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CSF Pleocytosis with Predominant Polymorph's in a Febrile Neonate without Meningitis

By Kamlesh K. Jha, MBBS, MD, FAAP; Shruti Trehan, MBBS, MD, FAAP; Shilpa Singh, MBBS, MD, FAAP; Sasidhar Goteti; Pragya Jha; Romeen Lavani, MBBS, MD, FAAP

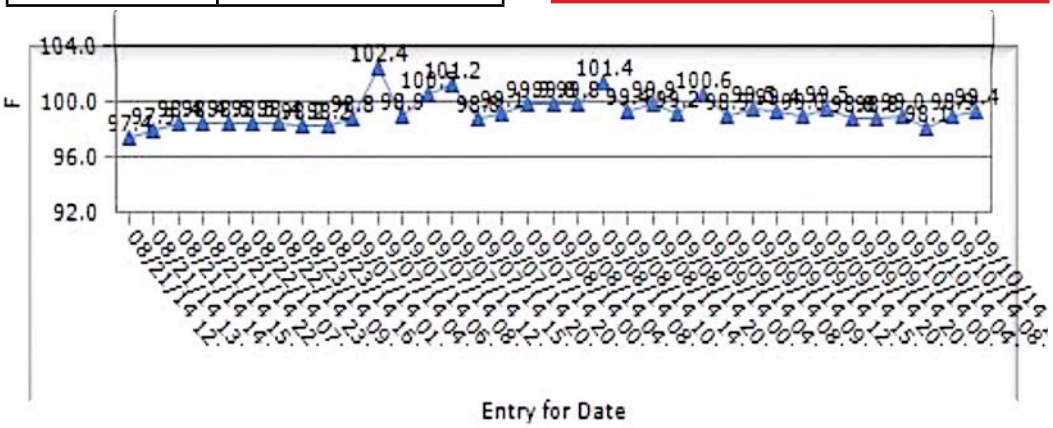
Case Report

A seventeen-day-old female neonate, who was well until 1 day prior to admission, was brought to the Emergency Department with complaints of fever. Initial temperature at home was 101F. At the time of taking the temperature, the neonate was covered with 3 blankets and a shirt top. The mother undressed her and rechecked Temperature after 10 minutes later. The temperature now was 99.1F (axilla), but the mother still decided to bring her to the Emergency Department (ED). The child had no cough, diarrhea, vomiting, abnormal movement, skin rash or poor feeding. She was feeding normally,10-15 minutes on each breast with about 1-2 oz of formula as supplement, every 2-3 hours. She continued to have about 10 wet diapers and 3-4 soiled diapers in a day. The only change the mother noted, on the day of admission, was episodes of intermittent crying and irritability. However, the child was easily consolable. No treatment was given to the neonate at home prior to bringing her to the hospital.

The neonate was born via C-section secondary due to breech presentation. Maternal GBS screen was positive, but rupture of membranes was done artificially 1 minute before delivery; the mother did not have fever or foul smelling discharge. Mom's antenatal HIV screen, Hepatitis B screen, and RPR screen were negative. The mother and neonate were both O-positive and Coombs negative. The 24-hour total bilirubin was in the low-risk zone. The neonate was discharged with mother at 72

Table 1	
CSF Values	
WBC	53.0H *(0.0-30.0 K/uL)*
Neutrophils	61 H *(0-8 %)*
Lymphocytes	9 *(5-35 %)*
Monocytes	30 L *(50-90%)*
RBC	0.0 *(K/uL)*
Glucose	39 L *(40-70 mg/dl)*
Protein	66 H *(15-45 mg/dl)*

"Since the neonate had fever, the decision was made to keep patient in the hospital and perform partial sepsis workup and serial clinical assessment."



Graph 1. To view a larger version of this graph, go to: http://www.neonatologytoday.net/newsletters/Graph1.pdf

Managing oxygen toxicity can be a challenge

Yet there are no published national guidelines for hyperoxia management.[1]

We appreciate the complexity of the challenges you face every day. That's why we're proud to offer **OXYGENISADRUG.com**, a comprehensive resource with information about:

- Supplemental oxygen therapy
- Consequences of hyperoxia
- Practice and protocols
- Historical perspectives

Though supplemental oxygen is necessary and often beneficial at appropriate doses, elevated levels can put patients at risk for hyperoxia with the potential for long-term tissue damage.[2]

It is possible to have too much of a good thing. Learn how to manage the challenge at **OXYGENISADRUG.com/toxicity**

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References: 1. Agency for Healthcare Research and Quality. National Guideline Clearinghouse website. http://www.guideline.gov/search/search.aspx?term=hyperoxia. Accessed August 18, 2015. **2.** Kulkarni AC, Kuppusamy P, Parinandi N. Oxygen, the lead actor in the pathophysiologic drama: enactment of the trinity of normoxia, hypoxia, and hyperoxia in disease and therapy. *Antioxid Redox Signal*. 2007;9(10):1717-1730.

Table 2					
DIRECT BILIRUBIN				0.3 *(0.0-0.8 mg/dL)*	
BILIRUBIN TOTAL SERUM	TOTAL BILIRUBIN				5.8 H *(0.0-4.9 mg/dL)*
CHEM 7 PROFILE SERUM	GLUCOSE SERUM			97 *(60-100 mg/dL)*	
	BUN			8 *(5-27 mg/dL)*	
	CREATININE			0.45 *(0.30-0.80 mg/dL)*	
	BUN/CREATININE RATIO			17.78 *(6.00-20.00)*	
	CALCIUM			10.7 *(9.0-10.9 mg/dL)*	
	SODIUM			137 *(135-145 mmol/l)*	
	POTASSIUM			5.2 *(3.9-6.9 mmol/l)*	
	CHLORIDE			103 *(98-115 mmol/l)*	
	CO2			20 *(20-29 mmol/l)*	
COMPLETE BLOOD COUNT	WBC			9.5 *(5.0-19.5 K/cmm)*	
	RBC			4.29 *(3.60-6.20 m/cmm)*	
	HEMOGLOBIN			14.5 *(12.5-20.5 g/dL)*	
	HEMATOCRIT			41.9 *(39.0-63.0%)*	
	MCV			97.7 *(88.0-123.0 fL)*	
	MCH			33.8 *(31.0-37.0 pg)*	
	MCHC			34.6 *(28.0-36.0 g/dL)*	
	RDW			15.1 H (11.2-14.4%)	
	MPV			10.0 *(7.0-10.2 fL)*	
	PLTs			433 H *(145-368 K/cmm)*	
	SEG (Abs)			5.6 *(1.0-9.0 K/uL)*	
	LYMPH (ABS)			3.3 *(2.0-17.0 K/uL)*	
	MONO (Abs)			0.5 L *(1.1-1.2 K/uL)*	
	EOS (ABS)			0.0 *(0.0-0.2 K/uL)*	
	BASO (ABS)			0.1 *(0.0-0.1 K/uL)*	
CSF CELL COUNT	TUBE NUMBER		3.0 *(K/uL)*		
	CSF WBC		53.0 H *(0.0-30.0 K/uL)*		
	CSF RBC		0.0 (K/uL)		
	CSF NEUTROPHILS		61 H *(0-8 %)*		
	CSF LYMPHOCYTE		9 (5-35 %)		
	CSF MONOCYTES		30 L *(50-90 %)*		
GLUCOSE SPINAL FLUID	CSF GLUCOSE	39 L *(40-70 mg/dl)*			
PROTEIN SPINAL FLUID	CSF PROTEIN	66 H *(15-45 mg/dl)*			
zzMDIFFERENTIAL	SEG (MAN)			55 *(40-72%)*	
	LYMPH (MAN)			34 *(17-45%)*	
	MONO (MAN)			5 *(2-8 %)*	
	EOS (MAN)			0 *(0-10%)*	
	LYMPH (Atyp)			1 *(%)*	
	BAND			4 *(0-8 %)*	

hour-of-life. Apgar score was 9 & 9. The neonate's older sister was ill at home; she had fever, and was vomiting.

On the arrival of the neonate in the ED, initial rectal temperature was 100F. There was no sign of respiratory distress; capillary refill and blood pressure were normal. Oxygen saturation on room air was 98%. Since the neonate had a fever, the decision was made to admit the patient in the hospital and perform partial sepsis workup and serial clinical assessment. The initial CBC was normal for age (Tab), with IT ratio of 0.06; chest X-ray and electrolytes were normal.

Three hours after admission to the pediatric ward, the neonate had fever of 102.4F (Graph 1). At that time, a decision was made to perform spinal tap to rule out intracranial infection, namely meningitis. After explaining the spinal tap procedure, written parental consent was obtained from the neonate's mother, and the procedure was performed.

The CSF analysis (Table 1) revealed no red blood cells with 53 white blood cells per high power field. Out of the total 53 WBCs, 61% were neutrophils. CSF glucose and CSF protein was 39mg/dl and 66mg/dl respectively. CSF gram stain showed no bacteria and final culture was negative. CSF HSV PCR and blood culture were also negative. Newborn Metabolic Screen was normal.

Immediately after the spinal tap, the neonate was started on IV Cefotaxime and Ampicillin. The medications were continued until CSF culture and HSV PCR were reported. The neonate received 72 hours of IV antibiotics. During the 72 hours of stay in the hospital, with the exception of few spikes of temperature with Tmax of 101.4F, the neonate remained hemodynamically stable, and continued to feed well. Unfortunately, the urine culture sample was lost. Since blood culture, CSF, and HSV PCR all came out negative, the neonate was discharged home on oral amoxicillin.

Discussion

Bacterial/viral intracranial infection results in significant mortality and morbidity in newborns. Examination of cerebrospinal fluid, including bacterial culture and HSV PCR, remains the most valuable test in diagnosing meningeal infection. Although CSF culture remains the gold standard test to diagnose bacterial meningitis, initial CSF cell count, glucose and protein values help clinicians tremendously in making a clinical impression, deciding treatment and counseling parents. Srinivasan et al 2012[1] found no difference in CSF WBC count between preterm and term infants in their first week of life and beyond (median 3cells/µl). Luz et al[2] found that the CSF WBC count can be up to 12 WBC/mm3 in full-term neonates. Byington et al,[3] in 677 infants with atraumatic lumbar punctures, (red blood cell [RBC] count <1000/mm^3) found the mean and median CSF white blood cell (WBC) counts were 4.3/mm3 and 3.0/mm3, respectively, with a range from 0 to 12/mm3.

Ahmed Amina et al[6] found the mean ±SD total CSF WBC count for 108 non-infected neonates was 7.3 ±14/mm3 (95% confidence interval 6.6 to 8.0/mm3). Mhanna MJ et al[7] found a decrease in the CSF WBC count, from a median of 14 WBCs/mm3 at 25 wk GA to a median of 8WBCs/mm3 at 34 week GA.

Lori A. Kestenbaum et al[4,5] in 380 infants, 0–28 days of age, found a median CSF WBC of 3/mm3 with a 95th percentile value of 19/mm3; whereas, infants between 29–56 days of age had a statistically lower median CSF WBC count of 2/mm3, with a 95th percentile value of 9/mm3 ($p<0.001$). A patient with a CSF WBC count of 320/mm^3, who had a mononuclear cell predominance, (i.e., 40% lymphocytes and 33% monocytes) was discharged with a diagnosis of probable aseptic meningitis. A patient with a CSF WBC count of 198/mm^3 had a negative CSF enterovirus PCR, including all other cultures, but treated presumptively for bacterial meningitis with antibiotics.

In our case, WBC count, as well as the percentage of segmented WBC cell, was definitely high enough to consider presumptive bacterial meningitis until CSF bacterial culture and HSV PCR came back negative. One thing which we did not order was CSF enterovirus culture. The "take home" message from this case would be:

(a) to do CSF enterovirus culture in all newborns whose CSF WBC count is higher than the highest normal number and,
(b) if percentage of segmented WBC cell is high, but the bacterial culture is negative, the option to discontinue IV antibiotic can be safely chosen after having a discussion with the parents.

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8th Annual Neonatal and Pediatric ECMO Conference
Aug. 1 - 3, 2016; Pittsburgh, PA USA
www.chp.edu/health-care-professionals/cme/other-cme/ecmo-educational-conference

Innovations in Neonatal Care: Breathing Easy - Respiratory Management in the Modern Era
Aug. 8-10; San Antonio, TX USA
www.innovationsconference.com

6th International Arab Neonatal Care Conference (ANCC 2016)
Sep. 29-Oct 1; Dubai
www.ancc2016.com

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- Optionally, a picture of the author(s) may be submitted.
- No abstract should be submitted.
- The main text of the article should be written in informal style using grammatically correct English. The final manuscript may be between 400-4,000 words, and contain pictures, graphs, charts and tables. Accepted manuscripts will be published within 1-3 months of receipt. Abbreviations which are commonplace in pediatric cardiology or in the lay literature may be used.
- Comprehensive references are not required. We recommend that you provide only the most important and relevant references using the standard format.
- Figures should be submitted separately as individual separate electronic files. Numbered figure captions should be included in the main Word file after the references. Captions should be brief.
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Getting it Right: Diagnosing True Infections in the NICU. It Matters!

Michael Narvey, MD

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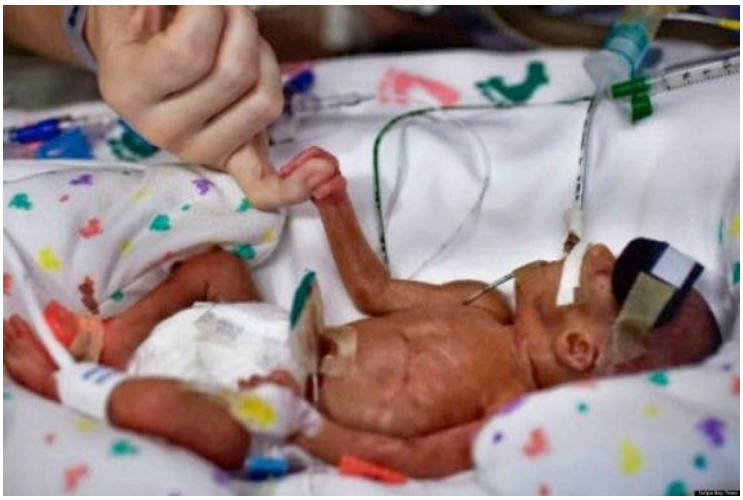


The scenario is often the same. Faced with a child born to a mother with risk factors for sepsis you decide to start antibiotics. The time comes closer to 36–48 hours when you must decide whether or not to continue. Each time we examine our results and look at cultures and try to do what is right. Yet defining right is sometimes hard for so many. If we had 100% sensitivity and specificity for all our tests it would be easy, but we don't. So what can we do?

If I had to have one wish, though, it would be that we could improve upon our diagnostic accuracy when it comes to treating suspected infections in the newborn. As health care providers we have an extremely loud inner voice trying to tell us to minimize risk when it comes to missing a true bacterial infection. On the other hand, so much evidence has come forth in the last few years demonstrating that prolonging antibiotics beyond 48 hours is not just unwise in the absence of true infection, but can be dangerous. Increased rates of necrotizing enterocolitis is just one such example, but other concerns due to interfering with the newborn microbiome have arisen in more recent years. What follows are some general thoughts on septic workups that may help you (and myself in my own practice) as we move ahead into the New Year and may we cause less harm if we consider these.

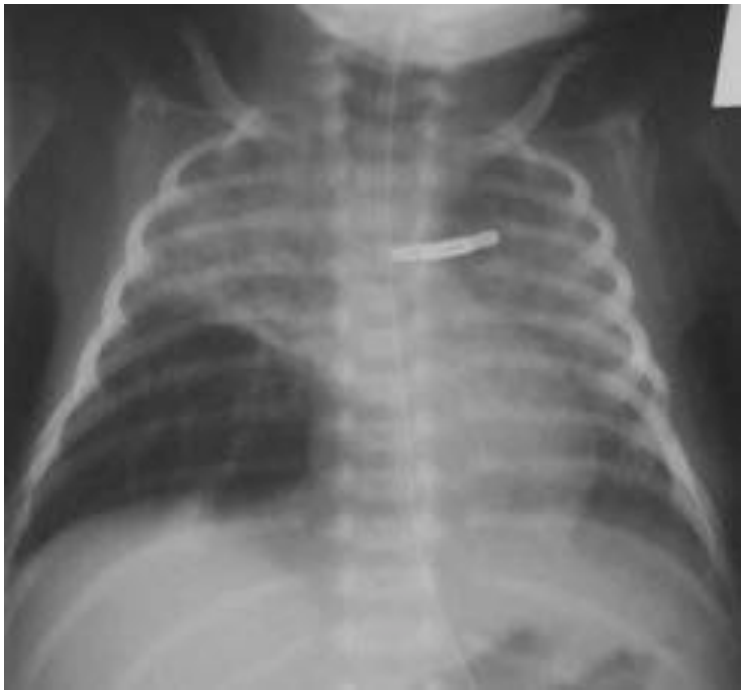
The Role of Paired Blood Cultures

Although not published by our centre yet, we adopted this strategy for late onset sepsis a couple years back and have seen a significant reduction in work-ups deemed as true infections since adoption. While the temptation to do only one blood culture is strong as we have a desire to minimize skin breaks, consider how many more there will be if you do one culture and get a CONS organism back. There will be several IV starts, perhaps a central line, repeat cultures, etc. If you had done two at the start and one was positive and the other negative you could avoid the whole mess as it was a contaminant from the start. On my list of do no harm, I think this may have the greatest benefit.

The Chest X-Ray Can Be Your Friend

While I am not a fan of routine chest X-rays, I do believe that if you are prepared to diagnose an opacification on a chest X-ray as being due to a pneumonia (VAP or in those non-ventilated), that you need to follow this up with a repeat X-ray 24–48 hours later.

If the opacity is gone, it was atelectasis as a true pneumonia will not clear that easily. Well worth the radiation exposure I say.



If You Are Going To Do a Work-Up, Make It a Complete One

We hear often on rounds the morning after a septic work-up that the baby was too sick to have an LP and that we can just check the CSF if the blood is positive. There are two significant problems to this approach. The first, which is a significant concern, is that in

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a recent study of patients with GBS meningitis, 20% of those who had GBS in the CSF had a negative blood culture. Think about that one clearly… relying on a positive culture to decide to continue antibiotics may lead to partially-treated GBS meningitis when you discontinue the antibiotics prematurely. Not a good thing. The second issue is that infants with true meningitis can have relatively low CSF WBC counts and may drift lower with treatment. Garges et al in a review of 95 neonates with true meninigits found that CSF WBC counts >21 cells per mm3 had a sensitivity of 79% and specificity at 81%. This means that in those with true meningitis, 19% of the time the WBC counts would be below 21, leading to the false impression that the CSF was "fine." If antibiotics were effective, it could well be by 48 hours that the negative CSF culture you find would incorrectly lead you to stop antibiotics.

Message: Do the CSF sampling at the time of the septic work-up whenever possible.

If We Aren't Prepared To Do a Supra Pubic Aspirate Should We Not Collect Urine At All?

This provocative question was asked by a colleague last week and is based on the results of a study which was the topic of the following post: Bladder Catherterizations for UTI: Causing more harm than good? The gist of it is that it would appear that in many cases the results of a catheter-obtained urine cannot be trusted. If that is the case, then are we ultimately treating infections that don't actually exist when the only positive culture is from a urine. I believe using point-of-care ultrasound to obtain specimens from a SPA will be the way to go, but in the meantime how do we address the question of whether a UTI is present or not? We may need to rely on markers of inflammation such as a CRP or procalcitonin, but that is not 100% sensitive or specific either; however, it may be the best we have at the moment to determine how to interpret such situations.

Watch video at:
www.ted.com/talks/carl_honore_praises_slowness

Lastly, Slow Down And Practice Good Hand Hygiene

So much of what I said above is important when determining if an infection is present or not. The importance of preventing infection cannot be understated. Audits of hand hygiene practice more often than not demonstrate that physicians are a group with some of the lowest rates of compliance. Why is that? As a physician I think it has nothing to do with ignorance about how to properly perform the procedure, but rather a tendency to rush from patient to patient in order to get all the things done that one needs to do well on service or call. If we all just slow down a little, we may eventually have less need to run from patient to patient as the rate of infections may drop and with it demand for our time.

If slowing down is something that you too think is a good idea you may want to have a look at the book *In Praise of* Slowness by Carl Honore (TED Talk www.ted.com/talks/carl_honore_praises_slowness), which may offer some guidance on how to do something that is more easily said than done. Here is hoping for a little slower pace in the new year. We could reap some fairly large benefits!

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The Development of New Pharmacological Therapies for Infants – The National Perinatal Association's Position of Support for Senate Bill S.2041 - Promoting Life-Saving New Therapies for Neonates Act of 2016

By Sue Hall, MD; Raylene Phillips, MD; Vincent C. Smith, MD; Cris Glick, MD; Mitchell Goldstein, MD; T. Allen Merritt, MD

Members of the NPA write a regular column in *Neonatology Today*.

Introduction

Historically, children and newborn infants in particular, have been underrepresented in the development of pharmaceuticals and biologics with pediatric indications, appropriate dosing, and risk benefit profiles. A new law has been proposed to address this disparity and further encourage new pharmaceutical development for newborns: United States Senate Bill S.2041 - Promoting Life-Saving New Therapies for Neonates Act of 2016.

Despite a recognition by Congress that children's interests are not being met with pediatric pharmaceutical development, very little progress has been made to meet this need. As a result, efforts to offer even more incentives to pharmaceutical companies such as those described in Bill S.2041 are being made. After a careful review of the history of pediatric pharmaceutical development, the National Perinatal Association supports this bill. At the same time, we call for accountability, transparency and a true public-private collaborative effort in the process of pharmaceutical development, testing, marketing and pricing of new products.

Background

Development and approval of new pharmaceuticals for neonates (newborn infants up to 28 days of age) is insufficient to meet the needs of our most fragile patients. Pulmonary surfactant had its origins in the academic research labs and was subsequently later transitioned to a commercial pharmaceutical product(s). Many of the pharmaceuticals utilized in Neonatal Intensive Care Units (NICUs) have their indication and dosing extrapolated from adult indications and dosing. This type of "off label" usage is necessary because many drugs have no Food and Drug Administration (FDA) approved use or dosing for neonatal-specific indications. These pharmaceuticals may provide clinical benefit as determined either anecdotally by clinicians or through small-scale clinical trials; their lack of FDA approval in some cases may be due to the fact that an adequate amount of research to ensure both safety and efficacy has never been done in babies. Occasionally, pharmaceuticals that are used "off label" in neonates have previously unrecognized adverse effects that can be serious and sometimes life-threatening. One example is Sildenafil, which ultimately required specific warnings limiting its use. Although an FDA indication specific to the neonatal population does not guarantee an absence of serious adverse effects with widespread use of a new pharmaceutical or biologic, appropriate FDA oversight can provide assurances that a pharmaceutical or biologic has undergone rigorous and extensive testing of safety and efficacy in this population.

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Neonates have their own unique physiology and pathology that makes them distinct from older children and adults. They have a range of age-specific medical issues, including metabolic and organ systems that are still maturing, less reliable metabolism and decreased clearance of pharmaceuticals and biologics. This is particularly true in preterm infants (those born at less than 37 weeks completed gestation). Because results of studies in older children and/or adults cannot be easily extrapolated to this distinct and vulnerable population, we need research and development of pharmaceuticals intended specifically for them.

There are many barriers to development of new pharmaceuticals or biologics for neonates. First, because neonates represent a relatively small target patient population, it takes longer for a company to recoup the significant investment required to develop, test and market a new pharmaceutical or biologic. Pharmaceuticals and biologics for neonates may qualify for "orphan" status, meaning that they treat fewer than 200,000 people in the U.S. on an annual basis or sales are not expected to recover the costs required for their development and marketing. This is particularly relevant since only about 200,000 preterm newborns are admitted to NICUs each year, and not every preterm infant will develop all of the conditions for which medications to improved prevention and/or treatment are needed (for example, retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia).

Second, performing clinical trials to determine pharmaceutical safety and efficacy in neonates is fraught with challenges. One issue is the enormous degree of variability in the population of preterm infants. Metabolic systems and processes (absorption, distribution, metabolism and excretion) can differ markedly from an infant that is born at 23 weeks gestational age, the cusp of viability, to infants born at 36 weeks and beyond. A pharmaceutical or biologic that might be safe and well-tolerated

by a 36-week gestation infant might be toxic to one born at 23 weeks. Consequently, trials need to be done in large numbers of preterm infants with a wide range of gestational ages. To realistically accomplish this goal, multicenter trials are essential. Coordinating such a research endeavor is complex and costly.

Third, conducting research on medication safety and efficacy in neonates involves the ethical consideration of obtaining informed consent from parents who are already distressed about having a sick baby. Even if basic science and laboratory research or research in populations of older children or even adults has been conducted to suggest a particular pharmaceutical or biologic may be helpful in the preterm infants, there is no way to accurately predict all potential side effects and adverse events so as to fully inform parents.

Finally, pharmaceutical development is an increasingly expensive proposition. The Tufts Center for the Study of Drug Development's 2014 has estimated that the cost to develop and bring a pharmaceutical to market is now $2.6 billion. Although this estimate has been challenged, there is no doubt the cost is astronomically high. While innovations may come from university scientists through basic science or "bench" research around new pharmaceuticals or biologics that could ultimately be useful in helping to prevent or treat conditions that are seen in neonates, the universities themselves are ill-equipped to take the risks and absorb the costs of conducting research on the scale and scope that is necessary to gain FDA approval of new medications, especially when approval is by no means assured. Similarly, universities are not in the business of producing, distributing, and/or marketing new pharmaceuticals or biologics; these tasks all are dependent on private industry for funding and expertise.

In the last several decades, the FDA has focused increased attention on the unique medication development and utilization needs of pediatric patients. In 1979, the FDA first required pediatric information to be included on pharmaceutical labels. In 1994, pediatric indication for pharmaceuticals was granted if pediatric dosing was established. It was not until 1997, when the Food and Drug Administration Modernization Act (FDAMA) was passed, that incentives were created to encourage drug testing of already branded drugs in pediatric patients; the main incentive was a 6-month patent extension, and hence, market exclusivity (including adult use of the medications) for any pharmaceuticals developed as a result of this legislation, termed "pediatric exclusivity." At the same time, pharmaceutical manufacturers were required to provide pediatric testing data with all new pharmaceutical applications.

The following year, legislation passed to require pediatric testing as part of any new pharmaceuticals which had potential uses in pediatric patients; this was known as the Pediatric Final Rule. Four years later, a federal court overturned this rule, but in 2003, Congress reinstated it through the Pediatric Research Equity Act (PREA). In 2002, the Best Pharmaceutical for Children Act (BPCA) was passed, extending the previously granted 6-month exclusivity extension provision through the year 2007. This law also allowed the FDA to invite the National Institute of Health (NIH) to obtain pediatric data on pharmaceuticals for which manufacturers declined to obtain the data; pediatric study results could then lead to approval of the pharmaceuticals for pediatric indications. One situation in which pharmaceutical manufacturers frequently declined to gather data on pediatric patients is in the case of generic pharmaceuticals, because these don't have the potential for large financial returns, such as might be seen with newer patented pharmaceuticals. Further, generic products are not eligible for the Orphan Drug Act.

These laws have cumulatively had the positive effect of stimulating a large number of clinical pharmaceutical trials in children, resulting in over 500 product labeling changes. In some cases, FDA-approved indications for use in children were added to pharmaceuticals already on the market; in other cases, new warnings and/or new dosing instructions were added to pharmaceuticals previously approved only for adults; and in still others, the clinical trials failed to show efficacy in infants and children. But while the number of studies leading to increased numbers of medications and drug-device combinations with pediatric labeling has expanded significantly over the past 10 years, there continues to be a dearth of new pharmaceutics, biologics and drug-device combinations developed specifically for the neonatal population.

NPA Position of Support

The National Perinatal Association would prefer that government-sponsored financial incentives would be unnecessary to encourage pharmaceutical companies to pursue pharmaceutical development for neonates, it recognizes that relying solely on government intervention and/or mandates for companies to develop and produce such pharmaceuticals is neither a practical nor a desirable solution in our society. The intent of Bill S.2041 - Promoting Life-Saving New Therapies for Neonates Act of 2016 is to address this situation by providing greater financial incentives to spur innovation. This bill would create a transferable "Neonatal Drug Exclusivity Voucher." Companies that test and develop pharmaceuticals and biologics for preterm or full-term newborns that are on a Priority List of Critical Needs for Neonates (also created by the bill), would be eligible to receive the voucher. The voucher would enable the product sponsor to extend their exclusivity in the marketplace by one year, and even to transfer this period of exclusivity to another pharmaceutical or biologic in order to help offset the costs of research and testing of new products for neonates.

While lobbying efforts for the needs of sick and aging adults are heavily funded, neonates cannot lobby or advocate for themselves. We must recognize and respond to this unmet need and speak up for those who have no adult voice. Without our efforts on their behalf, many sick and preterm infants may never reach adulthood.

The National Perinatal Association endorses S.2041 - Promoting Life-Saving New Therapies for Neonates Act of 2016 in the hopes that these long-neglected and vulnerable patients will be the recipients of therapeutic advances to improve their long-term survival and outcome.

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Medical News, Products & Information

Compiled and Reviewed by Tony Carlson, Senior Editor

SMFM Releases Statement on the Use of Antenatal Corticosteroids in Late Preterm Birth Period

The Society for Maternal-Fetal Medicine released a statement on the use of antenatal corticosteroids during the late preterm birth period for women at risk of preterm birth. The statement, is currently available online and was published in the July issue of the *American Journal of Obstetrics and Gynecology.* It comes on the heels of a study and a presentation at SMFM's annual meeting in Atlanta in February where researchers with the Eunice Kennedy Shriver National Institute of Child Health and Human Development and Maternal-Fetal Medicine Units Network (MFMU) presented findings that the administration of antenatal steroids in pregnancies at risk for late preterm delivery prevents respiratory and other neonatal complications.

The study, titled "Antenatal Late Preterm Steroids (ALPS): a Randomized Trial to Reduce Neonatal Respiratory Morbidity" was a randomized, double-blind, placebo-controlled trial at 17 tertiary medical centers around the United States from Oct. 2010 to Feb. 2015. The study enrolled 2,831 women with singleton pregnancies at high risk for late preterm delivery (34 0/7 to 36 6/7 weeks) who were randomized to receive antenatal betamethasone intramuscularly or a matching placebo. This study found a significant decrease in neonatal respiratory complications in the group given the steroid treatment. Investigators also found that these babies were less likely to have prolonged intensive care nursery stays, less likely to need postnatal treatment for respiratory complications, and less likely to develop bronchopulmonary dysplasia, which is a sign of chronic lung disease. Prior to this report, such treatment was only recommended with risk of preterm delivery before 34 weeks of gestation, as infants in the late preterm period were thought to be at little, if any, increased risk of complications.

Lead investigator, Cynthia Gyamfi-Bannerman, MD, MSc, the Ellen Jacobson Levine and Eugene Jacobson Associate Professor of Women's Health (in Obstetrics and Gynecology) from Columbia University Medical Center, put the findings in context, "The majority of preterm deliveries occur in the late preterm period. We now have a treatment that can significantly improve outcomes for these at risk babies." The study was co-funded by the NHLBI, with the aid of program officer Carol Blaisdell, MD and the NICHD under the guidance of Uma Reddy, MD.

In their statement, the Society for Maternal-Fetal Medicine recommends:

- In women with a singleton pregnancy between 34 weeks to 36 6/7 weeks of gestation who are at high risk for preterm birth within the next seven days (but before 37 weeks of gestation), SMFM recommends treatment with betamethasone, a corticosteroid demonstrated to decrease neonatal complications in preterm infants.
- In women with preterm labor symptoms in the late preterm period, SMFM recommends waiting for evidence of true preterm labor, such as a cervical dilatation of at least three centimeters or effacement of at least 75% before treatment with betamethasone.
- In women with late preterm pregnancies receiving betamethasone, SMFM recommends against the use of tocolysis in an attempt to delay delivery to complete the steroid course, since it is unclear if the benefits are outweighed by the risks of attempts to delay delivery.
- In women with late preterm pregnancies with a potential medical indication for delivery, SMFM recommends betamethasone not be given unless there is a definitive plan for late preterm delivery.

SMFM also recommends against the implementation of antenatal late preterm steroids protocol for conditions not studied in the randomized controlled trials.

Given that more than 300,000 pregnancies deliver in the late preterm period each year in the U.S., the study, along with recommendations for adoption by the Society for Maternal-Fetal Medicine, will have a significant impact on the health of newborns and infants.

To read the complete manuscript and statement, go to http://www.ajog.org/article/S0002-9378(16)00475-0/pdf.

For more information on SMFM publications, go to https://www.smfm.org/publications.

Gray Matter Abnormality Predicts Neurodevelopmental Problems in Smaller Premature Babies

Magnetic Resonance Imaging (MRI) of the brain is increasingly used to predict neurodevelopmental outcomes in premature infants, but the existing systems of analyzing or "scoring" those MRIs rely heavily on expert opinion. A new study led by clinician-researchers at Nationwide Children's Hospital has explored a more objective system for scoring MRIs - and in the process found that an often unreported abnormality of the brain's gray matter can indicate future impairment.

The abnormality, called moderate-to-severe gyral maturational delay, emerged as the only significant predictor of overall neurodevelopmental impairment in the study group of premature infants with extremely low birth weights. Gyral maturation delay also predicted cognitive delay; a combined outcome of cognitive delay and death; and a combined outcome of neurodevelopmental delay and death.

In contrast, when researchers used a more opinion-based scoring system, gray matter scores did not show a significant association with neurodevelopmental impairment.

"We let the data drive our model," said Laurel Slaughter, MD, a neurologist at Nationwide Children's and lead author of the study. "We measured numerous individual imaging factors and their correlation to outcomes, instead of deciding ahead of time what we believed would be important. There is still some subjectivity, and neuroradiologists are going to have slightly different readings or interpretations. But our model is more objective."

The study, published online in the April journal *Neonatology*, involved 122 infants born premature with a weight equal to or less than 2.2 pounds (1 kilogram). Brain MRIs were performed at term-equivalent age at Memorial Hermann Children's Hospital, Houston, under the supervision of Nehal Parikh, DO. Dr. Parikh, now a neonatologist at Nationwide Children's and Principal investigator in the Center for Perinatal Research in The Research Institute at Nationwide Children's, is the study's senior author.

At 18 to 24 months of age, the infants were tested using the Bayley Scales of Infant and Toddler Development III, and all had a standard neurologic examination for the presence of cerebral palsy.

Along with the findings involving gyral maturational delay, researchers discovered that diffuse cystic abnormality was a significant predictor of cerebral palsy with the data-driven scoring system. This result is consistent with several previous studies.

These predictors exhibited high specificity (95% to 99%), so when gyral maturational delay and diffuse cystic abnormality were found,

often impairments were as well. However, both predictors showed comparatively low sensitivity (30% to 67%), illustrating that the absence of gyral maturational delay and diffuse cystic abnormality does not always mean impairments are also absent.

"We can't predict with certainty that these babies are going to do well just because the MRIs looked good," said Dr. Slaughter, who is also an assistant professor of Clinical Pediatrics at The Ohio State University College of Medicine. "These are still significantly premature babies that we need to monitor."

According to Dr. Slaughter, the study may suggest to physicians that if these predictors are found, therapies should begin at the earliest moment that impairments become obvious. This research also focuses more attention on the brain's gray matter, while previous studies have focused on white matter.

"A lot of counseling of families regarding outcomes is based on white matter," she says. "Our findings show that you can't just rely on white matter as a predictor."

Citation: Slaughter L, Bonfante-Mejia E, Hintz S, Dvorchik I, Parikh NA. Early conventional MRI for prediction of neurodevelopmental impairment in extremely-low-birth-weight infants. Neonatology. 2016 Apr 7. [Epub ahead of print]

Artificial Placenta Holds Promise for Extremely Premature Infants

Researchers at the University of Michigan are working to improve survival rates in the tiniest, most premature babies in a groundbreaking way: through an artificial placenta that mimics the womb.

The technology hasn't reached a clinical trial, but researchers from U-M's C.S. Mott Children's Hospital and Extracorporeal Circulation Research Laboratory are making dramatic progress. An extracorporeal artificial placenta at the institution has kept five extremely premature lambs alive for a week. The lambs were transferred to the artificial placenta which utilizes extracorporeal membrane oxygenation (ECMO) without ever taking their first breath.

The ultimate goal of nearly a decade of sustained work: for an artificial placenta to help extremely premature babies with the greatest risks of disability or death continue critical organ development outside of their mother's womb.

'A Complete Paradigm Shift'

Despite significant advances in the treatment of prematurity, the risk of death and long-term disability remains high for extremely premature infants born before 24 weeks – these babies' tiny bodies simply are not prepared for life outside the womb.

"One of the gravest risks for extremely premature babies is undeveloped lungs that are too fragile to handle even the gentlest ventilation techniques," says George Mychaliska, MD, the Principle Investigator and Director of the U-M's Fetal Diagnosis and Treatment Center. "If a baby's lungs are severely immature, they cannot provide the brain, heart and other organs the oxygen they need to survive."

Mychaliska, who has been referred to as Michigan's "fetus fixer" for his renowned fetal intervention work, has been leading research to improve outcomes for premature infants.

"We thought 'why don't we solve the problem of prematurity by recreating the intrauterine environment?'" he says. "Maybe we should treat this tiny baby like a fetus. Maybe we should treat these babies as if they are still in the womb. This is a complete paradigm shift. Our research is still in a very preliminary stage, but we've passed a significant milestone that gives us promise of revolutionizing the treatment of prematurity.

"Although many of our current therapies are life-saving, they are not designed for premature babies and are often ineffective or contribute to complications," he adds.

How It Works

The innovative artificial placenta simulates the intrauterine environment and provides gas exchange without mechanical ventilation. By recapitulating normal fetal physiology to recreate the intrauterine environment, the artificial placenta holds the promise of normal growth and development outside the womb for extremely premature infants until they are ready for postnatal life.

The success of keeping lambs alive through this technique was a crucial milestone in securing a $2.7 million R01 NIH grant helping accelerate this research.

The Way Forward

Over the next five years, researchers expect to demonstrate that an artificial placenta can be used to simulate the intrauterine environment and support a fetal lamb from extreme prematurity to normal newborn physiology. The next step would be to determine if the milestones would justify preliminary clinical trials in extremely premature babies. Read the full story in the Michigan Health Lab.

This research was originally published in Current Opinion in *Pediatrics*.

Even Doctors Get Confused About Reflux Disease in Babies

Newswise - Millions of Americans currently use medication for their indigestion and reflux, so it may come as no surprise that parents and doctors also prescribe medicine for newborns with reflux. However, according to a new study, newborns are likely being over-treated the majority of the time with interventions – including surgery – that have risks for the infant.

Gastric reflux is common in infants because the band of muscle, or sphincter, that squeezes the top opening of the stomach shut, does not yet close at full strength, especially in premature babies. As a result, babies often have reflux and spit up after feeding. When reflux happens within several minutes of other more dangerous symptoms such as drop in heart rate, apnea, coughing or gagging, arching of the back, incessant crying, and wheezing, physicians may suspect gastric reflux disease, or GERD.

"Since the baby can't tell us what they are feeling, we use this association between the reflux event and these other symptoms and signs of discomfort to help diagnose reflux disease," says senior author on the study, Zubair H Aghai, MD, Professor, Director of Neonatology Research at Thomas Jefferson University, and attending neonatologist with Nemours duPont Pediatrics at Jefferson Hospital. "However, our study demonstrates that these symptoms may not be associated with reflux and should not necessarily indicate treatment."

Instead of relying on clinical symptoms, some of which can be either underreported or over reported by nurses or family members, the researchers used a more definitive approach. The researchers compiled the data of 58 infants. Based on their symptoms all of these patients were suspected to have GERD by their doctors. However, the researchers showed that when a gold standard test for gastric disease called the multichannel intraluminal impedance study (or the MII-pH) was performed, only 6 patients, or 10%, actually had GERD. The results were recently published in *Journal of Pediatric Gastroenterology and Nutrition*.

Treatment for GERD in infants includes two types of drugs. The first are drugs such as ranitidine (Zantac), famotidine (Pepcid), and lansoprazole (Prevacid), which reduce acid in the stomach. However, research suggests acid is not a major factor in infant reflux and use of antacid in infants can lead to increased risk for infection. The second type is called metoclopramide or reglan, which has a black box warning for the risk of causing permanent damage to a child's brain, leading to movement disorders. A third option is surgery to tighten the sphincter at the top of the stomach. All of these interventions come with risks for the infant, and are often prescribed on the basis of symptom association alone.

"The study suggests that doctors who suspect infants of having GERD should use the MII-pH to confirm the diagnosis before treating with medications or surgery," says Dr. Aghai. "Unfortunately, the reason the test isn't done more often is that it can require advanced training and expertise that isn't available at all institutions."

Other than providing medication when it's not needed, misdiagnosing GERD in infants also masks the real cause of the problem. "When the MII-pH comes back negative, we have to do a better job of investigating the root causes of the symptoms we're seeing," says Dr. Aghai.

The authors report no conflicts of interest.

Article reference: A. Funderburk, et al., "Temporal Association Between Reflux-like Behaviors and Gastroesophageal Reflux in Preterm and Term Infants," J Pediatr Gastroenterol Nutr., DOI: 10.1097/MPG.0000000000000968, 2016.

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Breast Milk Linked to Significant Early Brain Growth in Preemies

Newswise — Feeding premature babies mostly breast milk during the first month of life appears to spur more robust brain growth, compared with babies given little or no breast milk.

Studying preterm infants in the Neonatal Intensive Care Unit (NICU) at St. Louis Children's Hospital, the researchers found that preemies whose daily diets were at least 50% breast milk had more brain tissue and cortical-surface area by their due dates than premature babies who consumed significantly less breast milk.

The researchers presented their findings May 3rd at the annual meeting of the Pediatric Academic Societies, in Baltimore.

"The brains of babies born before their due dates usually are not fully developed," said senior investigator Cynthia Rogers, MD, an Assistant Professor of Child Psychiatry who treats patients at St. Louis Children's Hospital. "But breast milk has been shown to be helpful in other areas of development, so we looked to see what effect it might have on the brain. With MRI scans, we found that babies fed more breast milk had larger brain volumes. This is important because several other studies have shown a correlation between brain volume and cognitive development."

The study included 77 preterm infants. The researchers retrospectively looked to see how much breast milk those babies had received while being cared for in the NICU. Then, the researchers conducted brain scans on those infants at about the time each would have been born had the babies not arrived early. All of the babies were born at least 10 weeks early, with an average gestation of 26 weeks, or about 14 weeks premature. Because they are still developing, preemies typically have smaller brains than full-term infants.

First author Erin Reynolds, a research technician in Rogers' laboratory, said in gauging the effects of breast milk on the babies' brains, the researchers didn't distinguish between milk that came from the babies' own mothers and breast milk donated by other women. Rather, they focused on the influence of breast milk in general.

"As the amount of breast milk increased, so did a baby's chances of having a larger cortical surface area," Reynolds said. "The cortex is the part of the brain associated with cognition, so we assume that more cortex will help improve cognition as the babies grow and develop."

Preterm birth is a leading cause of neurologic problems in children and has been linked to psychiatric disorders later in childhood. Rogers and her team plan to follow the babies in the study through their first several years of life to see how they grow, focusing on their motor, cognitive and social development. As the babies get older, the researchers believe they will be able to determine the effects of early exposure to breast milk on later developmental outcomes.

"We want to see whether this difference in brain size has an effect on any of those developmental milestones," Rogers said. "Neonatologists already believe breast milk is the best nutrition for preterm infants. We wanted to see whether it was possible to detect the impact of breast milk on the brain this early in life and whether the benefits appeared quickly or developed over time."

Rogers said further investigation is needed to determine specifically how breast milk affects the brain and what is present in the milk that seems to promote brain development. She explained that because all of the babies in the study were born early it isn't clear whether breast milk would provide similar benefits for babies born at full term.

This work was supported by the National Institute of Mental Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Center for Research Resources and the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (NIH), grant numbers K23 MH105179, K02 NS089852, P30 HD062171, R01 HD057098 and UL1 TR000448. Additional funding was provided by the Cerebral Palsy International Research Foundation, the Dana Foundation, the Child Neurology Foundation and the Doris Duke Foundation.

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