Long-term Neurodevelopmental Outcomes of Very Preterm and Very Low Birth Weight Infants

Interdisciplinary Institute: Premature and High-risk Infants: Transitioning Home from the NICU

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Faculty Disclosure

In the past 12 months, I have not had any significant financial interest or relationship with the manufacturer(s) of the products or providers of the service(s) that will be discussed in this presentation.

This presentation will not include discussion of pharmaceuticals or devices that have not been approved by the FDA.
Objectives

- Describe the later childhood, adolescent and adult health and functional outcomes for PT and very low birth weight NICU graduates
- Describe the neurodevelopmental outcomes over the life course
- Recognize the factors that affect neurodevelopmental outcome in this group of children
What are the Survival Rates and Outcomes for Preterm Infants?
Definitions

- **Low birth weight**
  - < 2500g or 5lb 8oz
  - 8.2% of live births

- **Very low birth weight**
  - < 1500g or 3lb 5oz
  - 1.5% of LB

- **Extremely low birth weight**
  - < 1000g or 1lb 3oz
  - 0.8% of LB

- **Prematurity**
  - Birth at less than 37 weeks’ gestation
  - Extreme PT - < 32 wks’
  - Moderate PT – 32- 33%/7 wks’
  - Late PT - 34%/7-36%/7 wks’

- **Multiple births**
  - ~ 3% of all live births
  - Greater tendency to be high risk
  - Twin birth rate ~ 27/1000
    - 50% born preterm or LBW
  - Triplet birth rate 1.7/1000
    (natural rate 1/8000)
    - Majority born preterm or LBW

- **Postmenstrual age (PMA) or corrected gestational age (CGA):**
  - age following conception in wks (used after baby is born)

< 37 w: 11.73%  
(prelim 2012: 11.54%)  
34-36 w: 8.28%  
32-33 w: 1.52%  
28-31 w: 1.2%  
< 28 w: 0.73%

LBW: 8.1%  
VLBW: 1.4%  
ELBW: 0.69%


Colorado

PT: 11.7% (10.4-16.5%)
W: 10.8%
B: 16.5%
AI/NA: 13.5%
A/PI: 10.4%
H: 11.7%

Early PT: 3.4%
Late PT: 8.3%
### Survival Rates to Hospital Discharge:

**22-25 weeks’ Gestation**


<table>
<thead>
<tr>
<th>Cohort</th>
<th>Year</th>
<th>Denominator</th>
<th>22w (%)</th>
<th>23w (%)</th>
<th>24w (%)</th>
<th>25w (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICHD</td>
<td>2003-2007</td>
<td>Live births (LB)</td>
<td>6</td>
<td>26</td>
<td>55</td>
<td>72</td>
</tr>
<tr>
<td>VON</td>
<td>2009</td>
<td>LB</td>
<td>5</td>
<td>33</td>
<td>61</td>
<td>-</td>
</tr>
<tr>
<td>Canadian Neonatal Network</td>
<td>1996-97</td>
<td>Population-based (LB+SB)</td>
<td>1</td>
<td>17</td>
<td>44</td>
<td>68</td>
</tr>
<tr>
<td>EPIBel</td>
<td>1999-2000</td>
<td>Population-based</td>
<td>0</td>
<td>6</td>
<td>29</td>
<td>56</td>
</tr>
<tr>
<td>EPIPAGE (Fr)</td>
<td>1997</td>
<td>Population-based</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>50</td>
</tr>
<tr>
<td>EXPRESS (Sweden)</td>
<td>2004-2007</td>
<td>LB Population-based</td>
<td>12/7</td>
<td>54/34</td>
<td>71/60</td>
<td>82/73</td>
</tr>
<tr>
<td>Norwegian Infant Study</td>
<td>1999-2000</td>
<td>Admit to NICU Population-based</td>
<td>0</td>
<td>39</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>Switzerland</td>
<td>2000-2004</td>
<td>Population-based</td>
<td>0</td>
<td>5</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>Japan (single)</td>
<td>1991-2006</td>
<td>LB</td>
<td>25</td>
<td>47</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Japan (multi-center)</td>
<td>2003</td>
<td>LB</td>
<td>36</td>
<td>75</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>
### NICHD: Rates Death and Severe Neurodevelopmental Disability

<table>
<thead>
<tr>
<th>Gestational Age (Completed Wk)</th>
<th>Death Before NICU Discharge</th>
<th>Death at 18–22 Months’ Corrected Age</th>
<th>Death/Profound Neurodevelopmental Impairment</th>
<th>Death/Moderate to Severe Neurodevelopmental Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes for all infants in the sample</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 wk</td>
<td>95%</td>
<td>95%</td>
<td>98%</td>
<td>99%</td>
</tr>
<tr>
<td>23 wk</td>
<td>74%</td>
<td>74%</td>
<td>84%</td>
<td>91%</td>
</tr>
<tr>
<td>24 wk</td>
<td>44%</td>
<td>44%</td>
<td>57%</td>
<td>72%</td>
</tr>
<tr>
<td>25 wk</td>
<td>24%</td>
<td>25%</td>
<td>38%</td>
<td>54%</td>
</tr>
<tr>
<td><strong>Outcomes Only for Mechanically Ventilated Infants in the Sample</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 wk</td>
<td>79%</td>
<td>80%</td>
<td>90%</td>
<td>95%</td>
</tr>
<tr>
<td>23 wk</td>
<td>63%</td>
<td>63%</td>
<td>76%</td>
<td>87%</td>
</tr>
<tr>
<td>24 wk</td>
<td>40%</td>
<td>41%</td>
<td>55%</td>
<td>70%</td>
</tr>
<tr>
<td>25 wk</td>
<td>23%</td>
<td>24%</td>
<td>37%</td>
<td>54%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>22-26 Weeks</th>
<th>27-32 Weeks</th>
<th>22-26 w</th>
<th>27-28 w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>61%</td>
<td>86%</td>
<td>60.3%</td>
<td>90.2%</td>
</tr>
<tr>
<td>Mod.-severe CP</td>
<td>10%</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDI &lt; 70</td>
<td>37%</td>
<td>23%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDI &lt; 70</td>
<td>26%</td>
<td>17%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blindness</td>
<td>1%</td>
<td>0.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing loss</td>
<td>1.8%</td>
<td>1.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDI</td>
<td>45%</td>
<td>28%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Includes deaths within 12 hours of birth

### NICHD Neonatal Outcomes: Extremely Preterm < 25 weeks, 401-1000 g, born 1993-2009

<table>
<thead>
<tr>
<th>%</th>
<th>1993-2009* (excl w/n death 12h)</th>
<th>1999-2001+ (incl deaths w/n 12 h)</th>
<th>2001-2004+ (deaths w/n 12 h)</th>
<th>2003-2007** (incl deaths w/n 12 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>73.5</td>
<td>35</td>
<td>32</td>
<td>51.2</td>
</tr>
<tr>
<td>BPD</td>
<td>59.1</td>
<td></td>
<td></td>
<td>61.1</td>
</tr>
<tr>
<td>Gr 3/4 IVH</td>
<td>20.8</td>
<td></td>
<td></td>
<td>16.5</td>
</tr>
<tr>
<td>Mod-severe CP</td>
<td>9.6</td>
<td>11</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>MDI &lt; 70</td>
<td>40.1</td>
<td>44.9</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>PDI &lt; 70</td>
<td>28.4</td>
<td>27.9</td>
<td>34.9</td>
<td></td>
</tr>
<tr>
<td>Blind</td>
<td>1.8</td>
<td>2</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Hearing loss</td>
<td>2.9</td>
<td>2</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>NDI</td>
<td>42.5</td>
<td>50.1</td>
<td>58.7</td>
<td></td>
</tr>
</tbody>
</table>


Death + > 1 neonatal morbidity

Morbidity

Mortality

N= 669 hospitals
335,806 VLBW neonates
Postdischarge Outcomes are Associated with Major Neonatal Complications

- **Brain injury**: Grade 3 or 4 intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL); abnormal cranial sonogram (Hintz, et al. Pediatrics 2011; Bassler, et al, Pediatrics 2009; Carlo, et al, NEJM 2011)


- **Severe retinopathy of prematurity** (NICHD NRN studies)

- **Necrotizing enterocolitis (NEC)/Sepsis** (Schlapbach, et al. Ped 2011)

- **Emerging evidence**
  - Effects of ≥ 2 anesthesia exposures and LD (Flick, et al. Ped 2011)
# Impact of Mechanical Ventilation and Other Risk Factors on Neurodevelopmental Outcome

Adverse outcome defined as CP or Bayley MDI/PDI < 70

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorioamnionitis</td>
<td>1.4</td>
<td>0.5-4.0</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1.4</td>
<td>0.5-4.0</td>
</tr>
<tr>
<td>Poor postnatal growth</td>
<td>1.9</td>
<td>1.3-2.9</td>
</tr>
<tr>
<td>Any mechanical ventilation</td>
<td>3.0</td>
<td>1.2-7.5</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>3.8</td>
<td>1.1-11.1</td>
</tr>
</tbody>
</table>

Injurious Ventilation

“Gentle Ventilation”

Early lung injury, LPS, oxidant stress

MODS, multiple-organ system dysfunction syndrome

Slide courtesy of Kurt Albertine, PhD
Poor Weight Gain Increases Odds for Poor Outcomes

ELBW infants, in-hospital growth: **12.0 vs 21.2 g/kg/day**

- **Cerebral palsy**: Odds Ratio (95% CI) = 8.00 (2.07–30.78)
- **Bayley MDI <70**: Odds Ratio (95% CI) = 2.25 (1.03–4.93)
- **Neurodevelopmental Impairment**: Odds Ratio (95% CI) = 2.53 (1.27–5.03)

MDI = Mental Development Index

Outcomes at 18-22 Months Corrected Age by Weight Gain Quartile (Ehrenkrantz, Pediatrics 2006)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Quartile 1 (≤ 25%)</th>
<th>Quartile 4 (&gt; 75%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>21</td>
<td>6</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Abnormal ND</td>
<td>30</td>
<td>14</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>MDI &lt; 70</td>
<td>39</td>
<td>21</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>PDI &lt; 70</td>
<td>35</td>
<td>14</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HC &lt; 10%</td>
<td>31</td>
<td>22</td>
<td>.09</td>
</tr>
<tr>
<td>Rehospitalized</td>
<td>63</td>
<td>45</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>
### Summary of Neurodevelopmental outcomes in appropriate-for-gestational-age (AGA) and small-for-gestational-age (SGA) Infants who attained adequate vs delayed extrauterine growth*

<table>
<thead>
<tr>
<th>Neurodevelopmental outcomes in subgroups of VLBW premature infants</th>
<th>Adequate catch-up growth</th>
<th>Delayed extrauterine growth (EUGR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGA</strong></td>
<td>Good neurodevelopmental outcome</td>
<td>Decreased mental and motor function</td>
</tr>
<tr>
<td></td>
<td>[PDI: 101.7 (14.7)]</td>
<td>[PDI: 94.9 (22.9)]</td>
</tr>
<tr>
<td><strong>SGA</strong></td>
<td>Good neurodevelopmental outcome (similar to AGA with adequate catch-up growth)</td>
<td>Decreased motor function</td>
</tr>
<tr>
<td></td>
<td>[PDI: 101.8 (14.5)]</td>
<td>[PDI: 89.9 (17.4)]</td>
</tr>
</tbody>
</table>

*9 and 24 months

VLBW, very low birthweight
Neurodevelopmental Domains Affected

- Cognitive deficits
- Motor deficits
  - Gross motor – developmental coordination disorder (16%)
    - DCD associated with poorer academic performance (Roberts, DMCN 2011)
  - Fine motor (71%)
  - Cerebral palsy
- Sensory impairments
  - Vision: visual-motor integration/spatial skills (10-20%)
  - Hearing
- Behavioral and psychological problems
Minor Neurodevelopmental Difficulties: High prevalence, low severity dysfunction

- **Cognitive**
  - Mean IQ 8-14 points lower than FT
  - Borderline intelligence – IQ 70-84
    - 750-1500 g (20%); < 750 g (33%)
    - ≤ 1000 g (22%) [Gargus, et al. Pediatrics 2009]

- **Learning deficits**
  - 45% - 65% v. 11% FT
  - Reading, comprehension, written output, abstract thinking, math skills
  - Memory tasks and processing speed
Minor Neurodevelopmental Difficulties: High prevalence, low severity dysfunction

- ADHD, behavioral social problems
- Executive function deficits
  - Planning
  - Organizing
  - Problem solving
  - Working memory – retrieval
  - Inhibition
  - Attention
- Related to abnormalities neural connectivity involving cortical dorsal stream – parietal, frontal, hippocampal areas
Predicting Outcomes: Is sharing what we know from longterm studies helpful?

- **Advantages** – allows for more accurate measurement of
  - Intellectual abilities and academic achievements
  - Multidimensional outcomes
  - Newer morbidities
  - Measurement of disability and future needs
  - Interaction between prematurity and stimulating environmental factors

- **Potential Harms**
  - Poor prognostic ability of term-equivalent imaging and early ND testing
  - Parental distress/hypervigilance caused by finding evidence of brain injury (Pearce, Baardsnes, Acta Paediatrica 2012)
Challenges in Predicting Outcomes

- Available studies/data may not be relevant to current NICU practices and patient population
  - GA v. birthweight
  - Single center v. MCT trial v. population-based v. nation
  - Assessment tools used
  - Length of follow-up – age at assessment

- Difficulty in determining the independent effects of biologic v. environmental factors

- Must often piece together information from various studies to provide families with information that is meaningful and helpful
Minimal age for reliable neurodevelopmental prognosis (Voss, et al., Acta Paed 2007)

- Correct prognosis at:
  - 12 months corrected age: 59%
  - 3-4 years corrected age: 70%

- Cerebral palsy (CP) can be reliably diagnosed between 2-3 y CA

- Mental retardation (IQ < 70) without CP confirmed at age 6 y

- Accurate prediction of performance in later childhood, adolescence and adulthood is not reliable until 8 years of age
  - 24 month CA cognitive assessments better than 18 month CA in predicting age 8-9 yr IQ and cognitive impairment (Doyle, et al. Ear Hum Dev 2012)
  - Severe disability at 30 mo predicts severe disability at 6 y (EPICure)
Do ELBW Infants (< 1000 g) have the potential for recovery with increasing age?
NICHD: Unimpaired Outcomes at 18-22 mo

- 401-1000 grams bwt, born 1998-2001
  - Survival rate to hospital d/c: 60%
  - Unimpaired: 16%
  - Mild impairment: 22%
  - NDI: 22%

- Similar results reported by the UK (EPICure) and Fr (EPIPAGE)
# Brain Growth and Neurodevelopment

## Neuro/Intellectual Function at School Age with Subnormal Head Circumference at 8 Months

### Total Population

<table>
<thead>
<tr>
<th>Condition (criteria) (8 years)</th>
<th>HC (nl) (216)</th>
<th>HC (subnl) (33) 13%</th>
<th>RR</th>
<th>HC (nl) (199)</th>
<th>HC (subnl) (26)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological Impairment</td>
<td>~8%</td>
<td>21%</td>
<td>2.69*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(major neurological abnormality)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low IQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IQ &lt;70</td>
<td>3%</td>
<td>24%</td>
<td>7.48†</td>
<td>2%</td>
<td>12%</td>
<td>5.74</td>
</tr>
<tr>
<td>IQ &lt;85</td>
<td>27%</td>
<td>52%</td>
<td>1.91†</td>
<td>26%</td>
<td>46%</td>
<td>1.80</td>
</tr>
<tr>
<td>Limited Academic Skills</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(read/math/spell std score &lt;80)</td>
<td>31%</td>
<td>56%</td>
<td>1.81†</td>
<td>28%</td>
<td>54%</td>
<td>1.88</td>
</tr>
</tbody>
</table>

* P<.05 by chi square test
† P<.01

HC subnormal; 1.1 versus 1.2 kg, higher neonatal risk scores (1977-1979)

# Neurologic and Developmental Disability at Age 6: Marlow, NEJM 2005; 353:9-19

<table>
<thead>
<tr>
<th>Outcome</th>
<th>22 Wk (N=138)</th>
<th>23 Wk (N=241)</th>
<th>24 Wk (N=382)</th>
<th>25 Wk (N=424)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died in delivery room</td>
<td>116 (84)</td>
<td>110 (46)</td>
<td>84 (22)</td>
<td>67 (16)</td>
</tr>
<tr>
<td>Admitted to NICU</td>
<td>22 (16)</td>
<td>131 (54)</td>
<td>298 (78)</td>
<td>357 (84)</td>
</tr>
<tr>
<td>Died in NICU</td>
<td>20 (14)</td>
<td>105 (44)</td>
<td>198 (52)</td>
<td>171 (40)</td>
</tr>
<tr>
<td>Survived to discharge</td>
<td>2 (1)</td>
<td>26 (11)</td>
<td>100 (26)</td>
<td>186 (44)</td>
</tr>
<tr>
<td>Died after discharge</td>
<td>0</td>
<td>1 (0.4)</td>
<td>2 (0.5)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0</td>
<td>3 (1)</td>
<td>25 (7)</td>
<td>39 (9)</td>
</tr>
<tr>
<td><strong>At 6 yr of age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had severe disability</td>
<td>1 (0.7)</td>
<td>5 (2)</td>
<td>21 (5)</td>
<td>26 (6)</td>
</tr>
<tr>
<td>Had moderate disability</td>
<td>0</td>
<td>9 (4)</td>
<td>16 (4)</td>
<td>32 (8)</td>
</tr>
<tr>
<td>Had mild disability</td>
<td>1 (0.7)</td>
<td>5 (2)</td>
<td>26 (7)</td>
<td>51 (12)</td>
</tr>
</tbody>
</table>

| Survived without impairment     |               |               |               |               |
| As a percentage of live births  | 0             | 3 (1)         | 10 (3)        | 35 (8)        |
| As a percentage of NICU admissions | 0         | 3 (2)         | 10 (3)        | 35 (10)       |

| Survived without severe or moderate disability |               |               |               |               |
| As a percentage of live births | 1 (0.7)       | 8 (3)         | 36 (9)        | 86 (20)       |
| As a percentage of NICU admissions | 1 (5)         | 8 (6)         | 36 (12)       | 86 (24)       |

**Figure 2. Severity of Disability at 30 Months of Age Corrected for Prematurity and at 6 Years among 236 Children Who Were Assessed at Both Ages.**

A total of 63 children had severe disability, 82 other disabilities (moderate or mild), and 91 no disability.
Neurocognitive outcome and degree disability at 6 and 11 years of age

<table>
<thead>
<tr>
<th>Outcome</th>
<th>6 Years</th>
<th></th>
<th>11 years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 23 w</td>
<td>24</td>
<td>25</td>
<td>≤ 23 w</td>
</tr>
<tr>
<td>Cognition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No disability</td>
<td>25</td>
<td>21</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Severe disability</td>
<td>25</td>
<td>27</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No disability</td>
<td>12</td>
<td>14</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>Severe disability</td>
<td>25</td>
<td>29</td>
<td>28</td>
<td>22</td>
</tr>
</tbody>
</table>

- **Severe disability:**
  - MDI < 70
  - CP interfering w/ ambulation
  - Blindness
  - Deafness

- **Mild-moderate disability**
  - MDI 1-2 SD below mean
  - Some CP, orthotics, doesn’t interfere w/ ambulation
  - Unilateral blindness and/or deafness


Preterm children in special education in comparison with full term children (Ment et al.)
8 years - 54% v. 10%
12 years - 33% v. 10%

- Hack et al., NEJM 2002
- Wilson-Costello et al., Pediatrics 2007

<table>
<thead>
<tr>
<th>Impairment</th>
<th>20 mos.</th>
<th>8 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td>39%</td>
<td>16%</td>
</tr>
<tr>
<td>Neurosensory</td>
<td>29%</td>
<td>7%</td>
</tr>
</tbody>
</table>

- 74% survivors graduate from HS
Risk Factors for Cognitive Outcomes at 12 & 16 y

- Male gender, lower GA, lower bwt, CLD, ROP ≥ stage 3, severe brain injury, sepsis/NEC, ≥ 1 morbidity
- Preterm infants IQ and receptive vocabulary scores ↑ with ↑ age
  - ↑ Deficits in executive function, verbal fluency, planning, organization and working memory even after children with disabilities were excluded
- Predictors of poor outcomes at 16 yr
  - Neonatal brain injury and low maternal education

* These RF predict full scale IQ at 12 yrs
Neurological Outcomes

- Early developmental problems related to brain immaturity
  - Autonomic instability
  - Abnormal state regulation and behavioral organization
  - Motor problems – lack of graded flexion

- Late – abnormal brain maturation
  - Extreme immaturity or brain injury
  - Risk for long term cognitive, speech, motor, vision, behavior and attention problems
Adverse Neurocognitive Outcomes

• Birth-2 years
  – Feeding difficulties
  – Neurodevelopmental abnormalities
    • Transient dystonia
    • Cerebral palsy
  – Sensory issues
    • Blindness-vision loss
    • Deafness
  – Low developmental scores

• 2-4 years
  – Delayed communication skills
  – Socio-emotional difficulties
  – Mild sensory issues
    • Vision, auditory, tactile defensiveness
  – Cognitive delays
    • Low developmental scores
Very preterm ELBW Infants have multiple service needs between hospital discharge and 18-22 mo CA

- Visiting Nurse 58.7%
- OT or PT 59.9%
- Speech therapy 33.7%
- Early Intervention 55.7%
- Social Worker 25.6%
- Subspecialty care 68.8%

- Missed opportunities for referral to EIS (Tang, et al, Pediatrics 2012 [cpqcc])
  - 34% “high concern” infants not referred to EI

Preverbal skills as mediators of language development (De Schuymer, et al. Ear Hum Dev 2011)

- Preverbal social skills reflect part of processes through which children learn language
  - Ability to share attention to an object with another person (triadic interaction)

- Preterm infants have less developed
  - Dyadic interactions at 6 mo and triadic interactions at 9 and 14 mo (poorer preverbal skills)
  - Poorer receptive and expressive language skills at 30 mo
Minor Neurodevelopmental Difficulties

- Behavioral difficulties
  - Impulsive, distractable, poor attention span
  - Self-control
  - Separation issues
  - Depressed and/or internalizing behaviors

- Subtle neuromotor deficits
  - Poor gross motor skills, balance, coordination, postural control
  - Poor eye-hand coordination
School Age Neurocognitive Outcomes

4-5 years

- School readiness
- Cognitive impairment
- Motor impairment (clumsiness)
  - Fine motor incoordination
- Visual-spatial/visual-perceptual problems
- Social competence/behavioral immaturity

Early elementary

- ADHD-attention disorders
- Psychiatric symptoms
- Social competence difficulties
- Ocular impairments
- Poor auditory discrimination
- Special educational needs
Functional Outcomes

- Functional limitation
  - Restriction of ability to perform an essential activity
    - Self-care
    - Mobility and locomotion
    - Communication
    - Socialization
  - Compensatory dependence
  - Need for services above routine

- Percentage children with a health problem affecting >1 activity of daily living
  - 1001-1500g 34%
  - < 1000g 46%

- School age outcomes
  - Standard Placement 50%
  - Resource 30%
  - Special Education 20%
  - Repeat a grade 16%
The impact of preterm birth on adolescent and young adult outcomes
18 Year Outcomes of EI from IHDP Study

- 985 LBW infants recruited from 8 participating sites (Einstein), born 1984-85
- Stratified into 2 groups:
  - LLBW: < 2000 grams
  - HLBW: 2001-2499 grams
- 1/3 group (377) received an educational intervention from time NICU D/C until 3 yrs age
  - Weekly home visits for 1st yr; then every other week for yrs 2-3
  - Daily center-based educational program from 12-36 mos.

No statistically significant differences seen between the intervention (INT) and follow up only (FUO) ≤ 2000 grams LLBW groups at 3, 5 or 8 years
- Initially INT group had a 6.6 IQ pt advantage at 3 years
- Differences disappear by 5 yrs age

> 2000 grams HLBW group
- 14 pt IQ advantage at age 3 yrs decreased to + 4 IQ pts at 8 yrs and remained at + 3 IQ pts at 18 yrs
- Statistically significant elevations PPVT-III
  - + 5 pt higher reading; + 6 pt higher math achievement scores
  - No difference in self-reported behavior problems
- INT group had fewer risk behaviors
Adolescence to Young Adulthood

- Most motor difficulties, if persistent are less problematic as child adapts
- Increasing complexity of tasks
  - LD persist in 30-40%
    - Math most challenging
  - Nearly 50% ELBW children require PT or FT special educational assistance
- Grade repetition in 20-30%
- Attentional problems less taxing as children grow older

- More regular use prescription medication*

* Cooke, Arch Dis Child 2004; 89: 210-206
Adolescence-Adulthood

- Delinquency and risk-seeking behaviors less common than among NBW FT counterparts
  - Less drug and alcohol use
    - Marijuana, wine, beer
  - Less satisfied with appearance*
  - Fewer drive cars as teens
  - Less sexual activity
  - Less rule-breaking or following peer behaviors

* Cooke, Arch Dis Child 2004; 89: 210-206

Behavioral Outcomes and Evidence Psychopathology at 20 Years of Age

- **VLBW men**
  - Fewer delinquent behaviors
  - No differences in
    - Internalizing
    - Externalizing
    - Total problem behaviors

- **VLBW women**
  - More withdrawn behaviors
  - Fewer delinquent behaviors
  - Internalizing behaviors (anxious/depressed, withdrawn) borderline clinical cut-off (30% v. 16%, OR 2.2)

- **Parents report**
  - More thought problems
  - More attention difficulties but not more ADHD

- **Parents report more**
  - anxious/depressed (OR 4.4), withdrawn (OR 3.7) and attention problems (OR 2.4)

Hack et al., Pediatrics 2004; 114: 932-940
Intelligence of very preterm or VLBW young adults

- Mean IQ 97.6 ± 15.6
- Parental education moderates outcomes
  - Highly educated parents: +14.2 pts
- Higher birth weight SD: +2.6 IQ pts
- Each additional gestational week associated with +1.3 pt higher IQ
- Young mothers < 25 y: lower IQ
- Symmetric IUGR more pronounced effect on IQ than asymmetric GR

Weisglas-Kuperus, et al. ADC FNE2009; 94:F196
Perinatal Brain Injury and the Developing Brain

Timeline Developmental Processes in NS
(Herschkowitz, et al)

3rd trimester:
Fetal brain is forming secondary and tertiary gyri

- Exhibiting neuronal differentiation, dendritic arborization, axonal elongation, synapse formation and collateralization, and myelination
Early Brain Development

- Myelination occurs in phases during gestation
  - < 28 w: Little myelination between 28-36 w
  - 30-36 w: Increase in myelin in grey/white matter already myelinated
  - 37-42 w (PLIC, post-central gyri, corticospinal tracts)

AJNR 2002
CNS Complications in Preemies

- **Intraventricular Hemorrhage**
  - Incidence ↑ with small GA
  - Screening Head Ultrasound or CT/MRI
  - Complications: hemorrhagic cerebral infarct, porencephalic cyst, hydrocephalus, ventriculomegaly, PVL
  - Assess muscle tone – usually high tone in preemies up to 12-18 months.
  - Serial US, CT/MRI
  - Early intervention

- **Hydrocephalus**
  - Assess Head circumference and signs of ↑ ICP once/month if pt has hx of IVH
  - DD: catch up growth – Hydrocephalus HC >1.25 cm/wk, signs of ICP, changing neurological status
  - Serial US if signs/symptoms of ↑ ICP or ↑ HC
CNS Complications in Preemies

- **Periventricular leukomalacia:**
  - Ischemic infarction of white matter adjacent to lateral ventricle
  - Occurs in 25% infants <1500g
  - Diagnosed by US or MRI as white matter cysts as early as 1st wk if insult occurs in utero
  - Usually 2-8 wks after insult
  - Closely associated with CP, developmental delay, epilepsy, visual impairment
  - Assess development and visual assessment within first 6mo, Early intervention

- **Microcephaly**
  - HC < 3rd centile, if HC less than wt/length centiles, >2 standard deviations below mean
  - Primary or acquired
  - Major risk factor for mental retardation
Perinatal Brain Injury
What about preterm infants with milder or no evidence of injury?

- Lower grades IVH I-II poorer ND outcome at 20 mos. CA than infants with no IVH
  - Higher rates MDI << 70 (45%, OR 2), major neuro abnormality (13%, OR 2.6), ND impairment (47%, OR 1.83) [Patra et al., 2006]

- Among low risk preterm infants 28-33 weeks GA with normal cranial US, MRI reveals:
  - At 42 weeks’ postmenstrual age, gray matter volumes were not different between preterm and term infants
  - Myelinated white matter was decreased, as were unmyelinated white matter volumes in the region including the central gyri (Mewes et al., Pediatrics 2006)
Preterm Birth Affects All Areas of the Brain at 8 Y

- ↓ Cortical grey and white matter
- ↓ Subcortical grey
- ↓ Cerebellar volume
- ↑ CSF occipital horns, lat ventricles
- ↓ Gray/white matter differentiation
- ↓ Cortical surface area and complexity

Most vulnerable areas of PT brain
- Sensorimotor cortex
- Premotor cortex
- Mid-temporal cortex

Cerebral volumes related to
- FS IQ, verbal IQ, performance IQ, Peabody picture vocabulary test

GA, VM, PVL, chorioamnionitis significantly related to brain volume

JAMA, 2000; Pediatr Neurol, 2004; Pediatrics, 2005
Preterm Birth: Thalamic & Cortical Development

- Preterm delivery disrupts aspects of cerebral development
  - Thalamocortical system
  - Correlates w/ disability at 1 yr

- Volume reduction
  - Thalamus, hippocampus, orbitofrontal lobe, posterior cingulate cortex, and centrum semiovale (thinning corpus callosum)

- Reduced cortical surface area predicts neurocognitive abilities at 2 and 6 y

- Reduced thalamic volume predicted
  - Lower cortical volume
  - Decreased volume in:
    - Frontal and temporal lobes, including hippocampus
    - Parietal and occipital lobes
  - Reduced fractional anisotropy in the corticospinal tracts and corpus callosum

- Auxiliary circuits memory, attention, executive function

fMRI studies have identified alternate pathways for language development in PT children/adolescents.

Premature infants studied at 12 years of age have different patterns of activation when compared with their term counterparts in aspects of language processing, though they do not show any associated differences in performance scores.

Rely more heavily on right hemisphere for expressive language.
Relationship of early brain injury to psychiatric conditions in adolescence

- Germinal matrix/IVH increased risk for major depressive disorders (OR 2.7; 95% CI: 1.0-6.8) and obsessive-compulsive disorder (9.5; 3.0-30.1)
- Disruption of cortical-subcortical circuits
- Parenchymal lesions/ventricular enlargement increased risk for current ADHD–inattentive type (OR: 7.6; 95% CI: 2.0-26.5), tic disorders (8.4; 2.4-29.6), and obsessive-compulsive disorder (7.6; 1.39-42.0)
- Association persisted after control for cognitive and motor impairments
- Contribution of chronic stress needs to be studied
  - Hippocampus, amygdala

Arch Gen Psychiatry. 2011;68(7):742-752
Prematurity and the Risk of Autism/ASD

- At school age 1-2% LBW children reported to be within ASD spectrum
  - Lower BW, GA, male gender, chorioamnionitis, acute intrapartum hemorrhage, illness severity, abnormal MRI
  - Major motor, cognitive, visual and hearing impairments account for > 50% + MCHAT screens (Kuban, et al. J Ped 2009)
    - After adjustment for impairments: 10% screen + (2-fold ↑)
- 30-mo screen more predictive than 18-mo screen (Stephens, et al. PAS 2011, Abstract 2705.2)
  - 10% v 18% (high rates of language and cognitive impairment at 18 mo)
- 8% prevalence in < 26 wk GA PT at age 11 (Johnson, et al. J Ped 2010)
Sensory Issues
Behavior and Pain Perception: Acute Consequences

- **Stress responses**
  - Hormonal, behavioral, and autonomic
- **Changes in HR, RR, BP, blood vessel tone**
- **Changes in CBF, brain blood volume and oxygen delivery**
  - ↑ risk IVH and PVL

- **Short-term sequelae of prior noxious stimuli**
  - Lower threshold to tactile stimulation
  - Hypersensitive to pain
  - Chronic pain responses to local injury
  - Link with cumulative painful procedures and subsequent pain and stress behaviors
  - ↓ behavioral response to additional acute painful events at 32 wks’ corrected age
Longer-term Sequelae of Prior Noxious Stimuli

- Lack of normal pain sensitivity as toddler among ELBW children, esp. < 800g (1lb 12 oz)
  - ↓ pain sensitivity at 18 months corrected age
  - Child temperament and reported pain sensitivity appear independent
  - Muted pain response to the normal pain consequences of acute injury

- Gross motor coordination and motor planning less well developed

- At 4.5 yrs exhibit greater somatization by parent report

- At 8-10 yrs, overall NBW and ELBW children had similar perceptions of pain intensity
  - ELBW rated medical pain > psycho-social pain
  - Higher pain intensity to recreational pain

Buskila et al., Arch Pediatr Adolesc Med 2003; 157: 1079-1082
Visual Sequelae of Preterm Birth: Assess EOM, corneal light reflex, ability to fix; Ophthalmologist evaluation by 1 year of age

- Poor vision detected in ~2.5% VLBW children
- Visual function
  - Reduced visual acuity, color vision, contrast sensitivity
  - Field defects, eye motility disorders
- Reduced visual acuity
  - 47% all VLBW children
  - 34% VLBW children without ROP or neurological complications

**Strabismus**
- 6-fold increase by 10-12 yrs of age
- Overall incidence 13.5% at 3.5y for VLBW v. 2% born at term
- 5.9% VLBW children without ROP/neurological complications
- Esotropia dominating type
- Secondary functional amblyopia associated in many
10 Year Follow-up CRYO-ROP Study

- Treated eyes
  - Better distance and near visual acuity
  - Better anatomic status of fundus- normal appearing
  - Less blindness
  - Late retinal detachment ~ 14yrs of age more common in untreated eye

- ETROP Trial (2003, 2004)
  - Early Rx
  - ↓ Risk poor vision
  - ↓ Structural damage eye

- Effect ablative therapy for threshold ROP
  - Preserves peripheral vision
  - Reduction ~5-7% in visual field area in treated eyes
  - 27-35% deficit in visual field area in untreated eyes with severe ROP

- Contrast sensitivity
  - 33% reduction in unfavorable CS results with cryosurgery
Hearing Loss in High Risk Infants

- Prevalence permanent HL among NICU infants 1-3%
  - 10-20 x general population (v. 0.1-0.3% all LB)
- Auditory neuropathy/auditory dyssynchrony common (Berg et al., Peds 2006)
  - Abnormal ABR, normal OAE
  - Normal outer hair cell function
  - Abnormal neural function
  - No acoustic reflexes
  - Poor speech perception
  - Fluctuating HL
  - If maturational, normalizes bet 12-18 months

- Known risk factors
  - Damage to inner hair cells
    - LBW
    - Low Apgar score, asphyxia
    - ECMO (25% affected; 50% have progressive loss)
  - Ototoxic medications
    - GJB2-connexin 26 mutations
  - IVH
  - Hyperbilirubinemia
  - Acoustic (noise) trauma
  - Ventilation
  - Congenital infection - CMV
  - Sepsis, meningitis
  - Anatomical malformations
  - Family history
Sensory Motor Integration: Secondary to abnormal early stimulation

- Light, noise, touch, pain, oral
- Clinical symptoms in infants-toddlers
  - Feeding problems/aversion
  - Difficulty transitioning to solids (textures/tastes)
  - Excessive mouthing objects (sensory seeking behaviors)
  - Sensitivity to different stimuli (feet)
    - Grass, sand, carpet
    - Toe-walking without socks
    - Hyperactivity
    - Delayed language development
Summary of reported outcomes very PT or VLBW children

- Substantial ND morbidity in 1 in 4 v 1 in 25 FT
- CP in 10% v 0.1-0.2% FT
- School difficulties in up to 3 in 4 v 1 in 8 FT
- Hospital readmissions 2-3 x more frequent in early childhood, esp. respiratory illnesses
- Weigh less than average in childhood/adulthood, but reaches genetic height potential
- More restrictions in daily living/self-care abilities

- *Maternal education is the strongest predictor LT ND

Adulthood
- Intellectual disability in 1 in 22 v 1 in 250
- Behavioral/psychological problems in 1 in 40 v 1 in 500
- Vision or hearing problems or epilepsy in 1 in 25 v 1 in 500
- Higher systolic blood pressure
- Reductions in airflow on PFTs
- Self-reported HRQoL similar

Changes to Practice

- Assure that very preterm, very low birth weight children receive periodic developmental screening throughout childhood
- Assure that these children have access to longterm medical, therapeutic and educational services
- Prepare parents for the challenges of their infant’s continuing health and developmental care needs
- Provide parents with information, support and guidance to help them navigate the uncertainty in their child’s early outcomes
In closing,

- Extreme preterm birth has life-long implications for the health and well-being of the child and adult born prematurely.
- Rapid changes in the development and organization of the fetal brain – regional morphologic associations.
- Beyond biology and epigenetics, the “environment” in which these children are nurtured is critical.
- There is much yet to learn.

Thanks! Questions?