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EDITORIAL

Dear Readers,

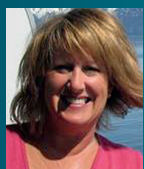
One of the most vulnerable organs in the first days of life – the neonatal brain – is in focus in this issue, the second edition of our Journal. Early detection of neurologic issues may increase the chance of a good long-term outcome. We leave the NCA tribute to the leading experts, our renowned professionals, who share their opinions and findings on the subject with you here.

To support ongoing clinical education, the Neonatal Care Academy is proud to have hosted two neonatal brain monitoring workshops in China (Beijing and Chengdu) and jaundice management courses in Spain (Madrid) and Romania (Cluj). We have a full schedule of educational offerings ahead in 2016. The course calendar will be posted soon on the NCA website (www.neonatalcareacademy.com). Please check back for opportunities in your area.

We wish you an interesting read and very much look forward to meeting you in person at one of our upcoming courses.



Yours,
PIERRE RADZIKOWSKI
Senior Director of Marketing
Newborn Care



TERESA BOONE
Director of Global Education

MONITORING THE NEWBORN BRAIN - WHICH TECHNIQUE FOR WHICH QUESTION?

TERRIE INDER, Chair, Department of Pediatric Newborn Medicine, Brigham and Womens Hospital Mary Ellen Avery Professor in Pediatrics, Harvard Medical School, Boston, MA

■ As survival of the high risk infants has continued to improve, greater emphasis has now been placed on improving neurological outcomes. The implementation of therapeutic hypothermia therapy in the term infant is a compelling example of neuro-protective strategies that have reduced mortality and neurodevelopmental disability. Similar considerations are underway in randomized clinical trials in the preterm infant including erythropoietin and melatonin. In order to understand and impact the neurological outcomes of the high risk infant, monitoring of the neonatal brain will be essential. To apply monitoring successfully, one must consider three key elements - what, why and the nature of the abnormality that you may wish to monitor?

In relation to the preterm infant, more than 500,000 newborns, roughly 12% of babies are born preterm in the United States¹. Preterm birth is a leading cause of long-term neurological disabilities in children² and has been estimated to have cost the U.S. health care system more than \$26 billion in 2005³. Special education services alone for preterm children in the USA prior to kindergarten are estimated to cost >\$1 billion annually. A disproportionate fraction of these costs originates from very preterm infants (VPT, <32 weeks gestation); while they represent just 20%

DELIVERY HISTORY
- Need for resuscitation
- Low Apgar scores
EEG/aEEG

CARDIAC
- Hypotension
- Low cardiac output
- Volume expansion
- PDA
NIRS - aEEG

RESPIRATORY
- Hypercarbia
- Hypoxia
- Increased Central Venous Pressure
- PPV and pneumothorax
NIRS - aEEG

CEREBRAL IMMATURITY
- Vascular immaturity
- Pressure Passive System
NIRS - aEEG

INTRAVENTRICULAR HEMORRHAGE

METABOLIC/ELECTROLYTES
- Hypoglycemia
- Hyponatremia
- Metabolic Acidosis
NIRS - aEEG

INFLAMMATORY
- Chorioamnionitis
- Sepsis
- Placenta/CSF-Blood Cytokines

HEMATOLOGIC
- Anemia
- Thrombocytopenia
- Coagulation disorders
Laboratory Blood Tests

Figure 1: The Pathophysiological Mechanisms Associated with Intraventricular Hemorrhage and the current Brain Monitoring Techniques for Evaluation including Electroencephalography (EEG and amplitude a-EEG), Near Infrared Spectroscopy (NIRS)

bility. The key period of risk for IVH is the first 72 hours of life in the very preterm infant where risk factors and the techniques that may be monitored to understand and intercept the impact of these factors are outlined in Figure 1.

disabilities and behavioral alterations that preterm infants commonly suffer⁵. Thus, how can monitoring of the preterm brain assist in insights into the nature of these underlying disabilities? Neuroimaging has provided key insights into this arena both in the nature and potential contributing pathways for alterations in brain development and outcomes⁶. Techniques, such as volumetric brain development⁷, surface based cartographic techniques and functional connectivity studies have defined alterations in the temporal lobe in reduced brain volumes, altered superior temporal lobe sulci and altered resting state functional connectivity in the preterm brain. These techniques have also provided insight into the impact of experience on brain development in the preterm infant⁸. It appears that pain and stressful experiences alter these regions. In addition, the term equivalent brain has been shown to have adult like hemispheric asymmetries present⁹. Preterm birth, particularly if time in the neonatal intensive care is spent in a quiet single room environment, can alter the trajectory of the formation of these asymmetries and has also been shown to be associated with impairment in early

Preterm Birth is a leading cause of long-term neurological disabilities

of all preterm births, they account for more than 2/3 of the costs associated with preterm birth³. An alarming 50-70% of these children will develop significant neurobehavioral impairment in cognitive, motor, educational and/or behavioral domains^{2,4}. To understand the role of brain monitoring to reduce this neurodevelopmental burden, it is important to separate the attributable risks from brain injury and alterations in brain development as the monitoring approach will differ. For example, high grade intraventricular hemorrhage (Grade III-IV IVH) is associated with a >50% risk for significant cerebral palsy and intellectual disa-

In addition, the definition of the presence and extent of IVH would be best defined by neuroimaging - either cranial ultrasound which is bedside and portable or magnetic resonance imaging with an extended repertoire of structural and functional techniques. Although the risk for IVH may be recognized by NIRS or EEG, and the presence of IVH by neuroimaging, the impact of this brain injury is high in a small number of preterm infants. Less than 10% of very preterm infants are affected by high grade IVH. Thus, although a reduction in high grade IVH is important to achieve, it does not appear that IVH is the major influence on the common

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childhood language development. These techniques focus more on structural and functional definition of alterations in brain development that may underpin the adverse neurodevelopmental consequences of preterm birth.

In summary, one can rationally consider which technique moving from the more conventional "tool approach" to the more holistic "concept approach" as demonstrated in Table 1A and 1B. To understand which technique must be considered for monitoring the newborn brain, one must assess three key elements - what, why and the nature of the abnormality that you may wish to monitor?



TERRIE INDER
Chair, Department of Pediatric Newborn Medicine, Brigham and Womens Hospital
Mary Ellen Avery Professor in Pediatrics, Harvard Medical School, Boston, MA

TOOL	STRUCTURE	FUNCTION
Cranial Ultrasound	2D and 3D renderings	Doppler CUS
Magnetic Resonance Imaging	Conventional injury Brain volumes Diffusion Microstructure	Functional MRI Resting State fMRI MR Spectroscopy
EEG/aEEG	Localize injury/anomaly	Background activity Abnormal activity
Near Infrared Spectroscopy	NA	Cerebral Blood Flow CMRO2
Magneto-encephalography	Abnormal structures e.g. focal epilepsy	Magnetic Field from Cerebral activity
Functional and Neurological Examination	NA	HHNE, Thomson, NNNS, APTB, Prechtl. Family evals. Infant/Child Outcomes

Table 1: A) The Tool Approach and B) Concept Approach to monitoring the Newborn Brain.

	CONCEPT	METHOD	MEASURE
STRUCTURE	Injury Regional & total volume Micro- and chemical structure	MRI	T1, T2 conventional DTI – Microstructure H-MRS – Chemical Cartography – maps
	Injury and Structure	Cranial US	2D, 3D
FUNCTION	Baseline cerebral blood flow	Cranial US NIRS rsfMRI	CUS Doppler CBF Synchronous networks
	Activated or functional cerebral blood flow	fMRI Diffuse Optical Tomography	Regional activation
	Cerebral activity	EEG aEEG	Background Abnormality
	Cerebral Metabolism	NIRS P_MRS	CMRO2 ATP
	Neurological Function	HNNE, NNNS etc.	Outcomes/Function

RELATION BETWEEN FUNCTIONAL AND STRUCTURAL BRAIN DEVELOPMENT IN EXTREMELY PRETERM BORN INFANTS

■ For neonates born extremely preterm, there is an important overlap of brain development – which normally occurs in the third trimester of pregnancy – with the Neonatal Intensive Care admission. Over the last decades major steps have been taken by studies evaluating developmental changes using neuromonitoring (functional brain development) and neuroimaging ((micro)structural brain development).

Amplitude - integrated electroencephalography (aEEG) – using the filtered and time compressed raw EEG – is widely accepted as a useful tool for continuous bedside neuromonitoring^{1,2}. In extremely preterms, the (a)EEG background pattern and spontaneous activity transients (SATs or bursts) in early life are found to correlate to long-term neurodevelopment³. The aEEG background can be influenced by brain injury, drugs – for example morphine – and overall illness⁴. Magnetic resonance imaging (MRI) is the most advanced tool to examine (micro-) structural brain maturation. In the last trimester of gestation immense volume expansion and gyrification of the cortical gray matter take place^{5,6} while at the same time the aEEG background pattern is maturing from a broad amplitude to a smaller bandwidth with increase of sleep-wake cycling (figure 1). This suggests the maturation

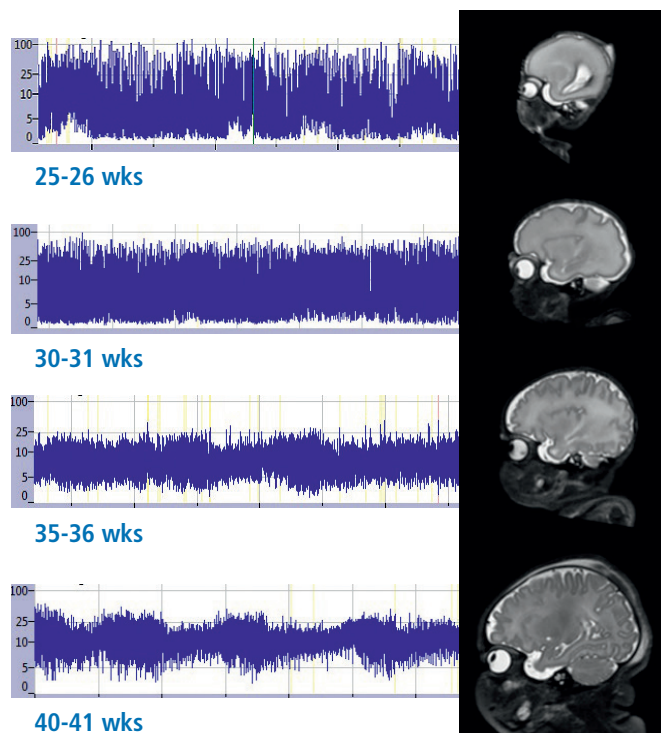


Figure 1: aEEG background pattern at four different time points showing the maturation over time, where the background patterns goes from a broad amplitude to a smaller bandwidth with sleep-wake cycling. The corresponding T2 weighted MRI images in the sagittal view are showing a near smooth brain at 25 weeks, with a brain folded similar to the adult brain at term age.

of the cerebral cortex to be reflected by changes in aEEG amplitude and background pattern.

One of the most critical events for brain development occurring in the late fetal phase is the growth of thalamocortical connections. The afferent neurons grow from the thalamus into the subplate where a waiting period takes place and the neurons synapse to the subplate neurons⁷. After 24 weeks of gestation fibers start to migrate from the subplate into the cortical plate to form synapses there. From the 29th week onwards cortical organisation is initiated with the formation of cortico-cortical connections^{8,9}. As soon as synapses are formed they will start to generate transient electrical signals, which correspond with SATs on the aEEG. The frequency and amplitude of SATs will decrease with increase of gestation, and are normally not found after term equivalent age¹⁰. Biagioni et al.¹¹ showed that EEG in the first week of life is correlated to structural cortical gray matter development on MRI around the same time.

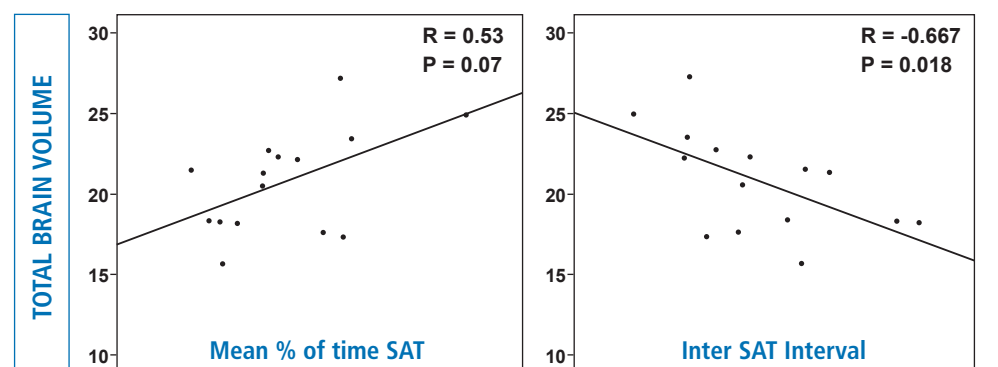


Figure 2: Image adapted from a paper by Benders et al. in Cerebral Cortex (13). A higher % of time detected as SAT was correlated to a higher total brain volume (in ml), where larger periods of intervals between SATs were negatively correlated.

The question remains whether there is a correlation between early brain activity (in the first days of life) and structural brain development over time. Natalucci et al.¹² found in extremely preterms a correlation between aEEG maturity in the first days of life and MRI brain maturation at term equivalent age. In our study published in 2014¹³ we found similar results. The total brain volume increased faster between 30 and 40 weeks of gestation in preterms showing more SAT events and/or less quiet intervals in the first days of life (figure 2). The same could be found for subcortical gray matter volume (basal ganglia and thalamus) and cortical surface.

aEEG can be used to monitor early brain function, and SATs are mirroring the development of thalamocortical connections, but also seem to be predictive of structural brain development over time. This is consistent with the idea that increased levels of early brain network activity are associated with better brain growth, showing the intimate relation between brain structure and function during brain development.



MANON JNL BENDERS, MD PhD, NATHALIE HP CLAESSENS, MD
Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands

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SIMPLIFYING aEEG MONITORING IN THE NICU

■ Amplitude integrated electroencephalography (aEEG) is a simplified, easy to use method for continuously monitoring the status of an infant's brain. It is characterized via patterns generated by overlapping the rectified and inverted EEG every 15 seconds, and plotting the brain activity on a semi-logarithmic scale against time. aEEG traces are then categorized according to background brain activity and seizure activity patterns.¹

Classifying the aEEG pattern may be challenging for those who are new to cerebral function monitoring. The Olympic Brainz Monitor™, with optional background pattern classification (BPC) software, continuously analyzes peak-to-peak EEG voltage and classifies the background pattern based on clinical criteria¹ (NOTE – BPC SW is currently not available for sale in the USA). This may help the neonatologist and/or bedside neonatal nurse with initial interpretation, and assist in classifying neurological changes over time. It may further help in

expediting a neurology consultation and/or diagnostic evaluation.

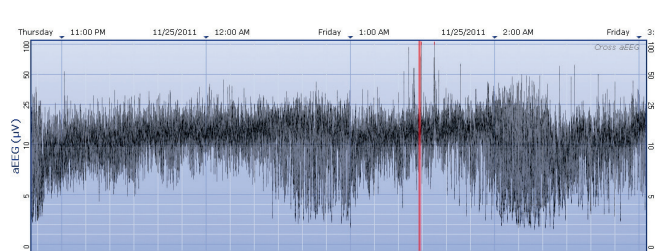
BPC software works by taking a sliding 2-minute window of aEEG and calculating upper and lower margins for the corresponding collection of aEEG values. As the aEEG advances the classifier applies a set of rules to the upper and lower margins to estimate the background pattern. In the event of high-impedance, the BPC detector is automatically disabled. The BPC algorithm is intended to classify sections of the aEEG that may correspond to background patterns as identified according to a scoring method published by Lena Helstrom-Westas et al., in full term neonatal patients (defined as from birth to 28 days post-delivery, and corresponding to a post-conceptual age of 37 to 46 weeks). The output of the BPC algorithm is intended to assist in the assessment of aEEG traces by qualified clinical practitioners, who will exercise professional judgment in using the information.



CFM
Olympic Brainz Monitor

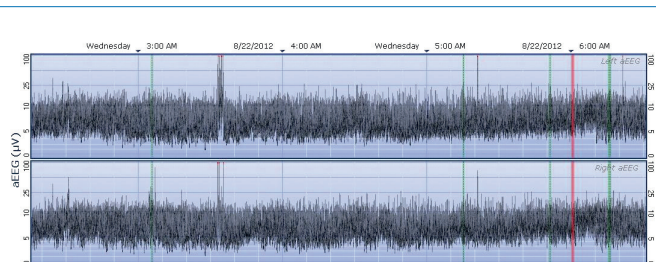
1. Continuous Normal Voltage (CNV) –

This pattern is a narrow wavy trace with upper limit above 10 μ V and lower limit above 5 μ V. SWC present.



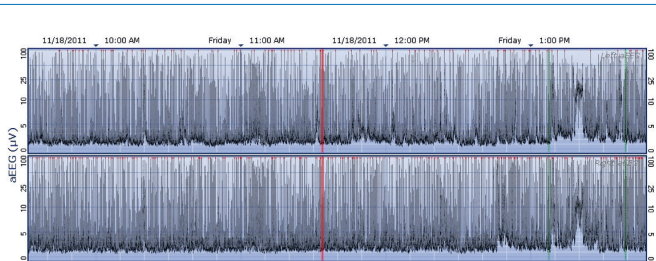
2. Discontinuous Normal Voltage (DNV) –

This pattern is a wide banded pattern with upper limit above 10 μ V and lower limit below 5 μ V. SWC absent.



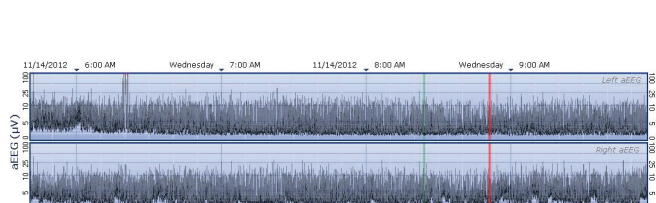
3. Burst Suppression (BS) –

This pattern indicates bursts of brain activity followed by periods of suppression with upper margin well above 10 μ V and lower margin below 5 μ V. A dark band appears at the lower portion of the pattern. SWC absent.



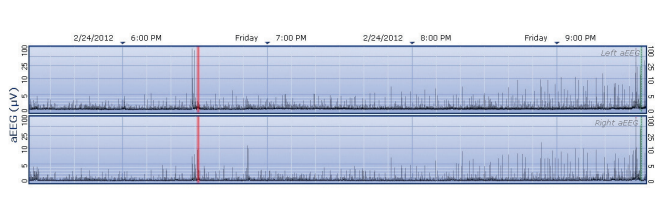
4. Continuous Low Voltage (CLV) –

This pattern indicates the brain activity in the lower voltage range with upper margin lower than 10 μ V and lower margin lower than 5 μ V. SWC absent.



5. Isoelectric / Flat Trace (FT) –

This pattern indicates the brain having extremely low or no activity. SWC absent.

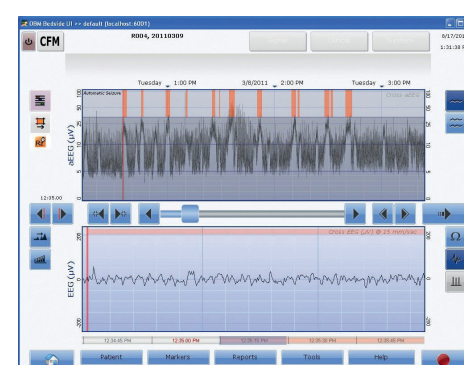


Integrated Software can help simplify Seizure and background pattern recognition

Neonatal seizures, which may be clinically subtle, are often difficult to recognize from the normal behaviors of the inter-ictal periods or physiological phenomena², making accurate recognition and treatment challenging in the busy NICU environment. Seizures are more common in the neonatal period than in any other time in life – as high as 57.5/1000 in < 1500 grams and 2.8/1000 in 2500 - 3999 grams². In cases of moderate to severe HIE, the incidence of seizure activity is > 50%⁴. Term infants with seizures may have very poor outcomes with up to a 20% fatality rate during the neonatal period. Survivors have a 28% - 35% risk for severe neurodevelopmental disability and a 20% - 50% risk for epilepsy⁵. Unidentified and untreated neonatal seizures can lead to a long-term impairment or death². It is because of this impact that seizure identification and measurement of therapy are of extreme importance to the clinician.

RecogniZe seizure detection software complements the Olympic Brainz Monitor by the automatic marking of possible seizures. It helps by identifying suspicious activity and guiding the clinician to the corresponding areas of the raw EEG signal for the purpose of validating the seizure(s). The RecogniZe seizure detection algorithm includes filtering of the raw EEG signal, parallel fragmentation of the signal into wave sequences, wave feature extraction and averaging, and elementary, preliminary and final detection. The cross-cerebral (P3/P4), bi-parietal - left (C3/P3) and bi-parietal - right (C4/P4) channels are used for event detection.

The algorithm then indicates the most probable location in the recoding of events that may correspond with seizure activity in the patient.



Cerebral function monitoring helps the clinician understand whether an infant has a brain injury and/or seizures, helps determine if there are changes over time, and may help in measuring the effectiveness of therapy. The Olympic Brainz Monitor can fill the critical role by providing an easy to use, and easy to interpret brain monitoring trend. BPC and RecogniZe software are designed to identify areas of interest and assist the clinician in making critical decisions during a period where time equals brain cells.



SAMUEL MANI, TERESA BOONE & JUDY MOORE

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The RecogniZe algorithm uses the following criteria:

- At least five similar consecutive waves
- Wavelengths equivalent or less than a frequency of 14 Hz
- Peak-to-peak amplitude greater than 5 μ V
- At least 21 seconds of continuous detection or 26 seconds of discontinuous detection in one minute of EEG signal

EDUCATION – THE KEY TO SUCCESS

■ Education is key to effective implementation of a medical device at a clinical site. We at Natus have long recognized the value of education and have an entire team devoted to you and your success. We understand that a NICU is an extremely busy environment and know the importance of providing education that is thorough, flexible, and repeatable. Our goal is to provide you not only quality product training, but to provide you with all of the tools you need to successfully implement your new device and document training proficiency – tools such as sample policy/procedures, competency evaluation check-lists, and parent/family education brochures. When you have new hires, we want to make sure they can be trained quickly and efficiently and offer in-service videos and quick guides to help them along. These tools also serve during annual competencies and help ensure all clinicians are receiving the same standard of training, every time.

When a new product within an existing standard of care is released, like a new phototherapy light, the education is usually related to new features and enhanced device capabilities. But, when a concept product comes around that marries current science

with technology, and changes the way clinicians practice, well, that's a whole different educational approach. The Olympic Brainz Monitor was one of those concepts. This type of education planning and execution are right up our alley as Natus has an extensive background teaching clinicians both science and technology, starting with our flagship ALGO hearing screener. When the concept of uni-



versal newborn hearing screening was introduced, scientific education paved the way to adoption. So when aEEG came along, we were ready!

As this 2nd edition of our Neonatal Care Academy Journal goes to press, I am thrilled to let you know that many of our educational support tools have been migrated to the Neonatal Care Academy site, providing you with a one-stop location to watch a scientific video, download a policy/procedure or print a parent education flyer.

You will also find our **2016 eSEMINAR CALENDAR** and can register for upcoming events right from the Neonatal Care Academy. **NEW** in 2016, many of our courses will offer 1.0 CE Contact Hours – **FREE**. Don't worry if you can't attend live, we will be posting additional courses with **FREE** CE Contact Hours for ON-DEMAND viewing.

We understand the neonatal intensive care unit (NICU) can be a confusing place for siblings of a preterm or sick baby. To support you in your family centered care model, we have developed the Natus Coloring Book, which is geared towards helping siblings understand what is happening in the NICU and to be a part of the family care approach. Children can join the Natus BABY as he takes the opportunity to answer basic questions about the NICU baby's care, and allows siblings to understand in a gentle way, through situational coloring. The colored pages can be used to decorate the baby's bed-space and help foster the sibling bond or as a memento once the baby goes home! Click on the link to download copies for your NICU and **PLEASE**, feel free to share with your colleagues!

www.natus.com/coloringbook

Natus Coloring Book - YOUR NEW BABY IS HERE!

Going forward in 2016, we will be adding our aEEG Certificate Course and Jaundice Management Certificate Course – comprehensive education programs to enhance your skill-set and earn CE Contact Hours. So, please check back regularly for NEW programs!

Finally, I am happy to release to you our first Natus Coloring Book - YOUR NEW BABY IS HERE!

Education shapes the practice of many medical device-driven programs, from screening to diagnosis. Opportunities to improve health care have expanded, and so have our educational offerings. Check back regularly to see what's new and how these tools can help you succeed!

TERESA BOONE
Director of Global Education

CEREBRAL FUNCTION MONITORING FROM A NURSE'S PERSPECTIVE

■ I remember the day well... "The baby needs to go on the cerebral function monitor (CFM), can you do that please?" I was terrified. I had never used the CFM before and due to the fact that I was on night shift, I had missed the training session. But I knew this baby was at risk for seizures because of a low pH post-delivery. After a bit of perseverance placing electrodes, I saw my impedance was good and we were monitoring!

It was after this shift I became the lead nurse in our unit for the CFM and my first priorities were to increase people's confidence with the monitor, and help them to understand it as a useful and necessary tool within neonatal and pediatric nursing. The easiest way to get to know how to use the aEEG monitor is to simply practice, practice, practice.

In my NICU and at other local hospitals, I provided numerous teaching sessions on how to position electrodes using the positioning aid on a doll. I also

taught clinicians how to insert the needle electrodes using an orange and how to use the devices via stimulation techniques, so that when the skills were required in real life it would be less daunting.

When placing the hydrogel electrodes on an infant, preparation is key. It can take up to 30 minutes to make sure the areas are adequately cleansed of any particulates that can disrupt the electrical impulses. It may feel a little time consuming, but putting the time in initially will result in a better picture in the long run and better traces for the infant. It is essential you are given the time to apply electrodes and start the device properly. I always encourage the medical team to insert the needed invasive lines first, and then place the CFM electrodes afterwards. This reduces the stress of the person applying the electrodes.

Empowerment is key in nursing. Nurses are the consistent workforce in the NICU as the more junior doctors rotate regularly. When nurses are skilled at placing electrodes and starting the CFM monitor it gives a sense of achievement and also an opportunity to help teach the junior doctors. I believe

that the CFM is a vital device in the NICU. It is easy to use and helps us provide the highest level of care for our patients. I think education is needed at all levels including electrode application and interpretation. The device has a built in HELP SCREEN which reviews electrode application and how to start a trace which is very good, particularly if you don't use the monitor often or have the opportunity to practice regularly.

Cerebral function monitoring is increasingly being recognized as the standard for monitoring infants with risk of seizures, or after hypoxic events. But it can also be used on pediatric wards providing vital information on young infants returning from the community with medical problems. I was personally involved in a few cases on the pediatric ward whereby clinical situations were identified earlier by using the CFM. I had the opportunity to show a poster with these findings at the JENS conference in Budapest this year, and an article is about to be completed and published based on these experiences.

Off the back of all my experiences using the CFM and explaining to parents why we were using the



device, I noted that there was limited information for parents to take away and review, therefore with the help of neonatologist Dr. Paul Clarke, neonatologist, we produced a parent information leaflet for our families, and for cross use on the pediatric ward. It was so well appreciated, that it was sent to the neonatal region coordinator and is now being used throughout our network. Recently I have moved locations and the same information leaflet will be implemented within my new region.

I am immensely proud to have been involved at the early adoption stage of a new tool and to continue to help others implement the CFM in their NICUs.



STACEY DIXON, RNC BSc NURSING
Trainee Advanced Neonatal Nurse
Practitioner, United Kingdom

UPCOMING EVENTS 2016 ON:
www.neonatalcareacademy.com

IMPRINT:

Natus Medical Incorporated
1501 Industrial Rd
San Carlos, CA 94070 USA
1-800-303-0306
1-650-802-0400

Editor In Chief:
Pierre Radzikowski
pierre.radzikowski@natus.com

Conception & Design:
www.icom-media.com
Printed in Austria

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