Dr. Lancaster, a native of Missouri, received his Doctor of Medicine from the University of Chicago. His residency in pediatrics and his fellowship in Neonatal-Perinatal Medicine were conducted at St. Louis Children’s Hospital at Washington University in St. Louis, MO. Dr. Lancaster is board-certified in pediatrics and neonatology. Dr. Lancaster joined Sunflower Neonatology Associates in the summer of 2008 and was named Medical Director at Research Medical Center the following year. At the start of 2019, Dr. Lancaster assumed the role of Medical Director of the Overland Park Regional NICU. He helped lead many program developments including whole body cooling for HIE, a comprehensive neurocritical care nursery for HCA Midwest and an 11 bed Small Baby Unit at OPR. He has spoken at many regional and national conferences on topics related to neuroprotection in the newborn. He is an active member of the Newborn Brain Society and continues his interest in neonatal neurocritical care, including the benefits of neuroprotective strategies for preterm and term infants. When he is not busy with caring for babies he enjoys traveling, reading and spending time with his family.
Protecting our Tiniest Humans: Primum Non Nocere

Thomas M. Lancaster, MD
Sunflower Neonatology Associates
Medical Director, NICU OPRMC and NCCN
Disclosure

I have no financial conflicts of interest to disclose. I have not received any financial benefit from this discussion.
Objectives

• Discuss various forms of preterm brain injury with focus on VLBW
• Learn about different grades of intraventricular hemorrhages in preterm infants
• Describe likely mechanism and outcomes for developing periventricular hemorrhagic infarction and post hemorrhagic ventricular dilatation
• Explore evidence based or best practices for minimizing brain injury in preterm brain injury, specifically IVH
• Provide an update on strategies for managing posthemorrhagic ventricular dilatation
Impact of preterm birth on brain outcomes

Magnitude of the Problem

*More than 2 million infants* are born yearly *worldwide* with birth-weight <1500 gm.

In the U.S. –
- 57,000 infants born yearly
- 90+% survive
- of survivors, 5 - 10% later exhibit “cerebral palsy”, and 25 - 50%, cognitive/behavioral deficits.

Long Term Outcome for Very Preterm Infants

4-5% risk of cerebral palsy, with 50% having an increased clumsiness and reduced physical ability

> 25% of children requiring educational assistance

25% developing behavioral problems including ADHD, social maladjustment at school and anxiety
Outcomes at 2 years

- NICHD NRN (United States)
- EXPRESS (Sweden)
- EPICure (United Kingdom)

**Mild or no disability**

**Moderate disability**

**Severe disability**

Frequency among survivors

Gestational age:
- 22wk
- 23wk
- 24wk
- 25wk
- 26wk
Fetal brain growth accelerated compared to newborn and beyond

Mathews, et al. 2018
Brain injury in VLBW comes in many forms:

• Intraventricular hemorrhage (IVH)
• Periventricular Hemorrhagic Infarction (PVHI)
• Post-hemorrhagic Ventricular Dilatation (PHVD)
• White Matter Injury (PVL)
• Cerebellar Hemorrhage (CBH)
• Occult Brain Injury of Prematurity
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Regional description of preterm brain injury

<table>
<thead>
<tr>
<th>Region</th>
<th>Disorder</th>
<th>cUS</th>
<th>MRI</th>
<th>Neuropathology</th>
<th>Clinical outcome including Neurodevelopmental Disability (NDD)</th>
</tr>
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<tbody>
<tr>
<td><strong>Germinal Matrix</strong></td>
<td>GMH-IVH I-II</td>
<td>+/-</td>
<td>+</td>
<td>Germinal matrix vasculature rupture into ventricle.</td>
<td>Inconsistent outcomes related to higher risk with more immature infants</td>
</tr>
<tr>
<td>IVH III - PHVI</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Large IVH Complicated by parenchymal venous infarction +/- PHVD.</td>
<td>Relates to severity with large IVH, PHVD and parenchymal involvement increasing risk of NDD</td>
</tr>
<tr>
<td>PHVD</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Hydrocephalus complicating IVH.</td>
<td>Increased risk for NDD that may be improved by appropriate intervention</td>
</tr>
<tr>
<td><strong>White Matter</strong></td>
<td>Cystic Injury</td>
<td>+</td>
<td>+</td>
<td>Cystic periventricular lesions now rare &lt;5%</td>
<td>Increased risk of cerebral palsy with diplegia</td>
</tr>
<tr>
<td>PWMLs</td>
<td>+/-</td>
<td>+</td>
<td></td>
<td>Glial scars in periventricular region</td>
<td>Increased risk of motor disability if PLIC involved. Number and placement may impact outcome</td>
</tr>
<tr>
<td>Loss of WM volume</td>
<td>-/+</td>
<td>+</td>
<td></td>
<td>Loss of axons and oligodendroglia</td>
<td>Increased risk for cognitive and behavioral disorders</td>
</tr>
<tr>
<td>Impaired myelination</td>
<td>-</td>
<td>+</td>
<td></td>
<td>Impaired maturation of oligodendroglia</td>
<td>Increased risk of delayed motor development, clumsiness and mild NDD</td>
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<tr>
<td><strong>Cerebellum</strong></td>
<td>Large CBH</td>
<td>+</td>
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<td>Hemorrhagic +/- ischemic injury</td>
<td>Increased risk of NDD, language impairment and autism</td>
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<tr>
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<td>-</td>
<td>+</td>
<td></td>
<td>Focal microvascular rupture</td>
<td>Not yet fully defined — mild to no risk for NDD</td>
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<td>Cortex</td>
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<td>Focal stroke</td>
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</tr>
</tbody>
</table>
Germinal matrix: An immature and highly vascular structure

- Gelatinous region
- Origin of neural & glial precursors
- Regresses at 34-36 wk
- Fragile vasculature

- Bleeding into germinal matrix = GMH
- Extension into ventricle = IVH
- Collectively = GMH-IVH

Figure: Adapted from Ballabh P. Pediatr Res, 2010
Figure: Courtesy of Dr. Harris Brent from Georgetown University
Incidence overall is trending down in preterm population

- 1970-80’s: 40-50%
- Overall incidence ≈ 20%
- Severe IVH: 5-10%

Gestational age & Birth weight → Close association

Handley SC et al. J Pediatr, 2018
Cizmeci MN et al. J Pediatr, 2019
Shankaran S et al. J Pediatr, 2020
Yeo KT et al. Arch Dis Child Fetal Neonatal Ed, 2020

Figure: Volpe’s Neurology of the Newborn, 2017, p 640
Incidence of IVH in very preterm infants unchanged
Grading Systems of GMH-IVH

• First classification by Papile et al. 1978

• Volpe classification
  • Joseph Volpe, 1989
    • *Recommended classification*

• A recent classification
  • EurUS.Brain Group, 2020
Grading Intraventricular Hemorrhage

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Volpe</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Germinal matrix hemorrhage</td>
<td>Grade I</td>
<td>Germinal matrix hemorrhage with no or minimal hemorrhage</td>
</tr>
<tr>
<td>Grade II</td>
<td>Blood within but not distending ventricular system</td>
<td>Grade II</td>
<td>IVH (10-50% of ventricular area)</td>
</tr>
<tr>
<td>Grade III</td>
<td>Blood filling and distending ventricular system</td>
<td>Grade III</td>
<td>IVH (&gt;50% of ventricular area; usually distends ventricle)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Parenchymal involvement of hemorrhage</td>
<td>Severe + periventricular hemorrhagic infarction</td>
<td>Grade III IVH with periventricular hemorrhagic infarction</td>
</tr>
</tbody>
</table>


† (Data from Volpe JJ. Neurology of the newborn, 3rd edn. Philadelphia: WB Saunders, 1995:424-428.)
Grade I IVH

Grade II IVH

Grade III IVH

Large GMH-IHV are at risk of developing PHVD

PHVD onset is typically 7-14 days following GMH-IVH
PVHD and PVHI – Most severe complications of IVH

Ventricular Dilatation and Parenchymal Hemorrhage

Post-hemorrhagic Ventricular Dilatation (PHVD)
= Ventricular dilatation following GMH-IVH

Periventricular Hemorrhagic Infarction (PVHI)
= Parenchymal hemorrhage following GMH-IVH

Equivalent of Papile Grade-IV
Acute/early preterm brain injury

Most common injury leads to spastic diplegia
Outcomes of babies <28 weeks for IVH, PHVD and PVHI

<table>
<thead>
<tr>
<th>Early Neurodevelopmental Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolisetti et al. n=1472 infants &lt;28 wk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>At 2-3 years</th>
<th>No GMH-IVH</th>
<th>Grade I and II</th>
<th>Grade III or PVHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND delay</td>
<td>3%</td>
<td>8%</td>
<td>18%</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>7%</td>
<td><strong>10%</strong></td>
<td>30%</td>
</tr>
<tr>
<td>Deafness</td>
<td>2%</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>Blindness</td>
<td>0</td>
<td>0</td>
<td>2%</td>
</tr>
<tr>
<td>Moderate/Severe Disability</td>
<td><strong>22%</strong></td>
<td><strong>43%</strong></td>
<td></td>
</tr>
</tbody>
</table>

- ND impairments more common with high-grade IVH
- Low-grade IVH is also at risk (*in contrast: Payne et al. NICHD data*)
Outcomes in ELGAN for IVH and PHVD

### Extreme Preterms, NICHD Data 2020

*n=4216 infants <26 wk*

<table>
<thead>
<tr>
<th>At 18-26 months CA</th>
<th>Normal cUS</th>
<th>IVH only</th>
<th>PHVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Outcomes</td>
<td>57%</td>
<td>51%</td>
<td>27%</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>9%</td>
<td>13%</td>
<td>43%</td>
</tr>
<tr>
<td>Deafness</td>
<td>2%</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Blindness</td>
<td>1%</td>
<td>1%</td>
<td>6%</td>
</tr>
<tr>
<td>ND Disability</td>
<td>14%</td>
<td>18%</td>
<td>47%</td>
</tr>
</tbody>
</table>

- Impairments more common in infants with PHVD
- Outcomes worse in PHVD requiring surgical intervention
High mortality and morbidity for PVHI

Outcomes of PVHI in the Current Era

- Mortality: 40%
  - Death/severe disability: 58%
- Cerebral palsy: 42%
  - Almost all hemiparetic
  - Majority independently walking
- Improved outcomes
  - Attributed to perinatal care

<table>
<thead>
<tr>
<th>Table II. Sonographic characteristics and outcome of included very preterm infants with PVHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive outcome</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Motor outcome</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>GMFCS scores</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
</tbody>
</table>
Influences on IVH and morbidities in VLBW infants

- Immature autoregulation
- Chorioamnionitis
- Outborn and transport
- Cord Milking vs DCC

- Antenatal steroids
- Mg prophylaxis
- Gentle noninvasive support
- Skin to skin
**Immature Autoregulation**

*Narrow regulatory control window*

- **preterm**
  - Severe RDS
  - Intubation
  - Mechanical vent.
  - Pneumothorax

- **term**

```
GMH-IVH
```

- Increased pCO₂
- Sodium imbalance
- Glucose imbalance

**References**

Leijser LM & de Vries LS. *Handbook of Clinical Neurology*, 2019
EBDoJ Mithras Mediatr, 2020
Early inotropes use is associated with higher risk of death and/or severe brain injury in extremely premature infants

Ahmad Nizar Abdul Aziz, Sumesh Thomas, Prashanth Murthy, Yacov Rabi, Amuchou Soraisham, Amelie Stritzke, Majeeda Kamaluddeen, Essa Al-Awad and Khorshid Mohammad

Section of Neonatology, Department of Pediatrics, University of Calgary, Alberta, Canada

Table 3. Dopamine, dobutamine, and normal saline use and short-term neurological outcomes adjusted for confounding factors.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Early Dopamine use</th>
<th>Early Dobutamine use</th>
<th>Saline boluses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AOR</td>
<td>95% CI</td>
<td>p value</td>
</tr>
<tr>
<td>Death and/or severe brain injury</td>
<td>2.3</td>
<td>1.1–4.8</td>
<td>.02</td>
</tr>
<tr>
<td>Severe brain injury</td>
<td>2.2</td>
<td>0.97–5.1</td>
<td>.06</td>
</tr>
<tr>
<td>IVH of any grade</td>
<td>1.5</td>
<td>0.8–2.9</td>
<td>.2</td>
</tr>
</tbody>
</table>

*aadjusted for: GA, Small for GA, birth outside the referral tertiary center, cord blood gas pH < 7, APGAR score <5 at 5 minutes of age, hypothermia <36.5°C on admission, Respiratory distress syndrome required surfactant, use of antenatal steroids, gender, mode of delivery, arterial pCO2 >60 mm Hg with acidosis, reintubation in the first 72 hours, and early onset sepsis.
Chorioamnionitis

- *Induces inflammation & infection*

- Meta-analysis, 85 studies, n=13,432
  - *Increase in IVH*
  - RR: 1.88 (1.61-2.19)

- *Increase in all grades of IVH*

- Controversial results for histologic chorioamnionitis
Transport of the Preterm Infant

- Traumatic insult, vibration, noise
- Transport itself or underlying disorder?

- U.S cohort, n=67,596
  - Increase in IVH
    - aOR: 1.75 (1.64-1.86)
  - Increase in severe IVH
    - aOR: 1.44 (1.22-1.70)

Mohamed MA et al. Arch Dis Child Fetal Neonatal Ed, 2010
Amer R et al. J Pediatr, 2018
Goswami I et al. Early Hum Dev, 2020
Delivery Room Resuscitation

- Mechanical trauma
- Oxidative stress, hemodynamic fluctuations

- Chest compressions
- Bicarbonate use
- Multiple intubation attempts
- Birth at off-peak hours

additional risk

Arnon S et al. J Perinatol, 2017
Oei JL et al. Pediatrics, 2017
Antenatal Steroids

Single most effective antenatal intervention

- Induction of maturation
- Hemodynamic stabilization
- Improved respiratory status

- Meta-analysis, 16 studies, n=6093
  - Decrease in IVH
  - RR:0.55 (0.40-0.76)

Delayed Cord Clamping
A common delivery room practice

- Hemodynamic stability
- Less inotrope, RBC transfusions

- Meta-analysis, 40 studies, n=4884
  - Decrease in IVH
  - RR: 0.83 (0.70-0.99)

- No decrease in severe IVH

Rabe H et al. Cochrane Database Syst Rev, 2019

Figure adapted from Illustrative Neonatology by Satyan with permission
Cord Milking

*Regarded as an alternative: A friend or a foe?*

- First meta-analysis, 7 studies, n=501
  - Decrease in IVH
  - RR: 0.62 (0.41-0.93)

- Recent RCT, n=474 infants
  - Increase in severe IVH <27 wk
  - Trial prematurely terminated

- Later meta-analysis, 19 studies, n=2014
  - Increase in severe IVH
  - RR: 1.95 (1.01-3.76)

Ref:
Al-Wassia H et al. JAMA Pediatr, 2015
Katheria AC et al. JAMA, 2019
Balasubramanian H et al. Arch Dis Fetal Neonatal Ed, 2019

*Figure adapted from Illustrative Neonatology by Satyan with permission*
Maternal-Preterm Skin-to-Skin Contact Enhances Child Physiologic Organization and Cognitive Control Across the First 10 Years of Life

Ruth Feldman, Zehava Rosenthal, and Arthur I. Eidelman

- 73 premature infants and 73 matched controls
- 1 hour of Kangaroo Care each day for 14 days
- Improved autonomic control at term
- Improved cognitive development throughout the first 10 years associated with better parent-infant interaction
  - Biological Psychiatry 2014
Gentle Care & Non-Invasive NICU Practices

- Non-invasive ventilation
- Less-invasive surfactant administration
- Volume-targeted ventilation

- Midline head positioning & bundle care
  - Not effective in a small meta-analysis
  - Recent multicenter cohort, n=561 infants <30 wk
    • Lower risk of IVH and severe IVH

Klebermass-Schrehof K et al. Neonatology, 2013
Klingenborg C et al. Cochrane Syst Database, 2017
Mian Q. Arch Dis Child Fetal Neonatal Ed, 2018
De Bijl-Marcus K et al. Neonatology, 2017
Romantsik O et al. Cochrane Database Syst Rev, 2017
Kochan M et al. J Perinatol., 2018
De Bijl-Marcus K et al. Arch Dis Fetal Neonat Ed, 2019
Figure from: Aguar M et al. NeoReviews, 2014
Neonatal care bundles are associated with a reduction in the incidence of intraventricular haemorrhage in preterm infants: a multicentre cohort study

Karen de Bijl-Marcus, Annemieke Johanna Brouwe, Floris Groenendaal, Gerda van Wezel-Meijler

Position Statement

Neuroprotection from acute brain injury in preterm infants

Michelle Ryan, Thierry Lacaze-Masmonteil, Khorshid Mohammad

Canadian Paediatric Society, Fetus and Newborn Committee, Ottawa, Ontario

Original Article

Neuroprotection Care Bundle Implementation to Decrease Acute Brain Injury in Preterm Infants

Prashanth Murthy, MD, Hussein Zein, MD, Sumesh Thomas, MD, James N. Scott, MD, Ayman Abou Mehrem, MD, Michael J. Esser, MD, Abhay Lodha, MD, Cathy Metcalfe, RN, Derek Kowal, RT, Leigh Irvine, MN, Jillian Scotland, RN, Lara Leijser, MD, Khorshid Mohammad, MD.*
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**TABLE 2.**
Pre-NPC and Post-NPC Implementations and Interventions in the Study Population

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<th>Characteristics</th>
<th>Pre-NPC Bundle (n = 301)</th>
<th>Post-NPC Bundle (n = 364)</th>
<th>P Value</th>
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<tr>
<td><strong>Hemodynamic management</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inotrope use in the first 72 hours</td>
<td>71 (23.6)</td>
<td>25 (6.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal saline boluses</td>
<td>112 (37.2)</td>
<td>68 (18.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical treatment of PDA</td>
<td>115 (38.9)</td>
<td>157 (43.3)</td>
<td>0.25</td>
</tr>
<tr>
<td>Surgical ligation of PDA</td>
<td>30 (10)</td>
<td>24 (6.6)</td>
<td>0.12</td>
</tr>
<tr>
<td>Timing of PDA treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the first 72 hours</td>
<td>32 (10.6)</td>
<td>32 (8.8)</td>
<td>0.29</td>
</tr>
<tr>
<td>After 72 hours</td>
<td>88 (29.2)</td>
<td>125 (34.4)</td>
<td></td>
</tr>
<tr>
<td>DCC</td>
<td>77 (25.8)</td>
<td>229 (64.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Respiratory management</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any hypercapnia &gt;60 mm Hg in the first 72 hours</td>
<td>116 (38.5)</td>
<td>124 (34.1)</td>
<td>0.26</td>
</tr>
<tr>
<td>Any hypocapnia &lt;35 mm Hg in the first 72 hours</td>
<td>132 (43.9)</td>
<td>126 (34.6)</td>
<td>0.017</td>
</tr>
<tr>
<td>Extubating success (total = 202, 106 before and 96 after the bundle)</td>
<td>83 (78.3)</td>
<td>81 (84.4)</td>
<td>0.27</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>14 (4.7)</td>
<td>6 (1.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Remained intubated for the first 72 hours</td>
<td>142 (47.2)</td>
<td>152 (41.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Extubation attempt within first 72 hours</td>
<td>107 (35.5)</td>
<td>96 (26.4)</td>
<td></td>
</tr>
<tr>
<td>Not intubated</td>
<td>52 (17.3)</td>
<td>116 (31.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Impact of minimal handling</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of opioids (fentanyl or morphine)</td>
<td>57 (18.9)</td>
<td>25 (6.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
FIGURE 2. Run chart before and after the implementation of the NPC bundle. The color version of this figure is available in the online edition.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Born Jan 1, 2013 to Sep 20, 2015 (n=342)</th>
<th>Born Sep 21, 2015 to Dec 31, 2018 (n=401)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died before age 21 months</td>
<td>38 (11.1%)</td>
<td>28 (7.0%)</td>
<td>0.049</td>
</tr>
<tr>
<td>Milder or severe disability:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP (any severity)</td>
<td>19/284 (6.7%)</td>
<td>11/344 (3.2%)</td>
<td>0.041</td>
</tr>
<tr>
<td>Visual impairment or blindness</td>
<td>7/287 (2.4%)</td>
<td>7/349 (2.0%)</td>
<td>0.711</td>
</tr>
<tr>
<td>Hearing impairment or deafness</td>
<td>3/286 (1.0%)</td>
<td>1/347 (0.3%)</td>
<td>0.333</td>
</tr>
<tr>
<td>Cognitive delay &lt;85</td>
<td>54/248 (21.8%)</td>
<td>35/215 (16.3%)</td>
<td>0.135</td>
</tr>
<tr>
<td>Any milder or severe disability</td>
<td>69/251 (27.5%)</td>
<td>46/218 (21.1%)</td>
<td>0.109</td>
</tr>
<tr>
<td>Severe disability:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP GMFCS 3-5</td>
<td>4/284 (1.4%)</td>
<td>2/344 (0.6%)</td>
<td>0.418</td>
</tr>
<tr>
<td>Bilateral blindness</td>
<td>3/287 (1.0%)</td>
<td>1/349 (0.3%)</td>
<td>0.332</td>
</tr>
<tr>
<td>Bilateral deafness</td>
<td>0/286 (0.0%)</td>
<td>1/347 (0.3%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Cognitive score &lt;70</td>
<td>21/248 (8.5%)</td>
<td>4/215 (1.9%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Any severe disability</td>
<td>22/251 (8.8%)</td>
<td>7/218 (3.2%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Death or any severe disability</td>
<td>60/289 (20.8%)</td>
<td>35/246 (14.2%)</td>
<td>0.049</td>
</tr>
<tr>
<td>Bayley III Outcomes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor score &lt;85</td>
<td>63/192 (32.8%)</td>
<td>59/190 (31.1%)</td>
<td>0.712</td>
</tr>
<tr>
<td>Language score &lt;85</td>
<td>79/186 (42.5%)</td>
<td>64/170 (37.6%)</td>
<td>0.354</td>
</tr>
<tr>
<td>Cognitive score &lt;85</td>
<td>54/248 (21.8%)</td>
<td>35/215 (16.3%)</td>
<td>0.135</td>
</tr>
<tr>
<td>Any motor, language, or cognitive &lt;85</td>
<td>113/190 (59.5%)</td>
<td>101/183 (55.2%)</td>
<td>0.403</td>
</tr>
</tbody>
</table>
# Brain Care Bundle by NICU Nurses

### Brain Care Recommendations: Postnatal Interventions
Infants < 30 weeks AND < 72 hours of age

<table>
<thead>
<tr>
<th>Action</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Achieve and Maintain Normothermia</strong></td>
<td>Aim to prevent hypothermia (&lt;36 °C) and hyperthermia (&gt;38 °C)</td>
</tr>
<tr>
<td></td>
<td>Use heat provision measures with close monitoring and documentation eg polyethylene plastic bag on blankets for infants ≤ 28 weeks, chemical warming mattress</td>
</tr>
<tr>
<td></td>
<td>Hypothermia associated with a higher risk of IVH (Miller et al 2011)</td>
</tr>
<tr>
<td><strong>Maintain Neutral/Midline Head Positioning</strong></td>
<td>Advise referral center of these practices</td>
</tr>
<tr>
<td></td>
<td>- Avoid prone positioning</td>
</tr>
<tr>
<td></td>
<td>- Maintain neutral/midline head position in sidelying or supine</td>
</tr>
<tr>
<td></td>
<td>- Maintain neutral/midline head position during handling and procedures</td>
</tr>
<tr>
<td></td>
<td>- Turn infant as a unit</td>
</tr>
<tr>
<td></td>
<td>- Head of bed elevated 30 degrees after NICU admission</td>
</tr>
<tr>
<td></td>
<td>- Complete x-rays with head of bed elevated</td>
</tr>
<tr>
<td></td>
<td>- X-ray completion a 2 person procedure</td>
</tr>
<tr>
<td></td>
<td>Turning infant’s head to the side affects jugular venous return and may affect intracranial pressure and cerebral blood flow</td>
</tr>
<tr>
<td></td>
<td>Tilting the head up and down in preterm infants alters cerebral blood volume (Pichler et al, 2001)</td>
</tr>
<tr>
<td></td>
<td>ICP lower with HOB elevated 30 degrees (Goldberg et al, 1983)</td>
</tr>
</tbody>
</table>

---

SickKids Guidelines on Bundle Care by Nurses
## Brain Care Bundle by NICU Nurses

### Brain Care Recommendations: Postnatal Interventions
**Infants < 30 weeks AND < 72 hours of age**

<table>
<thead>
<tr>
<th>Action</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gentle Diaper Changes</strong></td>
<td>Minimize fluctuations in cerebral blood flow since cerebral circulatory changes demonstrated with diaper changes, specifically abrupt changes in venous return and cardiac preload with elevation of lower extremities (Limperopoulos et al, 2008)</td>
</tr>
<tr>
<td>* Slightly raise buttocks to change diaper</td>
<td></td>
</tr>
<tr>
<td>* Avoid lifting legs</td>
<td></td>
</tr>
<tr>
<td>* <strong>Infants &lt; 1000 grams:</strong> open diaper for 4 days to minimize groin irritation and potential skin breakdown</td>
<td></td>
</tr>
<tr>
<td><strong>Gentle Care</strong></td>
<td>Prevent agitation and manoeuvres that may fluctuate cerebral blood flow</td>
</tr>
<tr>
<td>* Minimal and gentle handling</td>
<td></td>
</tr>
<tr>
<td>* Care by nurses with expertise in VLBW infant care. To facilitate expertise, co-care/training with an experienced nurse should be facilitated</td>
<td></td>
</tr>
<tr>
<td>* Gently weigh and change under sheet once daily</td>
<td></td>
</tr>
<tr>
<td>* A 2 person procedure for 72 hours</td>
<td></td>
</tr>
<tr>
<td>* Avoid changing bedsheet for 72 hours</td>
<td></td>
</tr>
<tr>
<td>* A 2 person procedure if required before 72 hours</td>
<td></td>
</tr>
<tr>
<td>* Provide nesting and containment</td>
<td></td>
</tr>
<tr>
<td><strong>Minimize Light:</strong></td>
<td></td>
</tr>
<tr>
<td>Prevent constant exposure to light</td>
<td></td>
</tr>
<tr>
<td>Cover isolette</td>
<td></td>
</tr>
<tr>
<td>No direct light in infants’ eyes</td>
<td></td>
</tr>
<tr>
<td><strong>Minimize Noise:</strong></td>
<td></td>
</tr>
<tr>
<td>Mute alarms swiftly</td>
<td></td>
</tr>
<tr>
<td>Do not place objects on isolette</td>
<td></td>
</tr>
<tr>
<td>Speak softly at bedside</td>
<td></td>
</tr>
</tbody>
</table>

SickKids Guidelines on Bundle Care by Nurses
## EurUS.Brain Group’s Recommendations, 2020

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 28</th>
<th>Later Scans</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28 weeks</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Every other week until term</td>
</tr>
<tr>
<td>≥28 weeks</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>At 6 weeks and at term</td>
</tr>
</tbody>
</table>

- Antenatal hemorrhage IVH due to resuscitation
- Maximum extent of IVH Complications
- Majority of hemorrhages
- Ongoing risk
- Surveillance before discharge

Grade III IVH

Volpe Classification Grade-III

Grade-III
IVH >50%

Post-hemorrhagic Ventricular Dilatation (PHVD)

- Ventricular dilatation following GMH-IVH

- Umbrella term that includes
  - Acute
  - Chronic stages

- Hydrocephalus (=chronic stage) also falls under this umbrella
Why Do Ventricles Enlarge?

Current pathophysiologic mechanisms

GM-IVH

Hematoma

Mechanical compression on periventricular tissue

Alteration in CSF dynamics

Blood clots
Outflow site fibrosis

Blockage of CSF drainage

Post-hemorrhagic ventricular dilatation

AL

TLR-4 activation
NF-kB-inflammatory response in choroid plexus

Hypersecretion of CSF

AQP1 blockage

Karimy JK et al. Nat Med, 2017
Romantsik O et al. Neoreviews, 2019
Can we reduce morbidity assoc with PHVD?

**DRIFT Trial**

*Drainage, Irrigation, Fibrinolytic Therapy*

- DRIFT (n=34) vs Standard treatment (n=36)
  - VP-shunt
    - 38% vs 39%  
  - Mortality/VP-shunt
    - 44% vs 50%
  - *Stopped early ➔ secondary hemorrhage*
    - 35% vs 8%

*Non-significant*

Figure adapted from Whitelaw A et al. Pediatrics, 2003
Balance in Favor of Early Intervention?

- Invasive
- Early surgery and anesthesia
- Risk of infection

- Preserved white matter volume
- Fewer VP shunts
- Improved outcomes
The ELVIS Trial

Early vs Late Ventricular Intervention Study

- RCT, 2006-2016
- 6 countries, 14 centers
- n=126 infants <34 wk
- Ultrasonographic criteria used
- Primary outcome: Death/VP-shunt

De Vries LS et al. Arch Dis Child Fetal Neonatal Ed, 2019
## DRIFT vs. ELVIS

<table>
<thead>
<tr>
<th>2-year outcomes</th>
<th>DRIFT</th>
<th>ELVIS early</th>
<th>ELVIS late</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal range</td>
<td>23%</td>
<td>78%</td>
<td>71%</td>
</tr>
<tr>
<td>&lt;-1 SD</td>
<td>26%</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>&lt;-2 SD</td>
<td>51%</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Motor score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal range</td>
<td>12%</td>
<td>61%</td>
<td>64%</td>
</tr>
<tr>
<td>&lt;-1 SD</td>
<td>15%</td>
<td>29%</td>
<td>15%</td>
</tr>
<tr>
<td>&lt;-2 SD</td>
<td>73%</td>
<td>10%</td>
<td>21%</td>
</tr>
</tbody>
</table>
## Comparison with Previous Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>ND Impairment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventriculomegaly Trial Group</strong>&lt;br&gt;Arch Dis Child Fetal Neonatal Ed, 1994</td>
<td>High-threshold&lt;br&gt;Increased ICP signs</td>
<td>49&lt;br&gt;47</td>
</tr>
<tr>
<td><strong>Kennedy et al. Acetazolamide Trial</strong>&lt;br&gt;Pediatrics, 2001</td>
<td>Increased ICP signs</td>
<td>66</td>
</tr>
<tr>
<td><strong>Whitelaw et al. DRIFT Trial</strong>&lt;br&gt;Pediatrics, 2010</td>
<td>DRIFT&lt;br&gt;High-threshold</td>
<td>46&lt;br&gt;58</td>
</tr>
<tr>
<td><strong>Leijser et al.</strong>&lt;br&gt;Neurology, 2018</td>
<td>Low-threshold&lt;br&gt;Increased ICP signs</td>
<td>5&lt;br&gt;52</td>
</tr>
</tbody>
</table>

- Intervening earlier is associated with more favorable outcomes
How should we approach PHVD?
Standardized approach to CUS evaluation for PHVD to guide management
Timing of Lumbar Punctures

Low-threshold Intervention
“Early Intervention”

High-threshold Intervention
“Late Intervention”

Waiting for Clinical Signs
“Very Late Intervention”

Increase in head circumference > 2 cm/wk
Bulging fontanelle
Separated sutures
Where to Plot?

New Reference Charts

- Charts by Levene, 1981
  - Starts from 27 wk
  - Not suitable for extreme preterms

- New reference charts:
  - Brouwer et al. Radiology, 2012
  - Longitudinal data on 625 infants
  - Starts from 24 wk

- Colorful adaptation by:
  - El-Dib et al. J Pediatr, 2020

Levene MI & Starte DR. Arch Dis Child, 1981
Figure adapted from El-Dib M et al. J Pediatr, 2020
Key Points: Ultrasonographic Follow-Up & Early Intervention

Green Zone
Key Criteria:
Ventricular size with the following
- VI ≤ 97th percentile
- AHW ≤ 6 mm

And
Absence of the following clinical criteria:
- HC growth > 2 cm per week
- Separated sutures
- Bulging fontanelles

Management:
- Observation in NICU
- cUS twice a week until stable for 2 weeks then every 1-2 weeks till 34 weeks PMA
- MRI at Term Equivalent
Key Points: Ultrasonographic Follow-Up & Early Intervention

Yellow Zone

Key Criteria:
Ventricular size with the following
- VI > 97th percentile
- AHW > 6 mm &/or TOD > 25 mm

And
Absence of the following clinical criteria:
- HC growth > 2 cm per week
- Separated sutures
- Bulging fontanelles

Management:
- Referral to a regional center for neurosurgical review
- Consider LP 2-3 times
- cUS 2-3X a week until stable for 2 weeks then every 1-2 weeks till 34 weeks PMA
- Neurosurgical intervention when no stabilization occurs
- MRI at Term Equivalent
Key Points: Ultrasonographic Follow-Up & Early Intervention

Red Zone

Key Criteria:
- VI > 97th percentile + 4 mm
- AHW > 10 mm &/or TOD > 25 mm

Or

Any of the following clinical criteria
- HC growth > 2 cm per week
- Separated sutures
- Bulging fontanelles

Management:
- Consider LP 2-3 times
- Neurosurgical intervention including either temporizing measures or VP shunt
- MRI at Term Equivalent
PHVD management summary

- PHVD ➔ Major risk factor for adverse outcomes
- ELVIS Trial: Earlier intervention improved outcomes
- PVHI has slightly better outcomes in the current era
  - Still a major risk factor for adverse outcomes
- Long-term follow-up into school-age is required
  - To appreciate higher cognitive challenges
Conclusions, parting words

• IVH is common in preterm infants, especially <28 weeks
• Grading systems have evolved over the years but most concerning complications still remain: PVHI and PHVD
• Strategies for reducing risk of IVH include a neuroprotective bundle with education and consistency of use
• Evidence based, standardize approach to PHVD likely improve short and long term outcomes
Questions

tlancaster@sunflowerneo.com