Family Support Coordinator at the National Association for Down Syndrome, for her review after I had written that nowadays the decision about how aggressive to be with anomalies such as duodenal atresia in a newborn with Down syndrome is not even a question at this point in time where it might be have been 40 years ago. Ann counsels families of infants with Down syndrome and she wrote back and said that she hears stories of prenatal and newborn counseling with physicians who continue to take the point of view that continuing a pregnancy of a fetus with Down syndrome is not a good idea or that Down syndrome kids will never progress beyond the developmental age of 5 years (Ann Garcia, personal communication, May, 2017). It is interesting to hear that at present, there is no uniformity in the medical community's attitudes toward the intellectual potential of children with Down syndrome. And sometimes the happiness that children provide their families is not just measured in their intellectual capacity. Parenthetically, Sheila Hebein, who served as Executive Director of NADS for 30 years and helped set up the Adult Down Syndrome Center at Advocate Lutheran General Hospital in the 1990's (4). Her son, Chris, was one of the first patients there. Chris is now 44 years old and works full time as a mail clerk, plays the piano every day, and helped to create an aerobics program for NADS (4).

Today, there are more discussions about the repair of congenital heart defects in infants with Trisomy 13 and 18 as traditionally it is taught that, as a group, their one-year survival rates are around 10%. That is the case for very low birthweight infants with trisomy 13 and 18 as summarized in a paper by Boghossian and co-authors (5). However, in a relatively recent paper in Pediatrics by Nelson et al, survival rates in infants with Trisomy 13 and 18 approached 30% as congenital defects were repaired and attempts "to maximize their potential" were undertaken (6).

For neonatologists, obstetricians and for pediatricians, it is important for each of us to arm ourselves with the most current clinical information, learn a bit about ethics, and to formulate our opinions based on all of these data (1-3) so we will be prepared to provide this information to our patients' families in counseling sessions after the diagnosis of a genetic syndrome is made.

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http://paclac.org/advances-in-care-conference/

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#### Clinical Pearls are published monthly.

Submission guidelines for "Clinical Pearls":

1250 word limit not including references or title page.

May begin with a brief case summary or example.

Summarize the pearl for emphasis.

No more than 4 references.

Please send your submissions to:

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A new tubing design meant to eliminate tubing misconnections has introduced new challenges for the NICU population. Pediatric providers must deliver medication in small volumes to tiny patients with high levels of accuracy. The new tubing design, known as ENFit®, could present dosing accuracy and workflow challenges.





#### **DOSING ACCURACY**

 The moat, or area around the syringe barrel, is difficult to clear. Medication can hide there, inadvertently increasing the delivered dose when the syringe and feeding tube are connected; patients may receive extra medication.

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 The moat design can increase risk for infection if residual breast milk or formula remains in the moat and transfers to the feeding tube.

#### WORKFLOW ISSUES

 Increased nursing workflow is seen with additional steps for clearing syringe moats, cleaning tube hubs, and using multiple connectors.

Improved standards are important to protect patients from the dangers of tubing misconnections. But we must avoid mitigating existing risks by creating new ones.

Individual hospitals should consider all factors impacting their NICU patients before adopting a new tubing design.

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A collaborative of professional, clinical, community health, and family support organizations focused on the health and safety of premature infants.

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# Upcoming Medical Meetings

International Neonatology
Association Conference (INAC 2018)
Jun. 22-24, 2018;
Ghent, Belgium
http://2018.worldneonatology.com

United States Breastfeeding Committee
Eighth National Breastfeeding
Coalitions Convening (NBCC)
August 4-5, 2018,
Atlanta, Georgia.

http://www.usbreastfeeding.org/p/cm/ld/fid=515

35th annual The Fetus & Newborn: Improving Outcomes in Perinatal and Neonatal Care conference September 5 - 8, 2018 Las Vegas, NV http://fetusandnewborn.com

Innovative Care of the Newborn Brain Lucile Packard Children's Hospital September 26-27, 2018 Palo Alto, CA https://tinyurl.com/neuronicu-sept

NANN's 34<sup>th</sup> Annual Conference Anaheim Hilton and Convention Center Anaheim, CA October 17-20, 2018 <a href="http://nann.org/education/annual-meeting">http://nann.org/education/annual-meeting</a>

The AAP Experience
National Convention and Exhibition
Orlando, FL
November 2–6, 2018
<a href="http://aapexperience.org/">http://aapexperience.org/</a>

Hot Topics in Neonatology®
Marriott Marquis
Washington, DC
December 3-5, 2018
<a href="http://www.hottopicsinneonatology.goog/">http://www.hottopicsinneonatology.org/</a>

NEO
The Conference for Neonatology
Coming February 2019
Orlando, FL
http://www.neoconference.com/

The 36<sup>th</sup> Annual Advances in Therapeutics and Technology Conference Snowbird, Utah March 26-30, 2019 http://paclac.org/advances-in-careconference/

Improving Access to Perinatal Care:
Confronting Disparities and
Inequities in Maternal-Infant Health
National Perinatal Association
April 3 - 5, 2019
Providence, Rhode Island
<a href="http://nationalperinatal.org/2019Conference">http://nationalperinatal.org/2019Conference</a>

Pediatrics Academic Societies
Meeting
Apr 27-30, 2019;
Baltimore, MD
https://www.pas-meeting.org/

For Additional Meeting Information, visit <u>NeonatologyToday.net</u> and click on the events tab.

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#### Introducing a New Section and a New Editor

Starting with the June, 2018 edition of Neonatology Today, Dr. Herbert A. Vasquez will be providing oversight of our Neonatology and the Arts section. Dr. Vasquez is a Board Certified Neonatologist who practices at Queen of the Valley Medical Center in West Covina.

This section will focus on artistic work which is by those with an interest in Neonatology and Perinatology. The topics may be varied, but preference will be given to those works that focus on topics that are related to the fields of Neonatology, Pediatrics, and Perinatology. Contributions may include drawings, paintings, sketches, and other digital renderings. Photographs and video shorts may also be submitted. In order for the work to be considered, you must have the consent of any person whose photograph appears in the submission.

Works that have been published in another format are eligible for consideration as long as the contributor either owns the copyright or has secured copyright release prior to submission.

Logos and trademarks will usually not qualify for publication.

This month's selection (see the next page) features a drawing (1 of 3 in a series) that Dr. Vasquez produced for the cover of the 2008 National Perinatal Association Annual Meeting brochure. The meeting focused on the topic of "The Spectrum of Violence in Perinatal & Neonatal Care: Reducing the Risks." In this graphic, the duality of the maternal and paternal interests in the fetus is illustrated. The raw emotion and stress is clearly evident as the parents must decide on the fate of a life created with assisted reproductive technologies.



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- 3. There is no charge for submission, publication (regardless of number of graphics and charts), use of color, or length. Published content will be freely available after publication (i.e., open access). There is no charge for your manuscript to be published under open access
- 4. The title page should contain a brief title and full names of all authors, their professional degrees, their institutional affiliations, and any conflict of interest relevant to the manuscript. The principal author should be identified as the first author. Contact information for the principal author including phone number, fax number, email address, and mailing address should be included.
- 5. A brief biographical sketch (very short paragraph) of the principal author including current position and academic titles as well as fellowship status in professional societies should be included. A picture of the principal (corresponding) author and supporting authors should be submitted if available.
- 6. An abstract may be submitted.
- 7. The main text of the article should be written in formal style using correct English. The length may be up to 5,000 words. Abbreviations which are commonplace in neonatology or in the lay literature may be used
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- 9. Figures should be submitted separately as individual separate electronic files. Numbered figure captions should be included in the main file after the references. Captions should be brief.
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