The 20th Annual Gravens Conference on the Physical and Developmental Environment of the High Risk Infant
Communication: Defining, designing and delivering effective human interaction in the NICU

January 30 - February 3, 2007

Sheraton Sand Key Resort
Clearwater Beach, Florida
The Development and Implementation of Potentially Better Practices to Support the Neurodevelopment of Infants in the NICU

Vermont Oxford Network / NIC/Q 2005
(Neonatal Intensive Care Quality Collaborative)

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Beckett Perkins
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Sue Laudert
Elizabeth MacMillan-York
Vermont Oxford Network

Mission

To improve the quality and safety of medical care for newborn infants and their families through a coordinated program of research, education and quality improvement projects.
Vermont Oxford Network  4 Key Habits

Habit for Change

Habit for Evidence-Based Practice

Habit for Collaborative Learning

BETTER PRACTICES
Clinical
Organizational
Operational

Habit for Systems Thinking
NIC/Q Goals

- Measurable improvements in quality, safety and cost of NICU care
- Develop new knowledge and tools for QI
- Disseminate the improvement knowledge

“To Fundamentally Change the practice of NICU care”
## NIC/Q Collaboratives

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- Benefis Healthcare, Great Falls, Montana
- Mississippi Baptist Medical Center, Jackson, Mississippi
- Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
- The Children’s Hospital of Southwest Florida/ Lee Memorial Health System, Fort Myers, FL
- Wesley Medical Center, Wichita, Kansas
Our Leader
The NIC/Q Process: Collaboration and Shared Learning

• Five Centers working together
• Coordinated by:
  – Clinical Expert: Dr. Stanley Graven
  – Facilitator: Jim Handyside
  – Clinical Leader: William Liu
• Collaboration and shared learning:
  – Four national NICQ conferences
  – Fifteen teleconferences
  – Web-based listserv
  – Sharepoint Website for document sharing and organization of resources
Steps toward our goal:
Shared learning

1. Identification of shared **AIMS**
2. Collect the **EVIDENCE**:
   - What do we know about brain development?
   - What is the clinical evidence for practice?
3. Identify **MEASUREMENT** goals and tools for assessment: **Challenging**!
4. **CASE STUDIES**: operational strategies and implementation of care practices
AIM:
Create an NICU environment that optimizes the neurodevelopment of the infant while supporting the well being of family and staff

• Develop and evaluate Potentially Better Care Practices
  • Begin to Implement these practices in the NICU setting
EVIDENCE

• Background:
  – Brain development: what do we know?
• The evidence for our potentially better care practices
• Challenges in demonstrating measurable evidence
Brain Development
What do we know?

- Genetically pre-determined neuronal development
- Stimuli-dependent neuronal development
  - Endogenous stimulation: activity-independent
  - Exogenous stimulation: activity-dependent
- Sequential theory of development
- Role of sleep
- Brain plasticity
Genetically Pre-determined
Brain Development, 1

Left: Histologic section of a mouse embryo at embryonic day 12.5. Right: Schema of the embryonic day 12.5 mouse brain in which the primordia of some forebrain structures are labeled. In addition, longitudinal and transverse subdivisions are indicated. The paired telencephalic vesicles make up the majority of the forebrain mass and can be subdivided into the pallium (roof) and subpallium. The pallium includes the cerebral cortex, which in mammals is further subdivided into various laminar structures: the neocortex, archicortex (hippocampus), and paleocortex (olfactory bulb and olfactory cortex). The subpallium includes components such as the striatum, globus pallidus, septum, and parts of the amygdala (not shown). Ventral to the telencephalon are the eyes and hypothalamic areas. Neurogenic (transverse) components are labeled in their basal plate: r1–r7 are rhombomeres; p1–p6 are the theoretical prosomeres.
Prenatal Neuronal Development

Fig. 7. Scheme of prenatal neuronal development in the prefrontal cortex. (From Mrzljak et al., 1983)
Endogenous Stimulation

• Activity-independent
• Drives appropriate synaptogenesis
Exogenous Stimulation

Activity-dependent Stimulation
Exogenous Stimulation: Sequential Theory of Sensory Development

• Sensory Systems develop from Tactile → Chemosensory → Acoustic → Visual

• Atypical onset and intensity of later developing sensory experiences (e.g. vision) may interfere with the development or function of an earlier developing system (e.g. auditory or chemosensory).

• Variable impact of sensory stimuli if it occurs prior to or after birth

• The exact amount, timing and sequence of sensory stimulation for the preterm newborn is unknown
Sensory Systems with Critical Periods

- Somatosensory (Touch)
- Kinesthetic/Proprioception (movement and position)
- Chemosensory (smell and taste)
- Auditory (hearing)
- Vision
The Role of Sleep:
Endogenous Stimulation occurs during (REM) sleep

• Appropriate consolidation of exogenous stimulation requires normal sleep architecture
• Alterations in sleep patterns may have adverse implications
Sleep Architecture

• Stages of sleep:
  – harder to define in premature infants
  – AS / REM
  – QS / NREM
  – Utilize behavioral markers

• Sleep cycles
  – Shift from ultradian to circadian activity patterns, concurrent with changing arousal thresholds
Ontogenetic hypothesis and the Importance of REM and NREM

Roffwarg, Science 1966;152: 608
REM/ NREM

• REM
  – Endogenous stimulation
  – Increased in early or immature brain, decreasing as the infant matures
  – Memory or experience consolidation

• NREM
  – Exogenous stimulation
  – Increasing importance with maturation
  – Memory or experience consolidation
Brain Plasticity:
The capacity, within genetically determined limits, to modify neuronal structure and function in response to environmental factors and stressors.

Synaptogenesis and Remodeling, Endogenous stimulation, Exogenous stimulation and Sleep
Normal Fetal Brain Development: MR Imaging with a Half-Fourier Rapid Acquisition with Relaxation Enhancement Sequence

Li Mei Lan, MD, Yasuyuki Yamashita, MD, Yi Tang, MD, Takeshi Sugahara, MD, Mutsumasa Takahashi, MD, Takashi Ohba, MD and Hitoshi Okamura, MD

wire = 58.9 ± 3.6%
Synaptogenesis vs. Synaptic Pruning (Hebbian Synapses)

Fig 2. Synapse overproduction and modification are key events that occur after birth in primate cerebral cortex. Onset of synapse formation occurs during prenatal development and appears to be independent of experience from the outside world (experience-independent). During logarithmic growth phase, experience may alter the types of synapses or perhaps the kinetics of synapse formation. Although little experimental evidence exists, experience also may be important during the extended phase of synapse remodeling that occurs in the preadolescent cortex. Drawing from Borgeois.11
Synaptic Density over time

Dynamic mapping of human cortical development during childhood through early adulthood


*Child Psychiatry Branch, National Institutes of Mental Health, National Institutes of Health, Bethesda, MD 20892; and ‡Laboratory of Neuro Imaging, Department of Neurology, University of California School of Medicine, Los Angeles, CA 90095-1749

http://www.loni.ucla.edu/~thompson/DEVEL/PNASDevel04.pdf
Relationship Summary

- Synaptogenesis
- Synaptic Pruning

Critical Period of Development

- Endogenous Stimulation/REM Sleep
- Exogenous Stimulation/NREM Sleep

NICU Hospitalization

28 wks, Term, 2-3 yo, Adult
Potentially Better Practices

S = Sleep
T = Tactile
C = Chemosensory
A = Acoustic
V = visual
Classification of Evidence (adapted from Muir and Gray 1997)

1. Systematic review of multiple well-designed randomized controlled trials
2. Randomized clinical trial
3. Trials without randomization: single group pre-post, cohort, time series or matched case-control studies
4. Non-experimental studies
5. Expert opinion based upon clinical evidence, descriptive studies or reports of expert committees
Neurodevelopmental Bundle #1: Potentially Better Practices with Recommended Implementation at Birth

Full Implementation for all NICU admissions.
Can begin as early as 23 weeks gestation
T-1: Tactile: At birth, provide containment and body flexion of the newborn

- Promotes sleep, decreased awakening during quiet sleep; longer periods of REM sleep
- **Improved physiologic stability: self-regulation, decreased signs of stress, improved neuromuscular development**
- Decreased pain response
- **Potential Risks: Overheating**

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T-2: At birth, provide perioral stimulation/non-nutritive sucking.
At 32-34 weeks utilize NNS to transition to nutritive sucking

- Systematic reviews: Decreased length of stay and improved pain response/ No harmful effects (Cochrane Review)
- **May facilitate transition to effective nutritive suck**
- Enhanced physiologic stability, improved behavioral state for feeding, diminished signs of stress, decreased pain response
- **Potential Risks:** Early weaning off of breast?

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Meta-analysis: Methods of evaluating where there is evidence from a large number of studies; RCT: Randomized Controlled Trials; Controlled, Experimental: Studies evaluating the intervention against a control group; Case Studies: Observational studies in individual cases; Opinion/Animal Studies: Studies based on expert opinion or animal models.
T-3a: Gentle Human Touch, Hand Grasping/ Facial Stimulation

- Systematic review: No benefit

- Physiologic effects: diminished motor activity/ behavioral stress. No differences in weight gain or behavioral organization

- Lower levels of active sleep (shift to less total sleep for massage/Dieter 2003)

- Safe w/o adverse effects

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T-4: At birth, decrease exposure to painful / negative stimulation

C-1: By 27-28 wks, provide exposure to mother’s scent; C-2: Minimize exposure to noxious odors

• Prenatal odor experiences shape the earliest neonatal preferences, and these preferences evolve rapidly based upon early postnatal experience

  • Olfactory preferences reinforced by exogenous cues associated with the mother’s scent

  • Breast milk smell may stimulate NNS (Bingham 2003)

• Familiar odors have calming or soothing effect when performing a painful procedure (Rattaz 2005; Goubet 2003) or with stress of separation from the mother (Varendi 1998)

• Newborn have discriminatory preference and response to pleasant vs noxious odors

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A-1: Minimize ambient noise levels around the infant’s environment

• Some evidence that excessive noise exposure in utero may lead to hi-freq hearing loss
  • Measurement: (Levy 2003; Robertson 1998)
  • Isolette noise: (Bess 1979; Blennow 1974; Ciesielski 1980)
  • Renovation has positive effect: (Philbin 2002; Walsh-Sukys 2001)

• Physiologic effects: on HR, BP, RR. Possible deleterious effect on neuro-endocrine system with adrenal hypertrophy and decreased immune response (in mice): And noise reduction appears to improve some of these physiologic changes: (higher O2 sat; less fluctuation in sats, more stable behavioral states)

• Sleep: Premies more easily aroused by noise than term infants (Gerber 1982); and sleep is clearly impacted by level of noise (Gadeke 1969); decreased noise results in more sleep time and time in quiet sleep (Zahr 1995, 1996), and pulsed noise has more impact (Miller 1983)

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V-1: At birth, provide exposure to low ambient light
V-2: At birth, avoid, exposure of the infant to direct lighting

- Visual sensory system does not require exogenous light stimulation until term delivery

- Lighting will interfere with essential endogenous wave activity and visual system development:
  - Excessive lighting may interfere with sleep and interrupt REM sleep (endogenous stimulation)
  - Direct light/ light flicker will interfere with synchronous wave occurrence
  - Sequential theory of sensory development

- Preterm infant more vulnerable to effects of direct lighting
  - Pupillary light reflex: more immature infant will receive more direct light

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S-1: Develop strategies that preserve normal infant sleep cycles

Support family involvement in care practices that promote sleep

Non-emergent care will be provided at appropriate times to minimize the disruption of sleep (with diurnal implementation if possible after 30 wks gestation).
S-2: Minimize exposure to narcotics and medications that disrupt or disturb sleep cycles

• Midazolam for sedation has not shown measurable benefit, and possible increased risk of IVH /ICH and death (Aranda 2005, Ng 2006)

• Continuous narcotic drips have no impact on pain mitigation (Simons 2003, Anand 2004, Carbajal 2005)

• Morphine: Hypotension (Hall 2005); Fentanyl: Chest wall rigidity and hypothermia (Okada 1998); prolonged ventilatory support (Aranda 2005, Bhandari 2005)

• Increased length of stay and risk for narcotic dependence (Franck 1998)

• Human microglial cells exposed to narcotics \(\rightarrow\) increased apoptosis

• Animal studies: morphine will disrupt neuronal development, proliferation, decrease dendritic length and arborization

• Narcotics may decrease REM sleep (Shaw 2005); SSRI’s are used as an animal model for REM sleep deprivation (Mirmiran 1981)

• Morphine and phenobarbital cause EEG depression (Bell 1993, Young 2000)

• Theophylline may disrupt total sleep: decrease total and active sleep, delay development of quiet sleep (Animal-rabbit); Human: Caffeine does not disrupt sleep stages nor duration in newborn. Questionable decrease in active sleep

• EtOH will decrease total sleep, primarily due to decrease in active sleep (Mannella 1998)
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Neurodevelopmental Bundle #2:
Potentially Better Practices with Recommended Implementation
by 31-32 weeks gestation
T-3b: Massage

• Systematic review: weight gain/ Others: Improve weight gain; possibly mediated through increased vagal activity and gastric motility

• Physiologic effects: increased range and regulation of behavior states, decreased stress and improved autonomic stability

• Possible beneficial effect on bone mineralization

• Improved post-massage sleep (w/ sesame oil application)

• Improved maternal: infant bonding

• Potential Risks: Physiologic instability; cost allocation for clinical time by nursing or occupational therapy

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| Against  |               |               |               |               | Vickers 2005 (Cochrane) |
T-3c: Skin-to-skin Contact

- Positive effect on behavioral state organization (more flexor tone; more alert wakefulness and orientation); and increased sleep (mostly quiet sleep)

- Improved physiologic stability (temp; improved respiratory function; less stress behavior)

- Maternal benefits: Improved parental: infant attachment; improved maternal mood/ confidence/ less stress

- Long term follow-up:
  - Improved head growth and longer period of breast feeding (Tessier)

- Higher IQ and improved Bayley scores (Ohgi)

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A-2: By 31-32 weeks, encourage audible exposure to mother’s voice

- In utero environment is primarily low frequency sound, with attenuation of higher frequency (>500-1000hz)

- In utero exposure to mother’s voice facilitates subsequent speech and language acquisition (Moon 2000, Hepper 1993, Mehler 1988)

- Infant can recognize and prefer mother’s voice distinguished from other female voices or controls (Hepper 1993; DeCasper 1980, Fifer 1989, Spence 1987, Querleu 1984)

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V-3: By 31-32 weeks, provide cycled lighting: minimum of 1-2 hours

- Continuous darkness does not improve outcomes

- Infants appear to have a circadian rhythm as early as 22 wks (de Vries) to 28-34 weeks (Mirmiran 1990), with diurnal variation in skin temperature (Updike 1985), heart rate (Mirmiran 1991), respiratory pause frequency and activity, blood amino acid levels (Mantagos 1989)

- Cycled lighting as low as 200 lux may be sufficient to entrain circadian rhythms.

- Cycled lighting: more weight gain (Mann 1986, Brandon 2002), more stable resp rates at night (Blackburn 1991), decreased LOS, improved Brazelton motor cluster scores (Miller 1995)

- No difference in weight gain (Rivkees 2004, Boo 2002), nor sleep-wake progression (Shimada 1993)

- Circadian rhythmicity may occur independent of amount of ambient light (endogenous exposure-independent mechanism)

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<th>Meta-analysis</th>
<th>RCT</th>
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<th>Case Studies</th>
<th>Opinion/Animal Studies</th>
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V-4: By 38 weeks, provide more complex stimulation of the visual system
Other Recommendations

• A: Develop methodology for noise assessment
• V-5: Provide night staff exposure to adequate lighting
• V-6: Provide adequate staff and family lighting
The challenge of establishing CLINICAL EVIDENCE

**Methodology:**
Select Low Risk Population  
Randomization  
Control w/o bias  
Adequate Sample size

Sample of Patient Population

**One or Multiple Interventions**
- Standard Care Practice
- New Practice

**Proximate Outcome**
- Outcome 1
- Outcome 2

**Short Term Outcome**
- Long-term Outcome 1
- Long-term Outcome 2

The GOAL:
Measurable improvement in Long-term Neurodevelopmental Outcome

Significant Measurable Difference
NICU Risk Factors are poor predictors of early outcome. Early outcome are poor predictors of school age outcome.


NICU Factors Poor Predictors of Long-Term Outcome

- NICU Predictors
  - High Risk
  - Moderate Risk
  - Low Risk

- Short-term Outcomes
  - Moderate- Severe Neurodevelopmental Impairment
  - Mild Neurodevelopmental Impairment
  - Normal

- Long-term Outcomes
  - Moderate- Severe Neurodevelopmental Deficits
  - Mild Neurodevelopmental Deficits
  - Normal

Increasing Gestational Age
Increasing Birth weight

EFFECTS OF BRAIN PLASTICITY
For Consideration…

• BRAIN PLASTICITY may lessen the negative effects of a high risk NICU environment, resulting in little measurable difference when comparing less supportive to more supportive care practices.

• Potentially better practices demonstrated to be safe, but with limited clinical evidence for long-term benefit, become more compelling when compared to existing practices with uncertain safety, and no evidence for benefit.

• Implementation of Bundles of Care may have a greater likelihood of resulting in measurable long-term benefit.