The NICU Journey: Impact on Long-term Outcomes

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The Early days of Neonatology and follow-up

Dr. Martin Couney’s incubator

Babies

RAPID CHANGES IN NEONATAL CARE AND EVOLUTION OF NICU’S IN THE USA in 1960’s

Dr. Louis Gluck
Director of the first NICU in the USA (1960)
Yale New Haven Hospital

Research Funding Accelerated in the 1960’s: Neonatal Medicine and Current Events Merge

NICU 1970-1980’s
The Modern NICU
- Open Pod NICU
- Private Room NICU

Neonatal NIH research funding Over Time
- **1960's:**
  - Butterfly scalp veins replace clysis for hydration (R. Usher)
  - Characterization of developmental maturation stages (C. Amiel-Tison)
  - Total parenteral nutrition
- **1970's:**
  - First generation ventilators designed for neonates (G. Gregory)
  - CPAP for RDS (G. Gregory)
  - Prenatal steroids for lung maturation
- **1980's:**
  - Surfactant administration to newborns (T. Fujiwara)
  - ECMO for respiratory failure (R. Bottlet)
  - Jet ventilation and HFOV
- **1990's-2000's:**
  - Artificial surfactant for RDS (M. Avery, J. Clements, Mead)
  - Inhaled nitric oxide for PPHN
  - Trials of room air resuscitation
  - Hypothermia for HIE

Decrease in Premature Infant Mortality Overtime

National Premature Birth Rates

PERINATAL MORBIDITY & GESTATIONAL AGE

Vulnerability of the preterm brain

Brain Development

Developmental Changes in Brain Volume

- Rapid brain growth in 2nd & 3rd trimester
- Maturational process:
  - Axon extension
  - Dendrite elaboration
  - Synaptogenesis
  - Glial proliferation and maturation
- Thalamocortical neurons project throughout the cortical grey matter reaching thalamic neurons by term equivalent
- The maturational process can be impaired by injury, ischemia or hemorrhage.

Volume changes in the Premature Infant brain after injury

- Cerebral white matter
  - Maturation specific vulnerability to injury
- Other susceptible areas of injury
  (Neuronal loss, gliosis):
  - Cortical & Deep grey matter
  - Cerebellum (27%)
  - Thalamus (40-60%)
- Risk Factors: IVH, extreme prematurity, fetal distress, increased venous pressure, systemic hypotension, impaired cerebral blood flow, systemic infection/inflammation, vulnerable oligodendrocytes

Brain Volume in Older Premature Infants and Adolescence

Periventricular-Intraventricular Hemorrhage

Volumeetric imaging of premature infants at age 8 & 12 years

- Using voxel-based morphometry and diffusion tensor imaging
- Improved imaging of regional WM volumes and thalamic volume (fiber tract organization)
- At both age time periods, PT infants have significantly lower total brain volume, cerebral grey matter and white matter regions.
- These differences do not persist into adolescence at age 14-15 years
- These studies inform our understanding of the impact of prematurity birth and interaction of the environment on the developing brain

Preterm | Term
--- | ---
Total Brain | 1319 ±14.5 | 1349 ±14.5 | 1391 ±23.5 | 1439 ±23.5
Cerebral Gray | 321 ±2.4 | 314 ±2.4 | 332 ±3.9 | 298 ±3.9
  - Left | 320 ±2.4 | 314 ±2.4 | 332 ±3.9 | 298 ±3.9
  - Right | 322 ±2.4 | 316 ±2.4 | 334 ±4.0 | 300 ±4.0
Cerebral White | 202 ±2.5 | 222 ±2.5 | 192 ±4.2 | 243 ±4.2
  - Left | 202 ±2.5 | 222 ±2.5 | 192 ±4.2 | 243 ±4.2
  - Right | 201 ±2.5 | 221 ±2.5 | 193 ±4.2 | 244 ±4.2
Total Cerebellar Volume | 126 ±1.7 | 132 ±1.7 | 125 ±2.9 | 138 ±2.9

Brain volume changes and injury as Predictors of Outcomes

- Correlate patterns of brain injury and brain volume at term equivalent via MRI with 2-year outcomes
- Popn: 325 PT infants ≤32 weeks' born between 1998-2000
- Geographically different cohorts
- MRI Scans: graded severity of injury (IVH, PVL and cerebellar hemorrhage)
  - Brain growth (measured using
    - Biparietal Width (BPW) and Interhemispheric distance (IHD)
  - Good correlation with three-dimensional volumetric measures as the "Gold Standard"

Neurodevelopmental Outcomes
- Using the Bayley Scales of Infant Development II (Melbourne and Australia) and III (St. Louis, MO)

Results:
- Brain injury overall (33%)
  - Severe brain injury (10%)
  - PVL (12%)
  - Cerebellar hemorrhage (10%)
  - IVH (19%)
- Impaired brain growth:
  - Small BPW (31%)
  - Increased IHD (34%)
  - Both patterns of impaired brain growth (7%)
  - Small BPW correlates with small HC, but IHD not correlated with HC

Neonatal MRI: Predictor of Neurodevelopmental Outcomes?
- Infants <32 weeks' represent ~2% of live births with >85% survival
  - Increased risk for cerebral palsy (5-10%), neurosensory impairment (cognitive, behavioral and social difficulties) that impair educational achievement, and require special educational support
  - How do we best identify those infants at greatest risk for disability, and would benefit from early intervention services?

Neuroimaging used to predict outcomes (HUS vs. MRI):
- Head ultrasound:
  - Most widely used
  - Detects IVH, PVL
  - Poor predictive of white matter abnormalities
- Brain MRI at term equivalent:
  - Increased severity of white matter abnormalities associated with poorer outcomes (cognitive and motor)
  - Premature infants with gray matter abnormalities had poorer cognitive scores
  - Presence of any moderate-severe white matter abnormalities in more sensitive than ultrasound findings of IVH/PVL in predicting severe neurodevelopmental impairment
  - Cerebellar (posterior fossa) abnormalities associated with cognitive impairment and moderate-severe CP

Conclusion:
1. Late brain imaging (MRI or HUS w/posterior fossa view) predicts neuromotor outcomes at 2 years
2. Late MRI is superior to HUS in predicting outcomes

Critical Periods of Risk and Brain Development
Periods of Risk to the Fetal & Neonatal Brain

Critical Periods of Risk: Pregnancy
- Maternal nutrition
- Prenatal care
- Chronic medical conditions (e.g., diabetes, hypertension, drug use)
- Chorioamnionitis
- Obesity
- Maternal stress/PTSD

Critical Periods of Risk: Neonatal Period
Neonatal morbidities associated with increased risk of neurodevelopmental impairment:
- Severe IVH (Grade 3 & 4)
- Severe RPD
- NEC
- Sepsis
- Severe Retinopathy of Prematurity (ROP)

Neonatal Risk Factors Associated with Neurodevelopmental Impairment

Circadian Rhythms and light exposure: Developmental Trends
- Circadian rhythmicity during pregnancy is essential for proper fetal intrauterine development
  - Maintained by regular maternal exposure to light-dark cycles
  - Disrupted circadian maternal environment is associated with IUGR, lower fetal adrenal cortisol
  - Maternal signals entrain (synchronize) the fetal "brain clock" and regulated by interactions between maternal-fetal hypothalamus in the suprachiasmatic nucleus (SCN), and placenta via maternal hormonal cues.

How does the NICU Environment Impact Premature infant Outcomes?


Watanabe S et al. Frontiers in Endocrinology 2013
Artificial Circadian Environments for Premature Infants

- **Melatonin replacement:**
  - No RCT evaluating effects on fetal development
  - Melatonin is unsafe for use in pregnancy and childhood
  - Thought to increase responsiveness to hormones involved in fetal development

- **Glucocorticoids:**
  - May interfere with child reproductive hormones (inhibits GnRH)
  - Induces seizures in neurologically impaired children

- **Let there be LIGHT!**
  - Environmental lighting may be used to substitute for loss of maternal signals to entrain premature infant biological clock
  - Creating daily light-dark (LD) cycles may be effective to entrain circadian clocks in PT infants
  - Human preterm infants can detect light as early as 28 weeks, and biologically responsive to effects of light

- **Visual receptors in the human retina perceive light (melanopsin (functional early at 31-33 weeks'), rhodopsin, cone opsins)**

- **Regular LD cycles improve PT infant growth and sleep cycles by 6 weeks after birth**

- **Continuous light conditions, including dim light may disrupt the circadian rhythms in PT infants**

- **Watanabe S et al. Frontiers in Endocrinology 2013**

Environmental Lighting in the NICU

- **Regular LD cycles were standard in the NICU in the 1950-1960’s**
- **Continuous lighting introduced with the modern NICU and use of isolettes**
- **Regular LD cycles absent from NICU’s 1990’s-2000’s**
  - Continuous Low level dim lighting and crib covers recommended by NIDCAP
  - Mimics In Utero lighting conditions
  - Actual bedside illumination in a NICU over 7 days can vary (figure)

- **Bedside Illumination and Monochromatic Light Red Filter**
  - Red filter used to introduce “Artificial nights”
  - Used in PT infants 1000-1500 grams at birth
  - Initiated after infant medically stable at 30-34 weeks PMA, or 4-8 weeks before discharge
  - Randomly assigned to continuous lighting, LD cycles using the Red Filter
  - **Results:**
    - Infants with the filter and exposed to LD cycles were more active during the daytime than night, and had better weight gain
    - Long-term developmental outcomes were not compared

- **Impact of Excessive Noise in the NICU**
  - Few research studies available evaluating the impact of NICU noise and long-term outcomes in PT infants
  - “Safe” sound levels in the NICU thought to promote healthy development in PT infants
    - High background noise may diminish speech discrimination and interfere with later language acquisition
  - **Current NICU recommendations:**
    - Standards for NICU design and noise limits:
      - Applies to bedside, staff work areas and family areas
      - Noise limits:
        - Should not exceed an average Leq of 45 dB over time, and an hourly L10 of 50 dB and Lmax of 65 dB (L10=measure of decibel level exceeded for 10% of the hour)
    - Actual NICU noise levels commonly exceed limits (70-117 dB)
    - Converse speech is ~60 dB
  - **Effects of Loud Noise:**
    - Increased physiological stress
    - Apnea, bradycardia, fluctuations in HR and BP, altered sleep-wake cycles, sensorineural hearing loss, increased agitation

- **Actions to Decrease Excessive Noise Exposure for Infants in the NICU**

- **NICU Design: Single Room vs. Open Bay NICU**
  - Recent NICU design trends from the open bay (open) to the single family room (SFR)
    - Family-centered neonatal care
    - Greater privacy and comfort for families
    - Greater environmental control
    - Space customization
    - Reduced noise
    - Decreased nosocomial infection rate
    - Improved neurobehavioral status of the infant
    - Decrease infant stress and maternal stress & anxiety
    - Family satisfaction
    - Staff satisfaction
    - Increased infant rate of weight gain and weight at discharge
    - Decreased time to full feedings

**References:**
- Hassanein SMA, et al / Maternal-Fetal and Neonatal Medicine 2013
- Watanabe S et al. Frontiers in Endocrinology 2013

**FIGURES:**
- Environmental Lighting in the NICU
- Impact of Excessive Noise in the NICU
- Actions to Decrease Excessive Noise Exposure for Infants in the NICU
- NICU Design: Single Room vs. Open Bay NICU
NICU Design: Single Room vs. Open Bay NICU

Potential problems:
- Concerns over infant safety
  - Need for more staff to effectively observe and monitor
- Isolation of nursing staff
- Reduced availability of collegial support and peer-to-peer teaching and observational learning
- Increased presence of families at the bedside during procedures
  - Increased staff anxiety
- Families experience increased isolation and stress
  - Spend less time at family gathering places where support from other parents is vital

Model for Medical and Neurobehavioral Improvements Related to SFR NICU:

- Family Centered Care:
  - Active partnership with parents
  - Better communication between families and staff
  - Patient satisfaction
  - Decreased parental stress
- Developmental Care:
  - Interventions to reduce stress and conserve energy for growth
  - Facilitates physiological stability (regulates motor activity, sleep/wake cycles, HR and O2 saturations)
  - Increased brain white matter maturation
- Parenting and Family Factors:
  - NICU visitation
  - Participation in infant care
  - Reduced maternal stress and better maternal-infant interaction
- Staff Behavior and Attitudes:
- Changes in Medical Practice:
  - Improved infection control practices

Model of Single Family Room Improving Outcomes Through Epigenetic Changes:

- Epigenetics: The impact of the environment on gene expression
  - Prenatal, during delivery, and postnatal
- Immature preterm infants are influenced by their environment
  - Health
  - Physiological function
  - Neurobehavioral organization & brain plasticity/remodeling
- Maternal care:
  - Modifies gene expression associated with behavior, and neuroendocrine response to stress
  - Enhance synaptic development and decreased methylation of glucocorticoid receptors of the hippocampus
- SFR NICU provides opportunities for enhanced maternal care and positive maternal-infant interactions

Kangaroo Care and Outcomes

Kangaroo care:
- Short-term:
  - Promotes multisensory stimulation
  - Inhibits the perception of pain and stress in the newborn
  - Organization of motor and physiological systems
  - Improved weight gain
  - Fewer infections
  - Lower mortality
- Long-term:
  - Better motor and cognitive performance
- Recommendations:
  - Skin-to-skin contact between mother and baby should start soon after birth
  - For premature infants, timing depends on stability of the infant and maternal/paternal availability


Kangaroo Care and Neurobehavioral Outcomes

- Objective: Evaluate the effect of kangaroo-mother care in preterm infant neurobehavior between 36 and 41 weeks post-conceptual age
- Population:
  - Prospective cohort study of preterm infants with GA 28-32 weeks admitted to the NICU
  - Infants had to be without clinical instability (e.g. in incubator, needing respiratory or hemodynamic support)
- Method:
  - Measure mother-infant bonding at 32 weeks’ PMA using Mother-to-Infant Bonding Scale (MIBS)
  - A score of 1 (high score associated with disorders in interaction)
  - Kangaroo care for at least 5 consecutive days with mother at the bedside full-time vs. conventional group with PT infants remaining in SCN until discharge with open parental visits and option for kangaroo visits 5X/week for 60 minutes
  - Neurobehavioral assessment with the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) evaluated at 36 and 41 post-conceptual weeks

Kangaroo Care and Neurobehavioral Outcomes

Results:
- Study population: 61 maternal-infant dyads
  - Kangaroo group (KAN)= 24
  - Conventional group (CON)=37
- Both groups similar in baseline characteristics

Kangaroo Group:
- Discharged 60 days earlier than CON group
- Discharged at younger post-conceptual age (37.9 vs. 39.3 weeks)
- Higher proportion exclusively breastfeeding (70.8 % vs 43.2%)
- NNNS: higher scores for Quality of movements, lower scores on Signs of stress and abstinence

Quality of movements: movements with greater amplitude, smoother and more harmonious, greater attention and orientation to external stimuli, less reflexes with asymmetrical responses, fewer signs of stress and abstinence during the NNNS

Newborn Individualized Developmental Care and Assessment Program (NIDCAP)

- Designed to support and provide care based on reading the PT infant’s cues
  - Infants exhibit autonomic behavioral signals (e.g. respiratory patterns, color fluctuations, gaging, muscle tone and movements, yawning, blinking, etc)
  - These behavioral signals reflect infant self-regulation and responses to environmental stress
  - Infants are then to be developed to respond to outside cues and to improve behavioral and emotional well-being, improve parental competence

Synactive Theory:
- Environments and care are responsive to infant thresholds of disorganization to promote well-being
- Minimize the discrepancy between the expectations of the PT infant’s brain and actual events in their environment

Benefits of NIDCAP?
- Reduced stress
  - During eye exams and transfer from the incubator
- Improved cognitive and motor outcomes
  - Short-term at 9 months corrected age
- Improved emotional functioning
- Enhanced parent confidence and competence
- Increased breast milk production

Metaanalysis:
- No difference in death or sensorineural disability at 18 mos CGA, CLD, IVH, hospital mortality, NICU, days on ventilator or oxygen
- Higher MDI or PDI scores on the Bayley Scales at 9 months, not at 18 or 24 months

Language Exposure in the NICU Environment: Single family room

Language Outcomes in Preterm Infants
- Delayed Receptive and expressive language processing
- Deficits in phonological short-term memory
- Lower cognitive scores on the Bayley Scales of Infant Development and Intelligence testing
- Specific language deficits can persist through school age
  - phonological short-term memory
  - Phonemic decoding and sight word reading
  - Syntax & semantics
  - Verbal language
  - Reading comprehension
- Auditory processing and the preterm brain
  - Respond to auditory stimuli by 24 weeks
  - Consistent auditory and visual responses by 28 weeks

Why Might There be a Problem with the language Environment in the NICU?
- In the uterus the fetus:
  - Mother’s voice every day
  - Low frequency, high intensity sounds
- PT infants prefer human voice to other acoustic stimuli
- 3 day old Term infants prefer mothers’ voice to other female voices

In NICU
- Monitors
- Respiratory Equipment
- Little language
- Visual input

Caskey M, Vohr B. ACTA Paediatrica 2013

Caskey M, Vohr B. ACTA Paediatrica 2013

Caskey M, Vohr B. ACTA Paediatrica 2013

Slides courtesy of Dr. B. Vohr
Measures of the Language Environment and Premature Infant Vocalizations

**Language Environment Analysis (LENA)**
- **Digital language processor**
- Records infant’s natural language environment
  - Advanced software with speech identification algorithms
  - Records % of time infant is exposed to language, television, background noise, silence, # words from adults (male or female), # conversational turns, and # infant vocalizations
- Infants fit vest at 32 weeks and recorded for 16 hours @ 32 & 36w

**LENA Variables**

<table>
<thead>
<tr>
<th>% Language in Environment of Open Bay NICU</th>
<th>32 weeks</th>
<th>36 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language</td>
<td>21.1%</td>
<td>27.5%</td>
</tr>
<tr>
<td>Electronic</td>
<td>26.0%</td>
<td>35.3%</td>
</tr>
<tr>
<td>Noise</td>
<td>29.7%</td>
<td>37.4%</td>
</tr>
<tr>
<td>Silence</td>
<td>13.2%</td>
<td>10.8%</td>
</tr>
</tbody>
</table>

1. Language exposure: 83% adult (88% female, 12% male)
2. Infant vocalizations 33% (increased significantly by 36 weeks)
3. For every increase of 100 adult words, infant vocalizations increased by 4%
4. Total # of adult words ranged from 144 to 26,000 words over 16 hours
5. Exposure to parent language was a stronger predictor of infant vocalizations and conversational turns compared to other adult voices

**Total Adult Word Count at 32 and 36 weeks**

<table>
<thead>
<tr>
<th>32 weeks</th>
<th>36 weeks</th>
<th>% change 160%</th>
<th>P&lt;0.0001</th>
<th>% change 95%</th>
<th>P=0.0012</th>
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<td>8556</td>
<td></td>
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**Impact of parent Visitation on Infant/Child Vocalizations:**

- Adult Talk has a Powerful Impact on Language!

**Total Child Vocalizations at 32 and 36 weeks**

<table>
<thead>
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<th>% Change 75%</th>
<th>% Change 95%</th>
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<tbody>
<tr>
<td>113</td>
<td>105</td>
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<tr>
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Caskey M. Peds. 2014, Slide courtesy of Dr. Vohr
**Language and Outcomes**

- More language exposure that infants and children receive from birth and age 3 years is associated with better rates of vocabulary growth, academic success and higher cognitive scores.
- The LENA System is an easy and reliable method to assess very early infant vocalizations and words produced.
  - May pave the way to identify infants and young children at risk for language delay and language intervention services.

**Maternal Post-Partum Depression and PTSD: The maternal-Infant Dyad**

“To begin my life with the beginning of my life, I record that I was born”

- Charles Dickens

- Human development does not start after birth, it is important not to ignore the importance of life in the womb.
- Normal growth and development of the unborn child can be adversely influenced by a number of factors including pregnancy complications, infections, teratogens, as well as maternal psychological health including depression, stress and anxiety.

**Bio behavioral model of prenatal stress**

![Figure 1: Biobehavioral model of prenatal stress and human fetal developmental and health outcomes.](Wadhwa 2005)

**Maternal stress and pregnancy outcomes**

- Cortisol
- ACTH
- Placental CRH

- Preterm birth
- IUGR
- LBW
- Maternal infection

![Figure: Maternal stress and pregnancy outcomes](Wadhwa 2004)

**Role of Family Environment and Maternal Mental Health on Outcomes**

- Approximately 4-6% of women experience *postpartum* Post-traumatic Stress Disorder (PTSD) after childbirth.
  - Due to or precipitated trauma during delivery or postpartum.
  - Unexpected C-section, emergency delivery, newborn admitted to NICU, post traumatic event.
- Approximately 1-5% of women experience *postpartum depression* after childbirth.
  - Can begin anytime during pregnancy or the first postpartum year.
  - Predisposing factors: poverty, poor social support, financial or maternal difficulties, recent major life event, infant admitted to NICU, family history of depression or anxiety, hormonal imbalance.
- Approximately 6% of women experience *postpartum anxiety.*

- Also be associated with PTSD (33-55%)
- *Postpartum* psychosis is a rare disorder of postpartum women occurring in 0.1% of all births.

**Maternal Stress/PTSD and Parent-Child Interaction**

- Regardless of social risk, higher levels of parental positive affect and sensitivity were related to:
  - More optimal cognitive development (p < .05 and p < .05 respectively).
  - Greater social-emotional competence (both p < .01).
- Increased levels of parental negative affect were related to:
  - Increased internalizing problems such as withdrawal, inhibition to novelty and anxiety (p < .05).
- Greater parent-child synchrony was associated with:
  - More optimal cognitive development (p < .01)
  - Social-emotional competence (p < .01).

![Figure: Maternal Stress/PTSD and Parent-Child Interaction](Treyvard JAACP 2011)
LONG-TERM developmental FOLLOW-UP

- To provide a continuum of specialized medical management for NICU graduates
- Identify deviations in growth, behavior, neurodevelopment, and facilitate medical management, support, and referral for intervention to ensure the best possible outcomes (e.g. ECI, rehab services (PT/OT/Speech therapy, feeding disorders clinic).
- Clinical outcomes research and quality improvement
- Teaching and education

NEST is Now 28 MONTHS OLD!!!

- DOB: 11/12/2013
- GA: 28 weeks'
- BW: Infinity
- CGA: No correction needed

Who do we see?

Referral is based on diagnosis and physician recommendation.
High risk patients include:

- < 1500 grams
- < 32 weeks' gestation
- NEC (> stage II)
- Twin-to-twin transfusion
- Bronchopulmonary dysplasia
- Seizures
- ECMO
- Physician referral
- Double volume or partial exchange transfusion
- ICH (Gr III-IV)
- Congenital Heart Disease (critical)
- Diaphragmatic Hernia
- NO therapy
- ROP (severe)
- PHN (severe)
- Congenital Anomalies
- IEE
- Research Study Patients
- Maternal substance abuse

Follow-up Visits

4-6 wks 6 mo 12 mo 18 mo 24 mo 3-5 yrs
Summary/Take Home Points

- The premature infant’s developing brain is extremely vulnerable to injury from conception, the neonatal period, and post-NICU discharge.
- Important to recognize the impact of the NICU environment on outcomes, and to implement strategies to reduce infant stress and neurobehavioral instability.
- The modern SFR NICU provides opportunities to optimize the PT infant environment and improve growth and neurodevelopmental outcomes.
- Providing a rich exposure to language throughout the NICU stay (especially parental voices) is vital to language outcomes long-term.
- Important to recognize the prevalence of maternal post-partum depression and PTSD and the impact on maternal-infant interactions.

Thank You!