NEONATOLOGY TODAY

News and Information for BC/BE Neonatologists and Perinatologists

Volume 6 / Issue 10
October 2011

IN THIS ISSUE

NEONATOLOGY TODAY

Editorial and Subscription Offices
16 Cove Rd, Ste. 200
Westerly, RI 02891 USA
www.NeonatologyToday.net

Neonatology Today (NT) is a monthly newsletter for Neonatologists and Perinatologists that provides timely news and information regarding the care of newborns and the diagnosis and treatment of premature and/or sick infants.

Upcoming Medical Meetings

(See website for additional meetings)

35th Annual Conference- Miami Neonatology 2011 and One Day Workshop, "Advances in Respiratory Care"
Oct. 26-29, 2011; Miami Beach, FL USA
neonatology.med.miami.edu/conference

Contemporary Management of Neonatal Pulmonary Disorders Conference
Nov. 3-4, 2011; Tempe, AZ USA
nalweb.com/cmnpdconference

Third Annual Phoenix Fetal Cardiology Symposium
Nov. 3-6, 2011; Phoenix, AZ USA
www.fetalcardio.com

NEO: The Conference for Neonatology
Feb. 23-26, 2012; Orlando, FL USA
www.neoconference.com

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Neonatal Seizures: Should the Role of Phenobarbitone Be Further Downgraded?

By Krishna K. Diwakar, MD; Praveen Kumar Remala, MD

Keywords

Neonatal seizures, Phenobarbitone

Seizures are a common reason for infants to be admitted to the Neonatal Intensive Care Unit (NICU). Descriptions and clinical observation remain the basis for diagnosis in most instances, despite the availability of various electrophysiological investigation.[1] The management of neonatal seizures continues to elude uniformity. Neonatologists and neurologists have varied opinions and preferences regarding anticonvulsants.[2]

Though widely used, the beneficial effects of routine anticonvulsants remain questionable.[3] Phenobarbitone continues to be the anticonvulsant of choice amongst most neonatologists.[2] It has been the practice at our center to use anticonvulsants viz. phenobarbitone as infrequently as possible. This study was undertaken to evaluate the usage of phenobarbitone in term neonates admitted for seizures and assess the early development of these patients.

Materials and Methods

Full term infants admitted to the Neonatal Intensive Care Unit of the Malankara Orthodox Syrian Church Medical College Hospital, Kochi, with clinically diagnosed seizures between June 2006 and April 2009 were included in the study. The history and clinical type of the seizures, and details of medication

> ***"The management of neonatal seizures continues to elude uniformity. Neonatologists and neurologists have varied opinions and preferences regarding anticonvulsants.[2]"***

were noted. A structured approach to treatment is the routine practice of the NICU – a protocol adhered to even in those referred infants who had received phenobarbitone or other anticonvulsants prior to referral. Plasma glucose levels were assessed using gluocostix *Accucheck Roche*® Values less than 45 mg /dl were considered hypoglycemic and infants were treated as 'symptomatic hypoglycemia.' If the infants had been euglycemic, blood samples were drawn for assessment of serum electrolytes, and the convulsing infant treated presumptively with 2 ml/kg of 10% Calcium Gluconate bolus. If seizures continued unabated, they were treated sequentially with 0.2 ml/kg of 50% magnesium sulphate, given intra muscularly, and if unresponsive with Pyridoxine (100mg) provided in the multivitamin combination (**Optinuerone Lupin*®). This combination was initially used due to the non-availability of the intravenous preparation of pyridoxine as a single drug in the local market but was incorporated into the

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Table 1 . Types of Seizure, Phenobarbitone and Outcome						
Type	**N**	**Pheno. Given N (%)**	**Died/Lost N**	**Follow-up Normal**	**Follow-up Abnormal**	**Fischer's Exact p for Outcome**
Focal Clonic	27	6 (22%)	1	24	2	0.06
Multifocal Clonic	24	11 (46%)	1	18	5	0.4
Focal to Mulitfocal	5	2 (40%)	2	3		
Tonic	9	5 (55%)*	2	3	4	0.02
Subtle	7			5	1	0.7
Total	**71**	**24**	**6**	**53**	**12**	
* 2 had multiple doses						

routine protocol when inborn born errors of metabolism were being detected with increasing frequency.

If the intensity and duration of seizures were reduced, infants were monitored till they were seizure-free for 48 hours and roomed in with the mother.

Injection of Phenobarbitone was given (20 mg/kg given intravenously) only to those infants who were unresponsive to the initial sequence of treatment or if the seizures recurred with the initial intensity and duration.

Infants were subsequently followed up, and their development evaluated by modified Bayley Score, or by structured questionnaire where physical follow-up was not possible. A development score below 2 Standard Deviations (SD) expected for specific age was considered as delayed. Statistical analysis was done using SPSS® and EPI-info statistical packages.

** Combination of 100 mg of pyridoxine, 1 mg of B12 and 100 mg of Thiamine, Ribiflavin 6 mg, Nicotinamide 100 mg, Pantothenic acid 5 mg.*

Results

Three-thousand nine-hundred sixty-eight infants were admitted to the Neonatal Intensive Care unit over a 34-month period between June 2006 and April 2009 of which 2562 were term infants. Seventy-one (2.8%) of these infants had seizures. The seizures were of various types (Table 1), and of different etiologies (Table 2).

Forty-seven (66%) of these infants did not require any anticonvulsants. Twenty-two of the remaining 24 infants received a single dose of phenobarbitone - with 8 of them receiving the drug at the referring hospital. The two infants who had received more than one dose, had presented with tonic seizures.

Infants with subtle seizures did not receive anticonvulsants.

The etiology for seizures varied from Inborn Errors of Metabolism (IEM) to electrolyte imbalance (Table 2). One-way Analysis of Variance (ANOVA) did not show any difference in the etiological group of infants who received phenobarbitone and those that did not.

Table 2. Etiology and Phenobarbitone		
Etiology	**Number**	**Total Phenobarbitone Given**
Asphyxia	**6**	**3 (1)**
Hemorrhage	**4**	**1**
Infarct	**4**	
Primary Dyselectrolytemia	**22**	**8 (1)**
Electrolyte Abnormality Associated with Other Problems	15	
Total Electrolyte Disturbances	*37*	
Isolated Hypoglycemia	**6**	**2**
Hypoglycemia Associated with Other Problems	5	
Total Hypoglycemia	*11*	
IEM	**15**	**6**
Meningitis	**8**	**2**
Undiagnosed	**6**	**2**
N	**71**	**24**
( ) number in parenthesis represent those patients given multiple doses		

Thirty-seven infants had electrolyte disturbances. While 15 of these were associated with other contributory factors, 22 had pure dyselectrolytemia. Eight infants with electrolyte disturbances had re-

Table 3. Dyselectrolytemia and Phenobarbitone Doses					
	N	**Single Pre-Admission Dose**	**Single Dose in Hospital**	**Multiple Doses**	**Total**
Hypernatremia	5		1	1	1
Hypocalcemia	6				0
Hypomagnesemia	16	1	1		3
Hyponatremia	2	1	1		2
Mixed Electrolyte Disturbance	8	1	1		2
Total	**37**				**8**

ceived phenobarbitone. While two of these had other associated etiologies, six had dyselectrolytemia as the sole attributable cause for the seizures (Table 3). Hypomagnesemia was the most common electrolyte abnormality that was treated with phenobarbitone, followed by hyponatremia (Table 3).

Three of the 71 infants, two with meningitis and one with severe perinatal asphyxia, died in the hospital. Among the 68 survivors, 65 infants could be followed-up, and assessed for motor developmental delay. Twenty-three of them had received phenobarbitone. The mean age of follow up was 15 months (range 6 – 36).

Delay in motor development was observed in 12 of the 65 infants. Infants who had presented with tonic seizures were associated with poor developmental outcome (RR 1.7, 10.3 at 95% CI, Fischer's exact $p < 0.02$) (Table 1).

Delayed development was noted in 7 of the 23 infants who had received phenobarbitone and 5 of the 42 infants who had not received any anticonvulsants -- implying a mild association between phenobarbitone and developmental delay (Chi-squared Fisher exact-p -0.06, O R 0.89. 11.7 at 95% CI.). However, logistic regression for confounding variables implied a more contributory role for etiology with statistically significant association seen with Asphyxia. - $p < 0.005$ (RR 3.5, 1024, CI 95%). (Table 4). Phenobarbitone taken in isolation was seen to be less contributory. (RR 0.725 – 4.3, 95% CI p - 0.21).

Discussion

It is the primary care physician or the general pediatrician who is often first to attend to a convulsing neonate. Therapy is commenced on the basis of clinical examination. The currently standard recommendations for using phenobarbitone and anticonvulsants often result in their being used as the first-line of therapy. Though phenobarbitone has been advocated after the presumptive treatment for hypoglycemia, hypocalcemia and hypomagnesemia,[4] we have observed that more often than not the anticonvulsant is initiated by the treating physicians much earlier than recommended in the sequence of therapy. Perhaps it is the impatience of the clinician to obtain an abrupt cessation of clinical seizure that prompts earlier usage of phenobarbitone.[2] The common association of dyselectrolytemia (Table 3), should make one realize the inappropriateness of embarking on anticonvulsants without treating the primary etiology. While hypocalcemia is often appropriately treated, we have observed that hypomagnesemia and sodium imbalance tend to be overlooked, with clinicians resorting to phenobarbitone if the response to calcium therapy was 'unsatisfactory.' A lower threshold to commence anticonvulsants was observed amongst some of the 'on-call' registrar, even at our center, where three infants with pure dyslectrolytemia were treated with phenobarbitione (Table 4).

The current recommendations for using anticonvulsants[4] before pyridoxine, seems to ignore the fact that phenobarbitone could show some response in pyridoxine-dependent seizures.[5] It has been our practice to use pyridoxine available in combination with thiamine (B1) and cyanacobalamine (B12) – if seizures were unabated after magnesium therapy – before commencing anticonvulsants. The subsequent diagnosis of IEM amongst many of the infants who had presented with seizures in our study (Table 2) makes us feel that the combination (Vitamins B1, B6, B12) used by default was more justifiable than using pyridoxine alone. It would, therefore, be better suited to use this easily available combination of parenteral vitamins before initiating anticonvulsant therapy.

Developmental outcome has always been a matter of concern while treating neonatal seizures. The effect of the seizure per se and that of long-term therapy with anticonvulsants have influenced protocols to a significant extent.[6] It was gratifying for us to observe

Table 4: Developmental Delay Analyzed for Confounding Variables. N = 65		
Associated Etiology	**RR 95.0% C.I.**	**p.**
Dyselectrolytemia	0.7, 1.7	0.797
ASPHYXIA	**3.5, 1025**	**0.005**
Inborn Errors of Metabolism	0.07, 8.5	0.833
Meningitis	0, 1.2E+30	0.843
Infraction / Hemorrhage	0.2, 11.7	0.652
Hypoglycemia	0.5, 27.2	0.188
PHENOBARBITONE	0.7, 4.4	0.21
Type of Seizures	0.97, 3.1	0.064

"We strongly feel that the protocols for managing neonatal seizures should downgrade the use of phenobarbitone (anticonvulsants) to a level below that of pyridoxine. It would also be worth keeping IEM in mind and consider using pyridoxine in combination as 'megavitamins'[8] while awaiting the screening reports for IEM."

that avoiding phenobarbitone did not adversely affect the early development of the infant. On the contrary, infants who had received phenobarbitone showed minimal association with delayed development (Chi2 Fisher exact-p -0.06, O R 0.89-11.7 at 95%CI). It should however, be recognized that etiology (Table 3) of the seizure tends to have greater influence on developmental delay (Asphyxia, p < 0.005 (RR 3.5, 1024, CI 95%). Therefore, 'symptomatic' therapy[7] with drugs like phenobarbitone has questionable justification.

Interestingly, in the present study, infants with intracranial hemorrhage in the absence of perinatal asphyxia, surviving beyond neonatal period did not necessarily have bad outcomes.

We, therefore, feel that treatment of neonatal seizure should not be a desperate combination of therapies to ensure total cessation of all seizure activity. Therapy should aim for reasonable attenuation and gradual decrementing of clinical seizure, and not necessarily for total seizure control. This would restrict clinicians from routinely initiating anticonvulsants[3] – more often for the completion of protocols than any significant clinical or therapeutic benefit.

It is necessary to recognize that electrolyte abnormality – a common association with other etiologies – contributes significantly to neonatal seizure. This information needs to be percolated further to the level of the primary care physician.

We strongly feel that the protocols for managing neonatal seizures should downgrade the use of phenobarbitone (anticonvulsants) to a level below that of pyridoxine. It would also be worth keeping IEM in mind and consider using pyridoxine in combination as 'megavitamins'[8] while awaiting the screening reports for IEM.

It is high time that a universally practical, revised protocol for managing neonatal seizures is implemented without further delay.

What is Already Known on this Topic

- Phenobarbitone is a commonly used drug to treat neonatal seizures.
- Treatment protocols recommend the use of phenobarbitone after presumptively treating for hypoglycemia, hypocalcemia and hypomagnesemia, but before administering pyridoxine.

What this Study Adds

- Most clinical seizures in the term neonate do not require phenobarbitone therapy.
- The significance of dyselectrolytemia as a common cause of neonatal seizures needs to be highlighted.
- Protocols should recommend the use of pyridoxine, preferably as a combination of parenteral 'megavitamins,' before commencing phenobarbitone.
- Withholding phenobarbitone from the regimen for immediate seizure control did not adversely affect the early development of the infant.

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Correspondence Author

Krishna K. Diwakar, MD, DNB, FRCPCH
Professor & Head,
Department of Neonatology
Malankara Orthodox Syrian Church
Medical College
Kolenchery PO
Kochi
Kerala – 682311
India

Krishna.diwakar@fulbrightmail.org

Praveen Kumar Remala. MD
Clinical Fellow
Department of Neonatology
Malankara Orthodox Syrian Church
Medical College,
Kolenchery PO
Kochi
Kerala – 682311
India

The Third Phoenix Fetal Cardiology Symposium (PFCS): Nov 3-6, 2011, Embassy Suites, Phoenix, Arizona

By Karim Diab, MD

The time draws near for the *Third Phoenix Fetal Cardiology Symposium*, which will be held on November 3-6 in Phoenix, Arizona. The course format will follow the successful two prior sessions and will include an interesting and innovative program that will focus on basic knowledge and techniques, as well as recent advances in the diagnosis and management of fetal cardiac disease. This year, however, the symposium features significant differences including the expansion of the symposium to four days and the addition of various didactic and interactive sessions, all given by nationally and internationally prominent faculty.

The first symposium took place in October 2008 in Phoenix and included 2.5 days of sessions focusing on various topics in fetal cardiac disease. The second symposium, held in 2010, was expanded to include a larger number of sessions and discussed screening for fetal cardiac disease, advanced imaging techniques, various fetal cardiac lesions and fetal arrhythmias. Last year's symposium was attended by almost two hundred physicians, nurses and sonographers. Attendees came not only from the United States but also from the Philippines, South Korea, Canada, Panama, and Bulgaria!

There are key aspects to highlight in this year's symposium. The four-day symposium is expanded to offer up to a maximum of 27 AMA PRA Category 1 Credits (compared to 18 in the previous year) with sessions that will include lectures, technical procedures and live demonstrations. This will provide a comprehensive understanding of the uniqueness of the fetal cardiovascular system with focus on basic aspects of fetal cardiology as well as recent advances in the field.

A major feature of this conference is the live case demonstration during which the actual technique of fetal cardiac imaging is performed live on actual patients in a separate area of the symposium and transmitted directly into the main conference room. This provides a practical session that helps acquaint physicians as well as sonographers with the technique of fetal echocardiography, which hopefully would help in improving screening for fetal CHD. The live case session will take place during the first day of the symposium. There will be normal and selected abnormal cases demonstrated, which provides the attendees with an exceptional educational opportunity. We hope that this will allow significant participation from the audience. There will also be other interactive sessions during the symposium such as the special jeopardy session on Saturday that will feature interesting fetal cases and will allow for more interaction from the audience.

"As such, the fetal symposium this year includes a comprehensive program that will cover various practical, technical and clinical aspects in the understanding and management of the fetal cardiovascular system."

In addition to the live cases, the first day will include: sessions discussing the techniques

for evaluating fetal cardiac function with a focus on the cardiovascular profile, maternal conditions affecting the fetal cardiovascular system, fetal echocardiography in multiple stages of gestation and genetics in fetal cardiac disease.

On the second day of the symposium, sessions will focus on fetal arrhythmias as well as structural heart lesions. The arrhythmia lectures will focus on the diagnosis and management of fetal bradycardias and tachycardias, while the lectures on structural heart lesions will discuss in detail specific malformations such as anomalies of the venous system, cardiac septation defects, HLHS, DORV, TOF, single ventricle and heterotaxy syndromes.

After the reception on Friday evening, there will be a fun and interesting dinner lecture on the evolution of fetal cardiac intervention before and beyond the Boston Children's Hospital experience presented by Dr. Wayne Tworetzky!

Saturday November 5th, will feature lectures that will focus on fetal myocardial disease and heart failure, pericardial disease, cardiac tumors and extra-thoracic anomalies affecting the fetal heart. In addition, there will be lectures discussing the mode of delivery of the fetus with CHD, cardiac issues in IVF, 3D and 4D fetal imaging and twin-twin transfusion syndromes. As noted above, the day will end with an interesting jeopardy session that we hope will elicit continuous participation from the audience!

On Sunday, the last day of the symposium, topics will include practical issues in fetal cardiac screening, helping the mother and family cope with the diagnosis of a heart defect in their unborn child and urgent postnatal surgery and intervention in the prenatally diagnosed fetus with cardiac defect. There will also be discussion of the utility of telemedicine as a tool in delivering fetal echocardiographic services to remote areas.

As such, the fetal symposium this year includes a comprehensive program that will cover various practical, technical and clinical aspects in the understanding and management of the fetal cardiovascular system. It will provide an immense educational experience that will benefit the attendees: from physicians, sonographers and nurses working in the fields of Pediatric Cardiology, Fetal Echocardiography, Obstetrics and Maternal Fetal Medicine, as well as any health care professional or staff who cares for neonates with cardiac disease.

Join us in shaping the future of fetal cardiology during a pleasant and educational break in sunny Arizona in November 2011!!

For more details about the program and registration, please visit the website at www.fetalcardio.com.

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The Third Annual Phoenix Fetal Cardiology Symposium

Phoenix Children's Hospital

Key sessions topics in this year's symposium:

- Live fetal cases demonstrations
- Fetal arrhythmias
- Fetal Cardiology Jeopardy
- Evolution of Fetal Cardiac Intervention

On Behalf of the Course Directors

Karim Diab, MD
Division of Pediatric Cardiology
Phoenix Children's Medical Group
Phoenix Children's Hospital
Assistant Professor of Pediatrics
University of Arizona School of Medicine
Phoenix, AZ USA

Routine Screening for Heart Disease Will Save Lives of Newborns

Washington, DC – The decision to include Critical Congenital Heart Disease in the standard list of recommended screenings for new babies costs little and will save lives as it recognizes the importance of early detection of heart defects, said Gerard Martin, MD, FACC, immediate past-chair of the Adult Congenital and Pediatric Cardiology Council of the American College of Cardiology.

Secretary of Health and Human Services, Kathleen Sebelius, announced on September 21st that Critical Congenital Heart Disease screening would be included on the Recommended Uniform Screening Panel, a list of 30 disorders for which newborns are routinely screened in the United States. She also adopted recommendations to direct the National Institutes of Health and the Centers for Disease Control to fund additional research on the impact of screening.

"Secretary Sebelius did the right thing," said Dr. Martin, Senior Vice President at Children's National Medical Center's Center for Heart, Lung and Kidney Disease, who led the ACC's campaign to ensure the screening is provided. "Physical examination alone has not been able to detect Critical Congenital Heart Disease in all babies. Pulse oximetry, an inexpensive, non-invasive test, in addition to a careful physical examination will improve detection."

Special Congressional Briefing Examines Role of Public Health in Congenital Heart Disease

Every 15 minutes in hospitals across America, a baby is born with a congenital heart defect (CHD), or a malformation of the heart's structure and function. Thanks to the advances in modern medicine, more than 80% of these babies are surviving into adulthood and living healthy and productive lives. The children and adults living with CHDs still face unique health challenges requiring specialized life-long care.

A recent briefing on Capitol Hill sponsored by the American Academy of Pediatrics and co-sponsored by the American College of Cardiology (ACC) and other leading cardiovascular societies and patient advocacy groups, highlighted the important role of federal and state programs in CHD research, surveillance, screening and prevention. Senators Richard Durbin (D-Ill.) and Thad Cochran (R-Miss.), co-hosted the event, Congenital Heart Defects: A Lifelong Disease.

Panelist Geoffrey Rosenthal, MD, PhD, FACC, professor of pediatrics at the University of Maryland School of Medicine, said CHD places an undeniable burden on the public health system, as well as families. The Congenital Heart Futures Act, passed into law as part of the 2010 health reform legislation, would establish a national surveillance program for CHD patients and serve as a step in the right direction to reduce this burden, he asserted.

Rosenthal also pointed to new activities related to research, care, surveillance and policy development, including the Congenital Heart Public Health Consortium (CHPHC), of which the ACC is a member. The Consortium looks to prevent, enhance and prolong the lives of those with CHD through public health activities, including health promotion and education. Additionally, national CHD registries and other CHD collaborative quality improvement and multi-center research activities will continue to advance the care and management of the tiniest heart patients, who are destined to need life-long specialized heart care. Ultimately there is still more work to be done, Rosenthal maintains. "We need to expand birth defect monitoring programs, reduce disparities and plan for adequate health services," he said. "How do we save those who are still dying? Physicians and the federal government have a critical role to play moving forward."

The federal government took a huge step towards improving early detection for CHD patients this week. Health and Human Services (HHS) Secretary Kathleen Sebelius announced that all U.S. hospitals will be required to screen newborns for CHD using pulse oximetry. The Secretary's Advisory Committee for Heritable Disorders in Newborns and Children had recommended adding pulse oximetry, an inexpensive and non-invasive test to the universal screening panel – a move the ACC and other professional societies and patient advocates in the CHD community have endorsed.

For more on the ACC's involvement in CHD, visit the Adult Congenital and Pediatric Cardiology (ACPC) member section on CardioSource.org. The ACPC Section has played a major role in strengthening educational programming for congenital cardiology care providers and has several significant accomplishments in science and quality, including the development of the IMPACT Registry™, which tracks diagnostic and interventional cardiac catheterization in pediatric and congenital heart disease patients. In addition, the ICD Registry™ now includes data elements specific to the pediatric population.

New Study Helps Clarify Symptoms and Characteristics of Acid Reflux in Neonates

Modifying stomach acid levels may not be enough to treat symptoms in neonates suspected of having gastroesophageal reflux disease. According to a study from Nationwide Children's Hospital, this is the first study to classify reflux and its associated symptoms in neonates based on how and what is refluxed.

Gastroesophageal reflux disease (GERD) is a frequent consideration in infants at risk of the life-threatening events chronic lung disease and dysphagia. Yet, the definition of GERD in neonates and infants and its treatment remains controversial. Acid suppressive medications and prokinetics are commonly prescribed to alter gastric acidity and improve gastrointestinal motility in neonates, yet such therapies can have harmful side effects.

"It's difficult to distinguish whether symptoms of reflux are part of a neonate's normal functioning or if they are disease-based," said study author, Sudarshan Jadcherla, MD, FRCPI, DCH, AGAF, neonatology and principal investigator in the Center for Perinatal Research of The Research Institute at Nationwide Children's Hospital. "As such, there are no definite standards to aid in the management of reflux among neonates in the intensive care unit, nor clarity regarding symptom recognition, nor standards to aid in the diagnosis of GERD."

Dr. Jadcherla, also Medical Director of the Neonatal and Infant Feeding Disorders Program and Professor of Pediatrics at The Ohio State University College of Medicine and Public Health, says that establishing objective evidence of gastroesophageal reflux events and the relationship of symptoms with the physical or chemical composition of the refluxate is essential to characterize whether patients have a disease that needs treatment.

To help characterize reflux events, Nationwide Children's investigators evaluated 30 neonates in Nationwide Children's NICU who were suspected to have GERD. Using pH-impedance studies, the team determined refluxate presence, composition, distribution and clearing time. Nurses also documented whether the neonates showed any respiratory symptoms (coughing, gagging, grunting), sensory symptoms (irritability, grimacing, crying) or physical movement such as stretching of their limbs, during the identified reflux events.

Findings showed that:

- Non-acid reflux events are of equal frequency as acid reflux events and the majority of events spread proximally above the upper esophageal sphincter.
- Acid clearance time per acid ph-impedance event was lesser than ph-only events.
- Infra-upper esophageal sphincter reflux was correlated with higher percentage of acid reflux events compared to

supra-upper esophageal sphincter reflux events.
- Supra-upper esophageal sphincter reflux events were associated with greater proportion of non-acid reflux events.
- Fifty-four percent of reflux events documented by pH-impedance were associated with symptoms. More than 87% of the pH-only events were associated with symptoms.
- Symptomatic acid reflux events were associated with longer acid clearance time.
- Prolonged acidity was associated with symptomatic acid reflux events in chronic lung disease patients.

"It is clear from this study that symptoms can occur with acid, non-acid, gas, liquid or mixed events," said Dr. Jadcherla. "So, treatment strategies based on modifying gastric acidity alone can be ineffective as acid is not the lone provoking agent."

Dr. Jadcherla says it is also clear why the management of GERD based on symptoms only is controversial, as there are reflux-type symptoms in the absence of reflux.

"Overall, this study helps clarify the definition of GERD: gastroesophageal reflux with increased frequency of respiratory, sensory or movement symptoms," said Dr. Jadcherla.

Prenatal Pet Exposure, Delivery Mode, Race are Key Factors in Early Allergy Risk

Prenatal pet exposure, a mother's delivery mode and race are influential factors in a child's risk of developing allergies by age two, according to a Henry Ford Hospital study.

In a study believed to be the first of its kind, Henry Ford researchers found that babies who have indoor prenatal pet exposure have a pattern of lower levels of the antibody Immunoglobulin E, or IgE, between birth and age two. IgE is linked to the development of allergies and asthma.

Key findings:
- IgE levels were 28% lower during infancy in babies who had indoor prenatal pet exposure compared to babies from pet-free homes.
- IgE levels were 16% lower in infants who had indoor prenatal pet exposure and were born vaginally compared to 43% in infants who had indoor prenatal pet exposure and were born by cesarean section.
- IgE levels were 33% lower in infants who had indoor prenatal pet exposure and were either European, Asian or Middle Eastern descent compared to compared to 10% lower in infants who had indoor prenatal pet exposure and were African-American.

The findings are published online today at *The Journal of Allergy and Clinical Immunology* at www.jacionline.org/inpress.

"We believe having a broad, diverse exposure to a wide array of microbacteria at home and during the birthing process influences the development of a child's immune system" says Christine Cole Johnson, PhD, MPH, Chair of Henry Ford's Department of Public Health Sciences and senior author of the study.

Dr. Johnson says the findings support the so-called hygiene hypothesis, which theorizes that early childhood exposure to infectious agents affects the immune system's development and onset of allergies and asthma.

Prior published research by Henry Ford's Department of Public Health Sciences has shown that pet exposure has a protective effect against early allergy development. She theorizes that babies born through the birth canal are exposed to a higher and more diverse burden of bacteria, further boosting the immune system's protection against allergies.

"Our findings may provide insight into the biological mechanisms that increase the risk for allergic disorders," Dr. Johnson says. She theorizes that "genetic variants" may explain the higher levels of IgE levels in African American newborns.

Henry Ford researchers followed 1,187 newborns August 2003 and November 2007 and collected blood samples for measuring IgE levels at birth, six months, one year and two years.

Of the birth mothers, 62% were African American and 33% were European Americans. Of the babies born, 751 were delivered vaginally and 436 were delivered cesarean. There was at least one indoor pet in the homes of 420 mothers.

The study was funded by the National Institute of Allergy and Infectious Diseases.

Enriched Formula Benefits Developing Brain and Heart

University of Kansas scientists have found new evidence that infant formulas fortified with long-chain polyunsaturated fatty acids (LCPUFA) are good for developing brains and hearts.

In the randomized, double-blind study, 122 term infants were fed one of four formulas from birth to 12 months; three with varying levels of two LCPUFAs (DHA and ARA) and one formula with no LCPUFA, and tested at four, six and nine months of age.

By simultaneously measuring the heart rate and visual attentiveness of infants while they looked at images of adult human faces, John Colombo and Susan Carlson found that infants who were fed fortified formula were more cognitively advanced and their heart rates were lower than infants who were fed formula without LCPUFA.

The formula with the lowest level of LCPUFA — 0.3% t level — was found to be sufficient to produce these benefits.

The study is the first randomized clinical trial of postnatal DHA supplementation to measure attention. Colombo, a neuroscientist who specializes in the measurement of early neurocognitive development, said that the findings add to the mounting evidence that these nutritional compounds positively affect brain and behavioral development.

DHA or docosahexaenoic acid is an essential long-chain fatty-acid that affects brain and eye development, and babies derive it from their mothers before birth and up to age two. But the American diet is often deficient in DHA sources such as fish.

ARA or arachidonic acid is another LCPUFA that is present in breast milk and commercial formula.

The study was designed to examine the effects of postnatal DHA at levels that have been found to vary across the world, said study co-director Carlson, A. J. Rice Professor of Dietetics and Nutrition at KUMC.

Colombo and Carlson's earlier work and collaborations influenced infant formula manufacturers to begin adding DHA in 2001.

The study was published in the October 2011 issue of *Pediatric Research*.

Fetal Electrocardiogram Helps in Early Detection of Neonatal Acidosis

University of Granada researchers have proved that fetal electrocardiogram (ECG) is the best method for detecting early acidosis and the risk of loss of fetal wellbeing. This method increases the change of having healthy fetuses, since it shows the effects of lack of oxygen in the heart and brain of the fetus, and points to the need for appropriate treatment. A study conducted at the University of Granada has proved that this system is better than pulse oximetry, which measures oxygen saturation in fetuses and allows estimation of risks to the fetus.

This study was carried out by Mercedes Valverde Pareja, a researcher at the Department of Gynecology and Obstetrics at the University of Granada, and conducted by professors Alberto Puertas Prieto, Alberto Salamanca Ballesteros and Francisco Montoya Ventoso. To carry out

this study, its authors conducted a prospective randomized study with 180 women in labour admitted to the dilation area of the University Hospital Virgen de las Nieves, Granada, Spain. Researchers found that women in labour monitored with fetal ECG and with recorded CTG compatible with risk of loss of fetal well-being, recorded a lower cesarean rate (30% vs. 46.7%), obtained better fetal Apgar test results and better values in fetal umbilical cord gas analysis at birth than those recorded with pulse oximetry. They also observed greater real-time monitoring, adequate signal and fetal ECG, providing more continuous information, thus helping the obstetrician to control the state of the fetus.

Advantages of the method

This study proved that fetal electrocardiogram is very useful to detect fetuses at risk of suffering acidosis. Once the risk is detected, the delivery is expedited before the fetus shows signs of acidosis and is affected. Moreover, this technique allows the detection of false RCTG positives.

To date, both methods of intrapartum fetal monitoring had been analysed separately (fetal pulse oximetry and fetal electrocardiogram), but there were no previous studies comparing them to each other to assess which one is more effective in detecting risk of loss of fetal welfare.

As Mercedes Valverde explains, "some people believe that both methods are equally effective and that they can be used in the same cases. With this work, we found that their effectiveness is not the same, as they operate at different levels of fetal physiology and therefore give some very precise data. Furthermore, if compared, fetal electrocardiogram (ECG-fetal) detects acidosis at an earlier stage, thus allowing for healthy fetuses."

The results obtained in this study were partially published in the *Journal Progresos en Ginecología y Obstetricia*, edited by the Sociedad Española de Ginecología y Obstetricia (Spanish Society of Gynecology and Obstetrics).

Study Examines Trends in Withholding Treatment for Infants in NICUs

Withdrawal of life-sustaining support and withholding lifesaving measures (such as CPR) appear to be the primary modes of infant deaths in a Neonatal Intensive Care Unit (NICU), according to a report in the July issue of *Archives of Pediatrics & Adolescent Medicin*e, one of the JAMA/Archives journals.

"Currently, most childhood deaths in the United States occur during the neonatal period and most neonatal deaths follow a decision to withhold or withdraw life-sustaining treatment," the authors write as background information in the article. Prior studies, conducted in the previous 30 years have shown that an increasing number of parents forgo life-sustaining treatment near the end of their child's life, and the number of children with do-not-resuscitate (DNR) orders also increased.

Julie Weiner, DO, of Children's Mercy Hospital in Kansas City, MO, and colleagues examined medical records of 414 infants who died between January 1999 and December 2008 at a regional referral neonatal intensive care unit to determine if trends towards decreasing use of cardiopulmonary resuscitation (CPR) at the end-of-life for infants in neonatal intensive care units had continued into present day.

Of the 414 infant deaths included in the study, 45% were due to major congenital anomalies (also known as birth defects; a physical anomaly that has cosmetic or functional significance). Seventeen percent of these infants were very preterm. Thirty-five percent of deaths were of very preterm births without congenital birth defects. During the ten-year follow-up period, 61.6% of infant deaths followed withdrawal of treatment, 20.8% followed withholding of treatment and 17.6% died despite attempted CPR.

The percentage of deaths that followed withholding of life-sustaining treatment also increased by an average of 1.03 deaths per year during the study's follow-up period. Most of this change was accounted for in very preterm infants (32 weeks or less gestation). For very preterm infants, deaths following withheld treatment increased by 0.7 per year, and during the study follow-up period, withholding of care significantly increased from less than 10% to more than 30%. Additionally, the use of CPR at death tended to decrease during the same time period.

"During the ten-year period, the primary mode of death in this regional referral neonatal intensive care unit was withdrawal of life-sustaining support," the authors conclude. "Significant increase in withholding of care suggests improved recognition of medical futility and desire to provide a peaceful death."

Genetic Clue to Common Birth Defects Found

Scientists at King's College London have, for the first time, uncovered a gene responsible for Adams-Oliver Syndrome (AOS), a condition which can cause birth defects of the heart, limbs, or blood vessels.

The study, published in *The American Journal of Human Genetics*, gives valuable insight not only into this particular condition, but also the possible genetic causes of these common birth defects found in the wider population.

The team of researchers, led by the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre (BRC) at King's College London and Guy's and St Thomas', say that these findings could lead to better ways of treating children with these defects and may, in the future, help to find ways to recognise and ultimately prevent them from occurring.

AOS is a rare developmental condition that affects less than 150 families worldwide. But birth defects of the heart, limbs, and blood vessels, seen in babies with the condition, are in fact relatively common in the general population – for example, 9 in every 1,000 babies are born with a heart defect.

The team of researchers set out to investigate the genetic cause of AOS in order to detect clues to the role genes might play in congenital birth defects.

Using modern DNA technology to examine the patterns and variation of genes within two affected AOS families, the team detected mutations in the ARHGAP31 gene. This gene regulates two proteins in the body with important roles in cell division, growth, and movement. Mutations in the gene result in an imbalance in the regulation of these proteins, most likely leading to a disruption of the signaling proteins that are critical for normal limb formation.

Professor Richard Trembath, Head of King's College London's Division of Genetics and Molecular Medicine and Medicine Director of the NIHR BRC, said, "Birth defects of the heart, limbs and blood vessels can cause distress for children and their families, and tragically can sometimes even be fatal."

"Through this study we have uncovered the first inherited factor associated with Adams-Oliver Syndrome, which gives us greater understanding of how associated birth defects develop. Understanding the genetic causes of rare diseases in this way not only helps us to understand the condition better, but it gives us a unique insight into the role of specific genes in human development on a broader scale."

"Ultimately, this knowledge may lead us to develop better ways of treating children with these kind of abnormalities, and one day we may even be able to prevent them from developing in the first place."

Global Neonatology Today Monthly Column - Mobile Phones and Global Health

By Dharmapuri Vidyasagar, MD, FAAP, FCCM

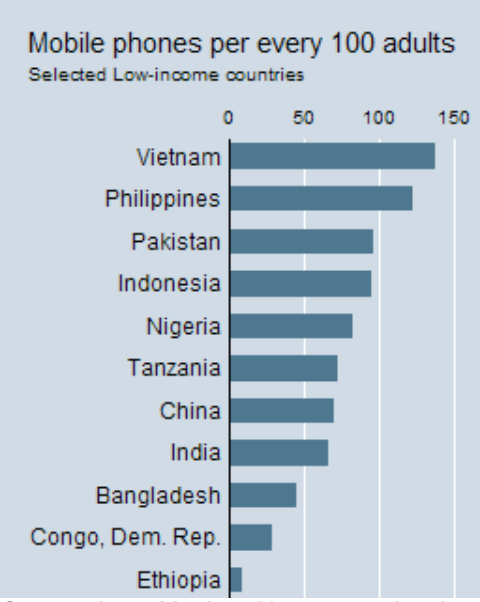
High IMR/MMR/NMR (NMR (Infant Mortality Rate/Maternal Mortality Rate /Neonatal Mortality Rate) in developing countries is a matter of concern. As discussed in this column over the last year, many developing countries have yet to meet the targets of Millennium Development Goals (MDGs) #4 and #5: reducing child mortality by two-thirds for children under age 5 and improving maternal health. The current limited number of healthcare providers cannot meet the demands of the countries and extend their services to remote areas. Health planners and health workers are keenly interested in using new technologies, such as mobile phones, to improve healthcare in developing countries. The advent of wireless communications using mobile phones has opened new venues to extend health services to the needy in remote regions.

The question, however, remains, is the mobile phone affordable and accessible to only the rich countries and rich people?

It is interesting to note that the penetration of mobile phones in some developing countries has been a lot faster than in developed countries. The table gives figures from the World Bank on the number mobile phones per 100/ adults, thus, proving the point that poor countries can afford to have mobile phones.

The second question is whether the mobile phone has the apps to provide the needed help to healthcare personnel and general public. Many individuals and groups are working on this very issue. Literature shows many success stories, but there is a long way to go (www.youtube.com/watch?gl=IN&v=LJDXlb6qyOo).

Finally, merely having a mobile phone and health related applications is not sufficient. The information should be accessible to the non-literate population: in a voice in their own language, and in appropriate visual forms to give recognizable messages to the seeker. Considering the enormous number of spoken languages around the world, these are major challenges facing the innovators in health technology and health education.



Source: Jorge Martinez Navarrete using the World Bank Data Catalog, year 2009 or latest available. Reprinted with permission.

According to Jorge Martinez Navarrete who works for the United Nations (UN) Economic and Social Commission for Asia and the Pacific in Thailand, applications for using mobile phones for healthcare in developing countries will be met sooner than later. He gives several examples of innovations that are either in place, being tested or in the pipeline. If true, that will be a major step forward. Let's hope so.

Source: HIFA2015 (Healthcare Information For All 2015) - www.hifa2015.org

"The Clock is Ticking!"

NT

Dharmapuri Vidyasagar, MD, FAAP, FCCM
University of Illinois at Chicago
Professor Emeritus Pediatrics
Division of Neonatology
Phone: +312.996.4185; Fax: 312.413.7901

dvsagarmd@yahoo.com

NEONATOLOGY TODAY

© 2011 by Neonatology Today
ISSN: 1932-7129 (print); 1932-7137 (online).
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