Outcomes of Children Born Extremely Preterm

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Outline -

- Changes in survival and survival without major morbidity
- Neurodevelopmental outcomes of children born extremely preterm -
  - Toddlers, children, and challenges to interpretation
- Are we asking the right questions?
  - Beyond traditional outcomes -
  - Possibilities for changing the trajectory of research and outcomes
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Survival of infants born extremely preterm

**EXPRESS 2** → Swedish national prospective study of survival and outcomes of infants 22-26 weeks’

- One-year survival among *live-born* infants:
  - 70% during 2004-07
  - 77% during 2012-16
  - −7% [95% CI, −11% to −2.2%], p = 0.003
Survival without major morbidity

**EXPRESS 2** → 1-year survival without any major morbidity (22-26 weeks’):

- 32% during 2004-2007
- 38% during 2012-2016
  - \(-6\% \ [95\% CI, -11\% \text{ to } -1.7\%], \ p = 0.008.\)

In California, survival to discharge without major morbidity improved among **VLBW** (~62% to 67%) from 2008-2017 (p<0.001)

- Largest gains among infants born <27 weeks’
- Substantial variation across sites.


Shifting focus to neurodevelopmental outcomes

• As the number of extremely preterm infants surviving to discharge increases, attention has appropriately shifted to understanding neurodevelopmental outcomes.

• Neonatal clinical trials now frequently include ~ 2-year neurodevelopmental endpoints as part of the primary outcome or a main secondary outcome.
How is “neurodevelopmental outcome” measured?

Follow up only to ~18 months - 3 years corrected age for the vast majority trials and prospective studies.

Gross Motor function

- Neurologic examination; diagnosis of cerebral palsy, severity by Gross Motor Function Classification System (GMFCS)
  

“Cognitive” and developmental assessment

- Bayley II → Bayley III → Bayley 4

Hearing and Vision
How is “impairment” or “disability” defined?

• “NDI”- a composite outcome
  • Combines criteria and cut points from several domains including motor, cognitive/developmental, neurosensory.
  • Generally categorized by severity - but definitions and cut points within each component varies among studies and cohorts.
    • None, mild, moderate, severe
Challenges to interpretation

• Relative prevalence of component, response to interventions.
  Marlow N. Arch Dis Child Fetal Neonatal 2013; 98:F554

• Changes in *instruments*—e.g., Bayley II vs. III (vs. Bayley 4...)
  o Bayley-III reported to underestimate developmental delay

• “NDI” definition and age at FU not consistent across studies.
  o Multiple definitions across literature even in “severe NDI”

• Differing rates of NDI, death or NDI across centers *within networks*.

• Family and functional perspective
Spectrum of neurodevelopmental outcomes

- Children born \(<26 \text{ weeks EGA}\) in NICHD Neonatal Research Network
- Neurodevelopmental assessment completed 2011-2014 at 18-26 months corrected age
- 2113 children evaluated; mean GA 25±1 weeks, mean BW 760±154 g.

Overall - neurological examination findings:
- 59% no abnormal or suspect findings; 19% suspect; 10% abnormal non-CP; 12% CP

Neurodevelopmental outcomes over time:
< 26-week EGA at 18-26 months corrected age

2011: N=436
2014: N=486

Decrease in severe CP over time:
< 26-week EGA at 18-26 months corrected age

Any CP 2011-2014: N=247 (12%)

- 2011: 70%
- 2014: 44%

Decrease in severe CP over time:
Australian Cerebral Palsy Register (ACPR)

Outcomes at age 2 years of infants <28 weeks’ GA
Comparison of 3 birth cohorts in Victoria, Australia

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Survivors, n</td>
<td>225</td>
<td>151</td>
<td>172</td>
</tr>
<tr>
<td>Survivors assessed, n</td>
<td>219 (97.3%)</td>
<td>149 (98.7%)</td>
<td>163 (94.8%)</td>
</tr>
<tr>
<td>CP</td>
<td>24 (11.0)</td>
<td>18 (12.1)</td>
<td>16 (9.8)</td>
</tr>
<tr>
<td>Blindness</td>
<td>5 (2.3)</td>
<td>4 (2.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Deafness</td>
<td>2 (0.9)</td>
<td>2 (1.3)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>No developmental delay</td>
<td>128* (58.4%)</td>
<td>81 (54.4%)</td>
<td>85 (52.1)</td>
</tr>
<tr>
<td>Mild developmental delay</td>
<td>51 (23.3)</td>
<td>32 (22.1)</td>
<td>52 (31.9)</td>
</tr>
<tr>
<td>Moderate developmental delay</td>
<td>24 (11.0)</td>
<td>14 (9.4)</td>
<td>20 (12.3)</td>
</tr>
<tr>
<td>Severe developmental delay</td>
<td>16 (7.3)</td>
<td>22 (14.8)</td>
<td>6 (3.7)</td>
</tr>
<tr>
<td>No disability</td>
<td>119 (54.3)</td>
<td>72 (48.3)</td>
<td>83 (50.9)</td>
</tr>
<tr>
<td>Mild disability</td>
<td>54 (24.7)</td>
<td>35 (23.5)</td>
<td>47 (28.8)</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>29 (13.2)</td>
<td>19 (12.8)</td>
<td>27 (16.6)</td>
</tr>
<tr>
<td>Severe disability</td>
<td>17 (7.8)</td>
<td>23 (15.4)</td>
<td>6 (3.7)</td>
</tr>
</tbody>
</table>

<25-week EGA outcomes at 18-22 months (birth 2000 to 2011)

Mortality decreased during this period: 70% → 64%

What about *later* outcomes of children born extremely preterm?
Importance of longer-term outcomes

- Later cognitive and behavioral outcomes are complex - influenced multiple factors
- Changes in, relative importance of various outcomes vary substantially among individuals and across different time points.
- Later follow up may provide critical additional outcomes and safety data, and information about changes over time.

Neurodevelopmental Disability at 6.5 years
EXPRESS cohort (birth years 2004-2007)

Serenius F, et al. JAMA Peds 2016; 170: 954

Major disability among survivors
23 weeks – 29%
24 weeks – 20%
25 weeks – 18%
26 weeks – 17%
27 weeks – 10%

Rates of major disability were similar across birth eras:
Predicting school age from toddlerhood??
Importance of longer-term outcomes

Only 47% remained in the same category →
• 21% moved to a better category, 32% moved to a worse category.

Serenius F, et al. JAMA Peds 2016; 170: 954
Predicting school age from toddlerhood?
Importance of longer-term outcomes

Bayley-III COG at 18-22 months and WISC IV FSIQ at 6-7 years


SUPPORT NEURO Hintz, Bann, Vohr, et al., *Pediatrics* 2018, PAS 2018
Movement ABC scores at 6-7 years - NEURO cohort

Overall, one-third with significant or moderate coordination challenges

Are we asking all the right questions?
What about outcomes important to families?

- **“Real life” endpoints**
  - Usual research/trial outcomes confusing, or only short-term endpoints; personalize data

- **Functional outcomes**
  - Concept of child’s health and well being in terms of function, activities, participation

- **Parent and child well-being**, family impact and interactions.

- **Daily life factors**

Re-hospitalizations and medical equipment: 
*Birth years 2013-2016, follow up at 22-26 months CA*

<table>
<thead>
<tr>
<th></th>
<th>22 weeks</th>
<th>23 weeks</th>
<th>24 weeks</th>
<th>25 weeks</th>
<th>26 weeks</th>
<th>22-26 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospitalized since discharge, N (%)</strong></td>
<td>20 (64.5)</td>
<td>171 (59.0)</td>
<td>311 (54.9)</td>
<td>360 (49.2)</td>
<td>415 (44.1)</td>
<td>1277 (49.9)</td>
</tr>
<tr>
<td><strong>If yes, median (IQR) # times</strong></td>
<td>3 (2-4)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>1 (1-3)</td>
<td>2 (1-3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Selected equipment/assistive devices n (%)</strong></th>
<th>22 weeks</th>
<th>23 weeks</th>
<th>24 weeks</th>
<th>25 weeks</th>
<th>26 weeks</th>
<th>22-26 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrostomy tube and/or tube feeding</td>
<td>6 (19.4)</td>
<td>52 (17.9)</td>
<td>81 (14.3)</td>
<td>75 (10.2)</td>
<td>80 (8.5)</td>
<td>294 (11.5)</td>
</tr>
<tr>
<td>Oxygen</td>
<td>3 (9.7)</td>
<td>33 (11.4)</td>
<td>33 (5.8)</td>
<td>36 (4.9)</td>
<td>30 (3.2)</td>
<td>135 (5.3)</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>1 (3.2)</td>
<td>19 (6.6)</td>
<td>29 (5.1)</td>
<td>23 (3.1)</td>
<td>22 (2.3)</td>
<td>94 (3.7)</td>
</tr>
<tr>
<td>Braces/orthotics</td>
<td>7 (22.6)</td>
<td>60 (20.7)</td>
<td>88 (15.5)</td>
<td>80 (10.9)</td>
<td>93 (9.9)</td>
<td>328 (12.8)</td>
</tr>
</tbody>
</table>
### Service Utilization at 1st HRIF Visit

**VLBW** = very low birth weight; **HIE** = hypoxic ischemic encephalopathy

<table>
<thead>
<tr>
<th>Medical specialties - currently receiving</th>
<th>VLBW N=4900</th>
<th>HIE N=193</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1845 (38%)</td>
<td>68 (35%)</td>
</tr>
<tr>
<td>1 to 2</td>
<td>2502 (51%)</td>
<td>90 (47%)</td>
</tr>
<tr>
<td>3 to 4</td>
<td>477 (10%)</td>
<td>30 (16%)</td>
</tr>
<tr>
<td>5 or more</td>
<td>76 (2%)</td>
<td>5 (3%)</td>
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<table>
<thead>
<tr>
<th>Special services - currently receiving</th>
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<tbody>
<tr>
<td>0</td>
<td>3369 (59%)</td>
<td>105 (54%)</td>
</tr>
<tr>
<td>1 to 2</td>
<td>1344 (27%)</td>
<td>65 (34%)</td>
</tr>
<tr>
<td>3 to 4</td>
<td>168 (3%)</td>
<td>21 (11%)</td>
</tr>
<tr>
<td>5 or more</td>
<td>19 (0.4%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

**Median age at follow up = 6 months**
The Impact to the Parent and Family – Depression, anxiety, trauma

• Parents of NICU babies at ↑↑ **risk for depression, anxiety, trauma** – may persist for years.
  
  ↑ stress, anxiety, trauma significantly associated with **dysfunctional coping**, cognitive and behavior/motor challenges in toddlerhood


• Maternal NICU trauma and anxiety symptoms linked to later ↑ perception of **child vulnerability**, affect parent-infant engagement.


• **Protective** effects of positive home environment on EPT/VPT outcomes; **negative** effect of parental stress and family dysfunction.

“Early Intervention”

• “Early intervention” may encompass many different components, services, disciplines –

  ▪ Concluded that early intervention **has a positive influence on cognitive outcomes through preschool and motor outcomes to ~ 2 years.**
  ▪ Early diagnosis and intervention for cerebral palsy – both child **and** parents.


Getting to follow up: Improved Referral of VLBW to HRIF in California after QI Initiative

- **Pre-intervention** period - birth 1/10-6/13: 83% referred
- **Post-intervention** period birth 7/13-12/16: 95% referred

Substantial ↑ in referral rates by sociodemographic and program-level factors - - but disparities remain.

**Getting to follow up:** Factors associated with successful 1st visit for infants born VLBW in California

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Associated with higher odds - -</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age (vs 20-29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>1.48 (1.27, 1.72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maternal prenatal care</td>
<td>1.92 (1.34, 2.77)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Birth weight (vs. 1251-1499 g)</td>
<td></td>
<td></td>
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<tr>
<td>&lt;=750 g</td>
<td>2.11 (1.69, 2.65)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>751-1000 g</td>
<td>1.81 (1.51, 2.17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1001-1250 g</td>
<td>1.34 (1.14, 1.58)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Severe ICH</td>
<td>1.61 (1.12, 2.3)</td>
<td>0.0093</td>
</tr>
<tr>
<td>Insurance (vs CCS or MediCal only)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMO/PPO + CCS</td>
<td>1.65 (1.19, 2.31)</td>
<td>0.003</td>
</tr>
<tr>
<td>Two parent 1 caregiver (vs. one only)</td>
<td>1.18 (1.03 - 1.36)</td>
<td>0.019</td>
</tr>
<tr>
<td>HRIF program VLBW volume (vs. lowest quartile)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd quartile</td>
<td>2.62 (1.88, 3.66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3rd quartile</td>
<td>1.55 (1.15, 2.10)</td>
<td>0.0045</td>
</tr>
</tbody>
</table>

| **Associated with lower odds - -**           |                      |           |
| Maternal race African American              | 0.65 (0.54, 0.78)    | <0.0001   |
| Miles from HRIF program (vs. lowest quartile) |                    |           |
| Highest quartile                            | 0.69 (0.57, 0.83)    | 0.0002    |
| 3rd quartile                                | 0.79 (0.65, 0.96)    | 0.018     |
Interventions and outcomes – Engagement in the NICU → home and community

• Innovative transition to home program (Brown): ↓ ER visits, rehospitalizations, health care use.

• Interventions beginning in NICU and continuing after DC, including “Triple P” (Brisbane) - improved Bayley III cognitive and motor score at 2 years.

• Family Integrated Care intervention (25 NICUs) → ↓ parent stress/anxiety, ↑ wt gain and breast feeding at discharge.

• Rethinking intervention – supporting parent mental health, responsive parenting
Health-related QoL

Quality of life at adolescence and adulthood for ELBW

• **Self-perceived HRQoL for NBW and ELBW**
  - Fewer ELBW than NBW respondents (24% vs 46%) reported “perfect health”.

• **Young adulthood: NO difference between NBW and ELBW in HRQoL (0.85 vs.0.88).**

• **Using indirect methods only**
  - ELBW with lower HRQoL teens → mid 30’s, especially among those with neurosensory impairments

Quality of Life for parents of adults born very preterm

Bavarian Longitudinal Study; prospective population-based, VLBW or VP born 1985-86

- WHO QoL (short) Instrument
  - Evaluated with respect to child functioning factors previous assessments - disability, mental health, academic achievement, peer relationships, parent-child relationship.

- Parent QoL predicted by child mental health and peer relationships.
  - Consistent with Saigal S, et al Pediatrics 2010
  - Participation limited (VLBW group = 59%, term = 74%), dropouts not random.

→ Importance of integrating psychological support and interventions

Wolke D, Baumann N, Busch B et al. Pediatrics 2017; 140: e20171263
### Cardiometabolic measures

- Respiratory outcomes
- Motor challenges
- Mental health

### HRQoL

- Relationships
- Independent living...
- Others

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**Preemie Voices -themes...**

- Importance of emotional, personal, psychological support; coping and resilience.
- Gratitude and living with “different abilities”.

Saigal S. Preemie Voices, Friesen Press, 2014
Challenges to reshaping the future

• Much is invested in the survival of the tiniest and highest risk babies.
  › We must now invest in the best possible life course outcomes for them and their families.

• *Truly* long-term research must be a priority.

• Pursue innovative research and intervention frameworks with outcomes important to families → beyond the NICU exit doors.