Are we Improving Long Term Outcomes of Preterm Infants? The Role of Risk Factors and Interventions.

Betty Vohr M.D.
Professor of Pediatrics
Alpert Medical School of Brown University
Buenos Aires
September, 2011
Dr. Betty Vohr

I have no relevant financial relationships to disclose.
Objectives are to describe:

Determine

- Effects of major neonatal morbidities on outcome
- Beneficial effects of neonatal interventions
- Evidence supporting neurodevelopmental recovery with increasing age.
The Neonatal Morbidities that frequently occur in ELBW infants do not occur in isolation.

- ELBW infants experience multiple morbidities and multiple interventions during their long-term residence in the NICU and some are associated adverse outcomes and some with improved outcomes.

- Preterm birth rates continue to ↑ in the US

- 62,000 VLBW infants < 1500 grams (1.46%)

- 30,000 ELBW infants < 1000 grams are born annually

- Survival of ELBW infants has increased to 66 to 88 percent
Hintz SR Arch Dis Child Fetal Neonatal Ed. 2005

Survival Rates by Gestational Age:
- 23 weeks: 23% (87-1988) vs 30% (99-2000)
- 24 weeks: 34% (both years)
- 25 weeks: 54% (87-1988) vs 70% (99-2000)

Gestational Age
Survival at limits of viability at NICHD Network Sites 1999-2001 to 2004-2005

Hintz SR. Pediatrics 2010
Morbidity: any of the following: BPD, IVH or NEC ≥ Bells 2

(Fanaroff AJOG 2007)

59, 46, to 45%  19, 14 to 12%
ELBW Infants are at ↑ Risk of Neonatal Morbidities

- Late onset Sepsis 40-60%
- Intraventricular Hemorrhage 10-22%
- Bronchopulmonary Dysplasia 30-45%
- Necrotizing Enterocolitis 6-10%
- ROP≤Stage 3 with Plus 6-30%
Relationship between Birth Wt Specific groups and Neonatal Morbidities 1997-2002

Fanaroff et al, A J Ob Gyn 2006
Let’s Examine the Effects of these 4 Major Neonatal Morbidities with Neurodevelopmental Outcomes.

- Abnormal HUS: IVH 3-4 and PVL
- Bronchopulmonary dysplasia/ventilation
- Sepsis
- Necrotizing Enterocolitis
Vulnerability of the brain of ELBW infants

ELBW infants are at increased risk of brain injury especially intraventricular hemorrhage and white matter injury from sepsis, hypoxia-ischemia & under-nutrition.
ELBW infants and brain hemorrhage

- VLBW Prevalence:
  - I-11%; II- 7%; III-9-12%; IV-5-12%
  - G III/IV- 12-15% of 23-24w

Complications:
- ↑ mortality
- Seizures
- PVL, Hydrocephalus
- Neurodevelopmental disabilities

Ment LR, Vohr BR. *Early Hum Dev*, 1996
White matter abnormalities

Cystic PVL

• 3-5% of VLBW
• Localized or extensive areas of necrosis
• Ex-vacuo dilatation (once cysts collapse)
• ↑ risk of CP and cerebral visual impairment

DeVries LS MRDDRR 2002
Counsell SJ Pediatrics 2003
Assoc of CP with Grade 3-4 IVH and PVL
2385 ELBW survivors (15% CP) 1995-98

<table>
<thead>
<tr>
<th>Neuro</th>
<th>No CP</th>
<th>Hemi</th>
<th>Di</th>
<th>Tri</th>
<th>Quad</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVH 3-4</td>
<td>14</td>
<td>67</td>
<td>35</td>
<td>59</td>
<td>48</td>
<td>.0001</td>
</tr>
<tr>
<td>cPVL</td>
<td>3</td>
<td>24</td>
<td>19</td>
<td>38</td>
<td>51</td>
<td>.0001</td>
</tr>
</tbody>
</table>

Some infants with IVH 3-4 and PVL do not develop CP

In contrast, a normal HUS in an ELBW infant does not always predict a good outcome

• 1743 infants 1/95 to 12/99 had a normal HUS both at 7 days and 47 days and were seen in FU.

• CP 9.4%
• MDI<70 25.3%
• PDI<70 29.2%

Laptook et al. NICHD, Pediatrics 2005
Other factors are assoc with ND morbidity for infants with N HUS (Laptook et al, NICHD, Peds 2005)

- Multivariate analyses completed

<table>
<thead>
<tr>
<th>Factor</th>
<th>CP</th>
<th>MDI &lt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Multiple</td>
<td>1.6</td>
<td>1.8</td>
</tr>
<tr>
<td>↓ Birth weight</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>↑ Ventilation</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Maternal race</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Maternal ed</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Public Insurance</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>
Major Neonatal Morbidities

• IVH 3-4 and PVL; Abnormal HUS

• Bronchopulmonary dysplasia/ventilation

• Sepsis

• Necrotizing Enterocolitis
Lung Immaturity is almost universal among ELBW infants

- In addition to surfactant many infants are treated with initial ventilatory and oxygen support.

- There is increasing evidence that less invasive ventilatory management has beneficial effects.
Severity of BPD < 1000 grams
Cohort of 3848 ELBW infants (77% BPD rate)

<table>
<thead>
<tr>
<th>BPD</th>
<th>None</th>
<th>Mild</th>
<th>Mod</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23%</td>
<td>31%</td>
<td>30%</td>
<td>16%</td>
</tr>
<tr>
<td>O₂ 28d</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>O₂ 36w</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+ ≥30% O₂</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CP</td>
<td>8%</td>
<td>11%</td>
<td>17%</td>
<td>27%</td>
</tr>
<tr>
<td>NDI</td>
<td>28%</td>
<td>34%</td>
<td>45%</td>
<td>62%</td>
</tr>
</tbody>
</table>

Cerebral Palsy Rate by Days of Ventilation
Walsh et al, J Pediatrics 05

N=5364 <1000g
Jan 95 to Dec 98
Ventilated 89%

Days

% CP

0 1 7 14 21 28 60 90 120

23% 28% 80%
Major Neonatal Morbidities

- IVH 3-4 and PVL; Abnormal HUS
- Bronchopulmonary dysplasia/ventilation
- Sepsis
- Necrotizing Enterocolitis
Why are preterm infants more susceptible to infection?

• Underdeveloped immune systems

• Repeated handling by multiple personnel

• Invasive interventions: Central venous catheters are the most common interventions associated with nosocomial infections.
Impact of Infections on Outcomes

• Study of 6093 ELBW infants born 93-01:
  • 65% had at least 1 infection.

• Infection groups were:
  sepsis, 32%
  sepsis with NEC, 5%
  meningitis ± sepsis, 3%
  clinical infection, 25%

• Infants were evaluated at 18-22 months

Stoll et al, NICHD, JAMA, 2005
There was an impact of all 4 Infection groups on Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral Palsy</td>
<td>1.4-1.7</td>
</tr>
<tr>
<td>Low MDI</td>
<td>1.3-1.6</td>
</tr>
<tr>
<td>Low PDI</td>
<td>1.5-3.4</td>
</tr>
<tr>
<td>Vision Impairment</td>
<td>1.3-2.2</td>
</tr>
</tbody>
</table>

Stoll et al, NICHD, JAMA, 2005
Major Neonatal Morbidities

- IVH 3-4 and PVL; Abnormal HUS
- Bronchopulmonary dysplasia/ventilation
- Sepsis
- Necrotizing Enterocolitis
Necrotizing Enterocolitis (NEC) in ELBW Infants

• The most common GI emergency
• It is a potentially devastating complication
• Assoc. with inflammation, infection & ischemia
• ≤1500G rate of 6-10%
• Preterm infants present at 3-4 weeks of age
• Occurs less often in infants receiving BM
## NEC in ELBW infants 1/95-12/98

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>No NEC</th>
<th>Med NEC (4.8%)</th>
<th>Surg NEC (5.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4401</td>
<td>239</td>
<td>293</td>
</tr>
<tr>
<td>Survival</td>
<td>79%</td>
<td>65%</td>
<td>55%</td>
</tr>
<tr>
<td>Hosp d</td>
<td>90</td>
<td>104</td>
<td>132</td>
</tr>
<tr>
<td>CP</td>
<td>15%</td>
<td>12%</td>
<td>24%</td>
</tr>
<tr>
<td>Deaf</td>
<td>1.5%</td>
<td>0.8%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Blind</td>
<td>1.0%</td>
<td>0.8%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Wt&lt;10th%</td>
<td>54%</td>
<td>61%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Hintz S, Pediatr March 2005
NEC, Sepsis & White Matter Injury
Shah DK J Peds 153;170-5,Aug 2008

• Both NEC & sepsis pose a risk for inflammatory-mediated WM injury

• < 30 w gestation; 40w MRI; seen at 2 years

• Mod/Severe WMA in 23% of infants with sepsis/NEC versus 12% with no sepsis/NEC

• White matter injury was assoc. with both low MDI (9% variance) and low PDI(11% variance)
What about school age effects of severe brain injury (IVH 3-4, PVL, ventriculomegaly)?
Characteristics of the 12-year cohort of the Indomethacin Prevention Trial.

<table>
<thead>
<tr>
<th></th>
<th>Preterm</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Brain injury</td>
<td>No brain injury</td>
</tr>
<tr>
<td></td>
<td>N = 34</td>
<td>N = 337</td>
</tr>
<tr>
<td>Neurosensory impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy, No (%)</td>
<td>17/34 (50%)</td>
<td>17/337 (5.0%)</td>
</tr>
<tr>
<td>Hearing aids, No (%)</td>
<td>4/33 (12.1%)</td>
<td>8/323 (2.5%)</td>
</tr>
<tr>
<td>Blind services, No (%)</td>
<td>5/32 (15.6%)</td>
<td>4/325 (1.2%)</td>
</tr>
<tr>
<td>Any neurosensory impairment, No (%)</td>
<td>21/34 (61.8%)</td>
<td>34/333 (10.2%)</td>
</tr>
</tbody>
</table>

Luu et al, Pediatrics, March 2009
## Educational placement

Luu et al, Pediatrics, March 2009

<table>
<thead>
<tr>
<th></th>
<th>Preterm</th>
<th>Term</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Brain injury</td>
<td>No brain injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individualized Educational Plan, n (%)</td>
<td>25/33 (76%)</td>
<td>117/334 (35%)</td>
<td>11/110 (10%)</td>
<td></td>
</tr>
<tr>
<td>Educational services</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remedial instruction in reading, n (%)</td>
<td>15/34 (44.1%)</td>
<td>93/336 (27.7%)</td>
<td>10/111 (9.0%)</td>
<td></td>
</tr>
<tr>
<td>Remedial instruction in writing, n (%)</td>
<td>15/34 (44.1%)</td>
<td>68/336 (20.2%)</td>
<td>4/111 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>Remedial instruction in math, n (%)</td>
<td>16/34 (47.1%)</td>
<td>100/335 (29.9%)</td>
<td>7/111 (6.3%)</td>
<td></td>
</tr>
</tbody>
</table>
12 Year Behavioural outcomes – CBCL ≥ 70

Luu et al, Pediatrics 2009

* p-value <0.005 preterm with brain injury vs term
** p-value <0.05 preterm without brain injury vs term

No difference between the 3 groups on the following subscales: withdrawn, somatic complaints, anxious/depressed, delinquent, aggressive
Random-Effects Meta-analysis for Studies Assessing Attention-Deficit/Hyperactivity Disorder. Diagnostic criteria were based on the Diagnostic and Statistical Manual of Mental Disorders, Third and Fourth Editions

6 preterm studies: RR= 2.64 for ADHD

It is apparent that ELBW Infants remain at ↑ Risk of these 4 Major Neonatal Morbidities.

What are some Interventions to prevent morbidity in the NICU and post-discharge?
ANTENATAL STEROIDS and IVH

- ANS result in a 50% ↓ in severe IVH by
  - Enhancing maturation of the germinal matrix
  - Stabilizing systemic blood pressure
  - Reducing the requirement for volume expanders.
  - Increased lung maturation and ↓ RDS
  - Increased survival without IVH

Wright L Am J Obstet Gynecol 1995;173:263,
Prophylactic low dose Indomethacin

- IVH is believed secondary to an increase in cerebral blood flow in the immature brain

- Indomethacin is known
  - Inhibits prostaglandin synthesis
  - Stabilizes cerebral blood flow
  - ↓ rate of IVH
  - Safe for preterm infants

Multicenter Randomized Indomethacin IVH Prevention Trial, 1989 - 1992
Ment et al 1994
IVH in the Indomethacin Prevention Trial for infants 600-1250g

Ment et al 1994

Indomethacin

- 12% Any IVH
- 1 infant

Saline

- 18% Grade III-IV
- 10 infants

P<.01

P<.03
36 Month Outcomes in the Indomethacin Trial

Indomethacin  Saline Placebo

• CP 12% 12%

• MDI 89.6 ± 19 85 ± 21

• Conclusion: There are no negative effects of Indomethacin on NDI outcome;
• Similar findings at 54 months.

Ment et al 1996; Ment et al 2000
2 y Outcomes of Infants < 1000 G who received Indomethacin in a second multicenter randomized Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Indo</th>
<th>Placebo</th>
<th>OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe IVH</td>
<td>9%</td>
<td>13%</td>
<td>0.6(0.4-0.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>12%</td>
<td>12%</td>
<td>1.1(0.7-1.6)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Schmidt et al 2001
Randomized Trials of High-Frequency Oscillatory vs Conventional Ventilation to Assess NDI

- Henderson-Smart et al, 2003 Cochrane Review
  - 3 trials with outcomes
  - 2 trials with no difference
  - 1 trial with ↑ adverse effects
  - Findings inconclusive

- Marlow et al 2006
  - Randomized controlled trial
  - Mode of ventilation had **no impact** on respiratory or NDI at 2 years of age
<table>
<thead>
<tr>
<th></th>
<th>CPAP</th>
<th>Intubation</th>
<th>OR/RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morley NEJM 2008</td>
<td>33.9%</td>
<td>38.9%</td>
<td>.80(.58-1.12)</td>
</tr>
<tr>
<td>25-28w Death/ BPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finer NEJM 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-27\textsuperscript{w} Death or BPD</td>
<td>47.8%</td>
<td>51%</td>
<td>.95(.85-1.05)</td>
</tr>
<tr>
<td>Death by 36w</td>
<td>14.2%</td>
<td>17.5%</td>
<td>.09</td>
</tr>
<tr>
<td>BPD</td>
<td>48.7%</td>
<td>51.0%</td>
<td>.91(.83-1.01)</td>
</tr>
<tr>
<td>↓ days vent</td>
<td>24.8d</td>
<td>27.7d</td>
<td>.03</td>
</tr>
<tr>
<td>↓ PNS</td>
<td>7.2%</td>
<td>13%</td>
<td>.001</td>
</tr>
</tbody>
</table>
| Conclusion: Results support consideration of early CPAP
| Target ranges of $O_2$         | 85-89% | 91-95%     |            |
| Death or Severe ROP            | 28.3%  | 32.1%      | .90(.76-1.06) |
| Severe ROP                     | 8.6%   | 17.9%      | .52(.37-.73) |
| Death before disc.             | 19.9%  | 16.2%      | 1.27(1.01-1.60) |
| Conclusion: The ↑ in Mortality remains a concern. |
## Randomized Trials of Inhaled Nitric Oxide

<table>
<thead>
<tr>
<th>Trial</th>
<th>Kinsella</th>
<th>Schrieber</th>
<th>Van Meurs/ Hintz</th>
<th>Ballard 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort</td>
<td>500-1250</td>
<td>&lt;27w</td>
<td>&lt;34w</td>
<td>&lt;1250g on vent</td>
</tr>
<tr>
<td>Neonatal Outcome</td>
<td>↓ Brain Injury</td>
<td>↓ death, ↓ CLD, ↓ IVH</td>
<td>No effects death/CLD &gt;1000 g↓ D/CLD &lt;1000 g↑ D/IVH</td>
<td>↑ survival without CLD 44 vs 37%</td>
</tr>
<tr>
<td>12-24m Outcome</td>
<td>No effects MDI, PDI, CP, Blind or Deaf</td>
<td>↓ NDI 24% vs 46% RR=.53</td>
<td>No effects death/NDI slight↑ mod/sev CP ↑ death/CP &lt;1000 g</td>
<td>No effects NDI 45% vs 49%</td>
</tr>
</tbody>
</table>
Phototherapy Intervention Trial

• Initiating PT

<table>
<thead>
<tr>
<th>Birth Weight Strata</th>
<th>Aggressive PT Begins</th>
<th>Conservative PT Begins</th>
</tr>
</thead>
<tbody>
<tr>
<td>501-750 g</td>
<td>ASAP after enrollment</td>
<td>≥ 8mg/dl</td>
</tr>
<tr>
<td>751-1,000 g</td>
<td>ASAP after enrollment</td>
<td>≥ 10mg/dl</td>
</tr>
</tbody>
</table>

• PT was continued for at least 24 hrs when started
• Type and number of lights determined by attending
• Target irradiance= 15- 40 µW/cm²/nm
### Phototherapy: Outcomes at 18-22 M


<table>
<thead>
<tr>
<th>Event</th>
<th>AG (%)</th>
<th>CON (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/NDI</td>
<td>52</td>
<td>55</td>
<td>0.94 (0.87, 1.02)</td>
</tr>
<tr>
<td>Death</td>
<td>24</td>
<td>23</td>
<td>1.05 (0.90, 1.22)</td>
</tr>
<tr>
<td>NDI</td>
<td>26</td>
<td>30</td>
<td>0.86 (0.74, 0.99)</td>
</tr>
</tbody>
</table>
## Phototherapy: Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AG (%)</th>
<th>CON (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or M/S CP</td>
<td>29</td>
<td>29</td>
<td>0.99 (0.86, 1.13)</td>
</tr>
<tr>
<td>Mod/Severe CP</td>
<td>4</td>
<td>6</td>
<td>0.71 (0.47, 1.07)</td>
</tr>
<tr>
<td>Death or MDI&lt;70</td>
<td>47</td>
<td>50</td>
<td>0.94 (0.86, 1.02)</td>
</tr>
<tr>
<td>MDI &lt;70</td>
<td>21</td>
<td>26</td>
<td>0.83 (0.71, 0.98)</td>
</tr>
<tr>
<td>Death or HL</td>
<td>26</td>
<td>27</td>
<td>0.97 (0.84, 1.12)</td>
</tr>
<tr>
<td>Perm HL</td>
<td>&lt;1</td>
<td>3</td>
<td>0.32 (0.15, 0.68)</td>
</tr>
</tbody>
</table>

1 Adjusted only for BW

Randomized Trial of Postnatal Dexamethasone for Severe RDS for infants < 2000G born 92-95

- Dexamethasone .25mg/kg given q12 h IV for the 1st week, then tapered
- Children evaluated at school age
- | Dexamethasone group | Controls | p     |
- | Disability          | 39%      | 22%   | .04  |
- | WISC III IQ         | 78 ± 15  | 84 ± 13| .008 |
- | HC cm               | 50 ± 3   | 51 ± 2 | .04  |
- | Height              | 123 ± 7  | 126 ± 6| .01  |

Yeh TF et al NEJM 2004
## Caffeine Therapy for Apnea of Prematurity for infants < 1250 grams

<table>
<thead>
<tr>
<th></th>
<th>Caffeine</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>1006</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>5.2</td>
<td>5.5</td>
<td>NS</td>
</tr>
<tr>
<td>BPD-36w</td>
<td>36</td>
<td>47</td>
<td>.001</td>
</tr>
<tr>
<td>ROP</td>
<td>39</td>
<td>43</td>
<td>.09</td>
</tr>
<tr>
<td>Brain injury</td>
<td>13</td>
<td>14</td>
<td>.44</td>
</tr>
<tr>
<td>NEC</td>
<td>29</td>
<td>38</td>
<td>.001</td>
</tr>
<tr>
<td>Surg PDA</td>
<td>4.5</td>
<td>12.5</td>
<td>.001</td>
</tr>
</tbody>
</table>

Schmidt et al. NEJM 2006
Caffeine Therapy for Apnea of Prematurity for infants < 1250 grams

<table>
<thead>
<tr>
<th></th>
<th>Caffeine</th>
<th>Placebo</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>1006</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>Death &lt; 18m</td>
<td>6.4</td>
<td>6.5</td>
<td>0.87</td>
</tr>
<tr>
<td>CP</td>
<td>4.4</td>
<td>7.3</td>
<td>0.009</td>
</tr>
<tr>
<td>Cog delay</td>
<td>34.0</td>
<td>38.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>1.9</td>
<td>2.4</td>
<td>0.41</td>
</tr>
<tr>
<td>Bilat blind</td>
<td>0.7</td>
<td>0.9</td>
<td>0.58</td>
</tr>
<tr>
<td>Death or dis.</td>
<td>40.0</td>
<td>46.0</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Schmidt et al NEJM2006
What is the mechanism of Benefit from caffeine?

• It’s a stimulant
• Earlier discontinuation of positive airway pressure explained 49% of the beneficial effect on outcome

• Postnatal age of last use of O2 accounted for 32% variance of improved outcome

• Less severe lung injury
Magnesium Sulfate

- Mechanisms:
  - Reduces vascular instability
  - Prevents hypoxic damage
  - Mitigates cytokine or excitatory amino acid damage.

A Case Control Study identified a sig ↓ CP
OR .14  CI 0.05-0.51

**MgSO₄ An Antenatal Intervention**

- Women at risk of preterm delivery at 24-31 weeks received 6 gm IV bolus at 2 gm /hr or placebo between (1997 & 2004)

- **Outcome:** Composite of death or mod/sev CP

<table>
<thead>
<tr>
<th></th>
<th>MgSO₄</th>
<th>Placebo</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>D or CP</td>
<td>10%</td>
<td>11%</td>
<td>0.91</td>
<td>0.71-1.17</td>
</tr>
<tr>
<td>Death</td>
<td>9.5%</td>
<td>8.5%</td>
<td>1.12</td>
<td>0.85-1.47</td>
</tr>
<tr>
<td>CP</td>
<td>1.9%</td>
<td>3.5%</td>
<td>0.55</td>
<td>0.32-0.92</td>
</tr>
</tbody>
</table>

Rouse DJ. NEJM, 2008;359:895-905
So, what can families expect?

How can physicians counsel families?

• What is the likelihood of a completely unimpaired ELBW infant?

• What does unimpaired mean?
NICHD Network Study  Gargus et al, 2009

• NDI: The presence of CP, Bayley scores< 70, bilateral blind or hearing loss with amplification.

• New classification includes:
  • **Mild impairment:** Bayley 70-84, mild CP, mild other neurologic findings, glasses, unilateral HL, unilateral blindness.

• Unimpaired: Bayley scores≥ 85, normal neurologic exam, normal hearing, normal vision, normal swallowing and normal ambulation.
4450 ELBW Infants <1000 Grams Livebirths
1998-01   NICHD Network

• Died                2100    34%
• NDI                 1147    22%
• Mild                1153    22%
• Unimpaired     850     16%

Gargus et al. Pediatrics 2009
Unimpaired Outcome: Gargus et al. Peds 2009
1998-2001 (N-6090 ELBW)

18-22 Month Outcomes by Gestational Age in ELBW

Gestational Age (weeks)

- 23 or less
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31+

1.2%
Neurodevelopmental Outcomes < 33 w
Vohr et al, NICHD Network 2005

- Outcome 22-26 27-32 p
  - Survival 61% 86% .0001
  - Mod/Sev CP 10% 6% .0001
  - MDI < 70 37% 23% .0001
  - PDI < 70 26% 17% .0001
  - Blind 1% .4% .01
  - Hearing Loss 1.8% 1.8%
  - NDI 45% 28% .0001
Neurodevelopmental Outcomes < 25w
Hintz S et al Pediatrics 127, Jan 2011 NICHD Network

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>35%</td>
<td>32%</td>
<td>NS</td>
</tr>
<tr>
<td>C-Section</td>
<td>41%</td>
<td>49%</td>
<td>.03</td>
</tr>
<tr>
<td>PDA Surgery</td>
<td>27%</td>
<td>36%</td>
<td>.004</td>
</tr>
<tr>
<td>Late onset Sepsis</td>
<td>50%</td>
<td>59%</td>
<td>.01</td>
</tr>
<tr>
<td>PNS</td>
<td>64%</td>
<td>33%</td>
<td>.0001</td>
</tr>
<tr>
<td>Mod/Sev CP</td>
<td>11%</td>
<td>15%</td>
<td>.15</td>
</tr>
<tr>
<td>MDI &lt; 70</td>
<td>45%</td>
<td>51%</td>
<td>.15</td>
</tr>
<tr>
<td>NDI</td>
<td>50%</td>
<td>59%</td>
<td>.07</td>
</tr>
</tbody>
</table>

Conclusion: Outcomes remain unchanged
Preterms < 1000 G need multiple Services: between discharge and 18-22 months

<table>
<thead>
<tr>
<th>Service</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visiting Nurse</td>
<td>58.7%</td>
</tr>
<tr>
<td>OT or PT</td>
<td>59.9%</td>
</tr>
<tr>
<td>Speech T</td>
<td>33.7%</td>
</tr>
<tr>
<td>Early Intervention</td>
<td>55.7%</td>
</tr>
<tr>
<td>Social Worker</td>
<td>25.6%</td>
</tr>
<tr>
<td>Sub specialty</td>
<td>68.8%</td>
</tr>
</tbody>
</table>

Recovery

• At 18-22 months ELBW infants exhibit significant NDI and SHCN.

• Is there a possibility of neurodevelopmental recovery after 2 years of age?
Case Report: What can the parents expect?

• Mother
• 30 y o G1P1
• Married
• Partial college
• Private insurance
• Prenatal care
• Antenatal steroids

• Baby boy
• 27 w gest, 1000g
• Surfactant, Indomethacin
• RDS, PDA, BPD, Sepsis x 2
• NEC with perforation
• Normal cranial ultrasounds
• Hospitalized 90 days
• Breast Milk
• Referred @ disc. to EI and Follow-up clinic
Early Bayley MDI scores of ELBW Baby
Is there any room for optimism?
Cognitive Development on Bayley, Stanford Binet and WPPSI to 12 y

- 6m: 63
- 12m: 49
- 18: 49
- 3y: 83
- 6y: 89
- 8y: 119
- 12y: 116
But

Is this child Unimpaired?
<table>
<thead>
<tr>
<th>Age</th>
<th>Neurologic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 m</td>
<td>Suspect, ↑ tone, jerky movements, EI</td>
</tr>
<tr>
<td>12 m</td>
<td>Abnormal ↑ tone lowers, spastic diplegia, EI</td>
</tr>
<tr>
<td>18 m</td>
<td>Abnormal, mild spastic diplegia, seizures, EI</td>
</tr>
<tr>
<td>3y</td>
<td>Starts special ed preschool full 5 days/week</td>
</tr>
<tr>
<td>6 y</td>
<td>Spastic diplegia, AFOs, walker, PT, OT, SE</td>
</tr>
<tr>
<td>8 y</td>
<td>CP, AFOs, walker, Special Education, OT, PT</td>
</tr>
<tr>
<td>12 y</td>
<td>CP, difficulty socializing, Special Education, uses a walker, receives OT and PT</td>
</tr>
</tbody>
</table>
Case Report: What are the Factors Associated with Cognitive Recovery?

- Mother
- 30 y o G1P1
- Married
- Partial college
- Private insurance
- Prenatal care
- Antenatal steroids
- Baby boy
- 27 w gest, 1000g
- Surfactant, Indomethacin
- RDS, PDA, BPD, Sepsis x 2
- NEC with Perforation
- Normal cranial ultrasounds
- Hospitalized 90 days
- Breast Milk
- Referred @ disc to EI and Follow-up Clinic
What is more important?

An Intact brain
or
An optimal environment
or
Both
Brain Volume Abnormalities by MRI persist in preterm children at school age

Preterm children compared to term controls have:

- ↓ cortical gray matter
- ↓ cortical white matter
- ↓ deep gray matter and cerebellar volumes
- ↑ in CSF (occipital horn + body of ventricles)
- ↓ gray/white matter differentiation
- ↓ cortical surface area and complexity

Peterson BS, Vohr B et al. *JAMA*, 2000
Relationship of Gestational Age to Brain Volume

- Inder et al showed the relationship between GA at birth and deep nuclear GM vol. at term. (Peds 2005)

- Gestational age, ventriculomegaly, PVL and chorioamnionitis were all significantly related to cerebral volumes for preterm study subjects at 8 years. (Peterson BS, Ment L et al, 2000)

Does Brain Size Matter??
Relationship of Brain Volume and Cognitive Outcomes at 8 Years of Age.

- Cerebral volumes were linearly related to Full Scale IQ, Verbal IQ, Performance IQ & PPVT for preterm subjects
  - Peterson BS, Ment L et al, 2000
- This is worrisome, but is there recovery of verbal and cognitive function?
Raw Scores on PPVT from 3-12 y
Indomethacin cohort  
Luu et al SPR 2008
<table>
<thead>
<tr>
<th>Variables in model</th>
<th>β regression coefficient (95% CI) N=355</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (100 g increment)</td>
<td>0.5 (-0.5, 1.6)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>-0.4 (-4.3, 3.4)</td>
</tr>
<tr>
<td>Male sex</td>
<td>-0.7 (-4.0, 2.5)</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>3.7 (0.3, 7.1)*</td>
</tr>
<tr>
<td>BPD</td>
<td>-2.4 (-6.1, 1.4)</td>
</tr>
<tr>
<td>Severe brain injury</td>
<td>-22.1 (-28.1, -16.2)*</td>
</tr>
<tr>
<td>Maternal age &lt; 20</td>
<td>-0.4 (-5.4, 4.6)</td>
</tr>
<tr>
<td>Maternal years of education</td>
<td>2.0 (1.3, 2.7)*</td>
</tr>
<tr>
<td>Single-parent household</td>
<td>-5.9 (-9.4, -2.3)*</td>
</tr>
<tr>
<td>Minority status</td>
<td>-8.4 (-12.2, -4.5)*</td>
</tr>
</tbody>
</table>

* p-value < 0.05  
Luu et al Pediatrics 2009
16 year Outcomes Indomethacin Trial

• Preterm Infants IQ and Vocabulary Scores ↑ with ↑ Age;

• At age 16 PT IQ: 88 ± 19 versus T 104 ±16

• PT adolescents, however, had ↑ deficits in executive function, verbal fluency, planning, organization and working memory even after children with disabilities were excluded.

• Predictors of poor outcomes @ 16 were neonatal brain injury and low maternal education.
Functional connectivity for PT and T groups @ 12y. Blue lines join regions correlated sig in both groups; red lines in one group.
Exploring Evidence for Catch-up in Cognition and Receptive Vocabulary

- 322 preterm < 1250g and 41 term controls
- Cognitive & language tests @ 8, 12, and 16 ys
- What are the characteristics of the children with good outcomes?
- Hierarchical growth-curve modeling to delineate group differences
- Cluster analysis to identify patterns of cognitive and receptive vocabulary development.
Patterns of cognitive development from the age of 8 to 16 years: A, WISC-III vocabulary raw score; B, WISC-III block-design raw score.

Term children in bold line.

Patterns of receptive language development from 8 to 16 years  Luu T M et al. Pediatrics 2011;128:313-322
For infants < 1250 g at 16 years

• PT children demonstrate sig. catch-up in vocabulary between 8 and 16 y.

• Subgroups of PT children have developmental trajectories similar to term children.
  – 56% for vocabulary
  – 46% for block design

• PT children who perform similar to term C have lower rates of Neurosensory impairment and mothers with higher education levels.
Multiple Factors Interact and Contribute to Outcomes of ELBW Infants

Antenatal/Perinatal
ANS, PNS. MgSO₄
Surfactant, illness
Gest. Age, Gender, Singleton

NICU Morbidities &
Interventions; Surfactant,
Vent. Support, PNS, iNO,
Indomethacin, Caffeine
Nutrition, Breast Milk

Home Environment
Maternal education
Genetics

Early Intervention and
Access to Long Term
Education, Therapeutic,
and Medical Support
Services
Our Hope is that with improved antenatal, neonatal, and post-discharge interventions, PT infants will have the opportunity to recover and lead happy productive Lives.