11th Annual Neonatal Conference
Thursday, April 6, 2017

Taglyan Cultural Complex
1201 North Vine St.
Hollywood, CA 90038

Presented by:
The Steven & Alexandra Cohen Foundation
Newborn and Infant Critical Care Unit
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>6:30 a.m.</td>
<td>Registration, Breakfast and Exhibits</td>
<td></td>
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<tr>
<td>7:45 a.m.</td>
<td>Opening Remarks</td>
<td>Nancy Blake, PhD, RN, CCRN, NEA-BC, FAAN</td>
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<tr>
<td></td>
<td></td>
<td>Director, Critical Care Services</td>
</tr>
<tr>
<td>8 a.m.</td>
<td>Withdrawal Prevention Protocol: A Model for Quality Improvement</td>
<td>Rambod Amirnovin, MD</td>
</tr>
<tr>
<td>9 a.m.</td>
<td>ROP: Building a Better NICU</td>
<td>Thomas C. Lee, MD</td>
</tr>
<tr>
<td>10 a.m.</td>
<td>Break and Exhibits</td>
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<tr>
<td>10:30 a.m.</td>
<td>Is This Baby Dysmorphic?</td>
<td>Linda Randolph, MD, FAAP, FACMG</td>
</tr>
<tr>
<td>11:30 a.m.</td>
<td>Brain Injury in Newborns</td>
<td>Sharon Fichera, RN, MSN, CNS, NNP-BC</td>
</tr>
<tr>
<td>12:45 p.m.</td>
<td>Lunch and Exhibits</td>
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<tr>
<td>1:45 p.m.</td>
<td>PDA: Controversies and Treatment Options in 2017</td>
<td>Shahab Noori, MD</td>
</tr>
<tr>
<td>2:45 p.m.</td>
<td>Neonatal GI Obstructions</td>
<td>Eugene S. Kim, MD, FACS, FAAP</td>
</tr>
<tr>
<td>4 p.m.</td>
<td>Evaluations and Door Prizes</td>
<td></td>
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</tbody>
</table>
Preventing Withdrawal in the Neonatal ICU
11th Annual Neonatal Conference
April 6, 2017

Rambod Amirnovin, MD
Medical Director, Quality & Process Improvement
Division of Critical Care Medicine
Children’s Hospital, Los Angeles

Disclosures:

I have no financial disclosures nor will discuss any off-label device or medication usage.
Objectives:

- Recognize the different “sedation” medications common in the NICCU and their benefits.
- Recognize the secondary (unintended) effects of using sedation medications.
- Background on creation of a withdrawal prevention protocol - historical perspective.
- Withdrawal prevention protocol and withdrawal assessment tool (WAT 1)
- Preliminary results in the CHLA NICCU

The critically ill patient requires sedation & analgesia...

**OPIOIDS:**
- Fentanyl
- Morphine
- Hydromorphone

**BENZODIAZEPINES:**
- Lorazepam (Ativan)
- Midazolam (Versed)

**Analgesia**
- Sedation

**Sedation**
- Anxiolysis
Consequences of Long Term Use

- **Tolerance**
  - The need for increasing doses of a medication to achieve the same effect.
- **Dependence**
  - Ongoing use of a substance is required for normal physiological functioning.
- **Withdrawal**
  - A constellation of signs and symptoms that occur when a patient who is dependent on a drug is rapidly removed off the drug.
- **Addiction**
  - The psychological “need” or craving for a substance leading to compulsive behaviors.

More Consequences of Long-term Opioids & Benzos:

- Prolonged hospital stay
- Feeding intolerance and gut dysmotility
- Increased brain atrophy
- Death
Delirium

- Acute alteration in level of consciousness
- Fluctuating course
- Inattention
- Impaired information processing
- Medical trigger

- Two types:
  - Hyperactive
  - Hypoactive

Risk Factors

- Hypotension
- Hypoxia
- Anemia
- Metabolic imbalance
- Acidosis
- Toxins
- Inflammation/infection
- Medications
  - Opiates
  - Benzodiazepines
  - Diphenhydramine
Treatment

- Pain ➔ Opiates
- Anxiety ➔ Benzodiazepines
- Movement ➔ Muscle relaxants
- Withdrawal ➔ Give weaned medication
- Delirium ➔ Remove trigger(s)

Differentiating the Processes

<table>
<thead>
<tr>
<th></th>
<th>Pain</th>
<th>Anxiety/Agitation</th>
<th>Withdrawal</th>
<th>Delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs/Symptoms</td>
<td></td>
<td></td>
<td></td>
<td>Lack of tracking or focus, restless</td>
</tr>
<tr>
<td>Risk Factors/Time Course</td>
<td></td>
<td></td>
<td>&gt; 5 days of opiates/BDZ &amp; recent decrease</td>
<td></td>
</tr>
<tr>
<td>Response to Opioids/BDZ</td>
<td></td>
<td></td>
<td>Sx improve with appropriate medication</td>
<td></td>
</tr>
<tr>
<td>Scoring Systems</td>
<td>COMFORT/FLACC</td>
<td>RASS</td>
<td>WAT-1</td>
<td>pCAM-ICU</td>
</tr>
<tr>
<td>Treatments</td>
<td></td>
<td>Replace missing medication</td>
<td>Non-pharmacologic/Anti-psychotics</td>
<td></td>
</tr>
</tbody>
</table>
Historical Perspective:

- Shorten duration of opioid and benzodiazepine use.
- Minimize adverse effects of these drugs.
- Shorten patients’ length of stay
  - CHLA hospital LOS in patients with sedation > 5 days:
    - PICU: 28.7 days median
    - CTICU: 29.9 days median
- Minimize symptoms of withdrawal and over-sedation.

Collaborative Process Improvement

Process Improvement Aims:
- Minimizing variation “mass customization.”
- Integrating predictable and evidence-based care ...when available!
- Decreasing work-load and multi-tasking by clinicians
- Measure process to improve it or detect its failures
Educational User’s Manual

Withdrawal Prevention Protocol (WPP)
Children’s Hospital, Los Angeles
Background and User’s Manual

Educational Testing

**PRE/POST**

<table>
<thead>
<tr>
<th>ICU Room</th>
<th>CV Room</th>
<th>PCU Room</th>
<th>ALL Rooms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reports</td>
<td>16</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>TOTAL RV</td>
<td>196</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Response Rate</td>
<td>70%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>% Correct</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
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</tbody>
</table>

**POST/POST**

<table>
<thead>
<tr>
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</tr>
<tr>
<td>% Correct</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
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</tbody>
</table>
Process Metric: Worksheet Compliance

CTICU / CV ACUTE: Demographics
7 or more days of opioids

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>N (&gt;7 days opioids)</td>
<td>52</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Age, days</td>
<td>12 (2,167)</td>
<td>10 (1,188)</td>
<td>0.98</td>
</tr>
<tr>
<td>Males, N (%)</td>
<td>28 (53.8%)</td>
<td>37 (69.8%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Race, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latino</td>
<td>29 (55.8%)</td>
<td>28 (52.8%)</td>
<td>0.92</td>
</tr>
<tr>
<td>White</td>
<td>16 (30.8%)</td>
<td>12 (22.6%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Black</td>
<td>4 (7.7%)</td>
<td>5 (9.4%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>3 (5.7%)</td>
<td>8 (15.1%)</td>
<td>0.35</td>
</tr>
<tr>
<td>PIM-2 Score</td>
<td>-4.1 (-4.9, -3.2)</td>
<td>-4.1 (-4.9, -3.2)</td>
<td>0.62</td>
</tr>
<tr>
<td>STAT Mortality Category ≥4</td>
<td>32 (61.5%)</td>
<td>34 (64.2%)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Continuous variables presented with median (and interquartile range) and analyzed with Mann-Whitney U test. Categorical variable presented absolute number (and percentage) and analyzed with the Yates-corrected Chi-squared test.
CTICU: >/= 7 d. Opioid Infusion
Outcomes & Balance Metrics

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Length of Stay (days)</td>
<td>41.7 (34.8, 74.8)</td>
<td>34.1 (25.9, 58.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Opioids Days, Total OUTCOME</td>
<td>30 (19, 51)</td>
<td>19 (13, 28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Opioids Days, Post Extubation OUTCOME</td>
<td>18 (8, 25)</td>
<td>7 (5, 11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percent of WAT-1 ≥4 (%) BALANCE</td>
<td>14.1 (3.9, 22.1)</td>
<td>6.8 (2.1, 14)</td>
<td>0.02</td>
</tr>
<tr>
<td>Max Daily Morphine Equivalents (mg / Kg)</td>
<td>6.4 (4.8, 8)</td>
<td>4.9 (4.4, 6.2)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Patients with 7 or more days of opioid infusions, CTICU to D/C. Data are medians (IQR).

Empiric Cost Savings Analysis:
Patients with >/= 7 Days of Opioids

<table>
<thead>
<tr>
<th>CTICU</th>
<th>PICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Patients In Study Period</td>
<td>6.4%</td>
</tr>
<tr>
<td>% of Patient Days In Study Period</td>
<td>28.7%</td>
</tr>
<tr>
<td>Total Patient Days Saved</td>
<td>7.6 days * 67 pts = 509 patient days</td>
</tr>
<tr>
<td>Empiric Cost Analysis (Not Actual)</td>
<td>$1500 * 509 pt days = $610,800</td>
</tr>
</tbody>
</table>
Withdrawal Prevention Protocol

1. Initiate WAT-1 \textit{Before} Weaning Patients
   WAT-1 Scores Every 6 Hours
2. Record Pre-Wean WAT-1 Scores as “Baseline”

\begin{tabular}{|c|c|}
\hline
\textbf{Date} & \textbf{Baseline WAT Scores} \\
\hline
\end{tabular}

\textit{\textbf{Withdrawal Assessment Tool-1}}

- Any loose /watery stools
- Any vomiting/wretching/gagging
- Temperature > 37.8°C
- State SBS≤ 0 or asleep/awake/calm = 0
- Tremor
- Any sweating
- Uncoordinated/repetitive movement
- Yawning or sneezing
- Startle to touch
- Muscle tone
- Time to gain calm state (SBS≤ 0)

WAT Scores are \textbf{Extremely Non-Specific but Highly Sensitive for Withdrawal.}

Total Potential Sore: 12
3. Choose longer-acting medication and dose

<table>
<thead>
<tr>
<th>Current Infusion Dose</th>
<th>PO Methadone (preferred) (Max Dose: 10 mg)</th>
<th>IV Hydromorphone (if PO/NG not an option) (Max dose 2 mg)</th>
<th>PRN IV Hydromorphone (Max dose 2 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone Drip</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.005 mg/kg/hr</td>
<td>0.1 mg/kg/dose PO Q6H</td>
<td>0.02 mg/kg/dose IV Q4H</td>
<td>0.02 mg/kg/dose IV Q2-4H PRN</td>
</tr>
<tr>
<td>0.01 mg/kg/hr</td>
<td>0.1 mg/kg/dose PO Q6H</td>
<td>0.04 mg/kg/dose IV Q4H</td>
<td>0.04 mg/kg/dose IV Q2-4H PRN</td>
</tr>
<tr>
<td>0.015 mg/kg/hr</td>
<td>0.1 mg/kg/dose PO Q6H</td>
<td>0.06 mg/kg/dose IV Q4H</td>
<td>0.06 mg/kg/dose IV Q2-4H PRN</td>
</tr>
<tr>
<td>0.02 mg/kg/hr</td>
<td>0.15 mg/kg/dose PO Q6H</td>
<td>N/A</td>
<td>0.08 mg/kg/dose IV Q2-4H PRN</td>
</tr>
<tr>
<td>0.025 mg/kg/hr</td>
<td>0.15 mg/kg/dose PO Q6H</td>
<td>N/A</td>
<td>0.08 mg/kg/dose IV Q2-4H PRN</td>
</tr>
<tr>
<td>0.03 mg/kg/hr</td>
<td>0.15 mg/kg/dose PO Q6H</td>
<td>N/A</td>
<td>0.08 mg/kg/dose IV Q2-4H PRN</td>
</tr>
</tbody>
</table>

What if Infusion Dose High?

**Surgical Patient**
- Start assessing for weak 24hrs post operatively
- EXCEPT tracheostomy: start assessing immediately after first tracheostomy change; ECMO after decannulation

**Non Surgical Patient**
- Assess daily for initiation of weaning
- EXCEPT during therapeutic hypothermia

<table>
<thead>
<tr>
<th>Patient Status</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPASS 5 or 7</td>
<td>Initiate WPP</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>N/PASS &lt; 1</td>
<td></td>
</tr>
</tbody>
</table>

**Risk Stratification for Withdrawal**
- **Low to Moderate Risk**
  - Opioids < 7 days
  - Decrease dose each day by 30% of original dose
- **High Risk**
  - Opioids 8-30 days
  - Decrease dose every other day by 20% of original dose
- **Very High Risk**
  - Opioids >30 days
  - Decrease dose every other day by 10% of original dose
4. Determine withdrawal risk category
   a. Moderate - 5-7 days
   b. High - 8-30 days
   c. Very high - >30 days

5. Complete Withdrawal Prevention Protocol Worksheet
   - RN Staff Fills Out Q6 Hour WAT-1 & # of PRN’s last 24 hrs.
   - MD/NP Team Fills Out Daily Change
   - Anyone can write comments: e.g., “PRN does not help”
6. Assessing for Withdrawal

- Daily review and interpret WAT-1 score
- Daily review # of prn’s
- Wean per protocol

>72 hrs since wean (methadone) or >36 hrs since wean (lorazepam/hydromorphone), withdrawal unlikely

* Remember the goal is to minimize symptoms, not eliminate them.

---

**Preliminary NICU Data:**

<table>
<thead>
<tr>
<th></th>
<th>No-WPP n=390</th>
<th>WPP N=57</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (gms)</td>
<td>2420 (1120 – 3150)</td>
<td>2620.5 (902 – 3228.5)</td>
<td>0.7</td>
</tr>
<tr>
<td>Birth Head Circumference (cm)</td>
<td>32 (26.5 – 34)</td>
<td>33 (25 - 35)</td>
<td>0.2</td>
</tr>
<tr>
<td>Male (%)</td>
<td>54.17</td>
<td>53.57</td>
<td>0.9</td>
</tr>
<tr>
<td>Gestational Age (Weeks)</td>
<td>36 (29 - 38)</td>
<td>36 (28.5 – 39)</td>
<td>0.7</td>
</tr>
<tr>
<td>Length of Stay (Days)</td>
<td>40.5 (19 – 83)</td>
<td>32 (17 – 67)</td>
<td>0.3</td>
</tr>
<tr>
<td>NEC (%)</td>
<td>9.43</td>
<td>1.69</td>
<td>0.0463</td>
</tr>
<tr>
<td>Central Line Days</td>
<td>24 (10 – 47)</td>
<td>8 (1 – 19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Discharge Weight (gms)</td>
<td>3817.5 (3003 – 4730)</td>
<td>3060 (2440 – 4155)</td>
<td>0.009</td>
</tr>
<tr>
<td>Discharge Head Circumference (cm)</td>
<td>35.5 (34 – 37.5)</td>
<td>34 (30.5 – 37.3)</td>
<td>0.1</td>
</tr>
<tr>
<td>Days on Benzodiazepines (Continuous + Intermittent)</td>
<td>18 (9 – 41)</td>
<td>16 (7 – 31)</td>
<td>0.3</td>
</tr>
<tr>
<td>Days on Opioids (Continuous + Intermittent)</td>
<td>22 (12 – 44)</td>
<td>20 (11 – 35)</td>
<td>0.6</td>
</tr>
<tr>
<td>Cumulative Doses of Fentanyl Drips (Morphine equivalents)</td>
<td>438.5 (223 – 783)</td>
<td>258 (169 – 450)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Cumulative Doses of Midazolam Drips (Lorazepam equivalents)</td>
<td>339 (167-641)</td>
<td>235 (197-426)</td>
<td>0.3</td>
</tr>
<tr>
<td>Days on Ventilator</td>
<td>16.5 (9 – 29.5)</td>
<td>17 (10 – 32)</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Acknowledgements:

• Ting-Yi Lin, MD (NICCU WPP Project Lead)
• Deepti Mathur, MD
• Thomas Chavez, Mstat
• Rachel Portman, MD (NICU Medical Director)
• Philippe Friedlich, MD (Division Chair)
• Lara Nelson, MD (Team Content Expert & Lead)
• Phuong Lieu, PharmD (Pharmacy Project Lead & Content Expert)
• Carol Okuhara, RN, NP
• Nelson Sanchez-Pinto, MD
• Jin Kim, PharmD
• Joyce Koh, MD
• John Rodgers, MD
• AND dozens more individuals. . .

References


References


Inventing a New NICU

Thomas Lee, MD
Vision Center

No Financial Disclosures
Paris World’s Fair

Incubators:

First developed by E.S. Tanier in France in 1880

Modeled after warming chambers in the poultry section of Paris Zoo
New York Worlds Fair (1939-1940)

FIBROBLASTIC OVERGROWTH OF PERSISTENT TUNICA VASCULOSA LENTIS IN INFANTS BORN PREMATURELY*

II. Report of Cases—Clinical Aspects

T. L. TERRY, M.D.
Boston, Mass.
Cryo-ROP Classification:

Zone I:
Twice radius from optic nerve to the fovea (macular involvement)

Zone II:
Nasal involvement to temporal Equator

Zone III:
Residual crescent anterior to Zone II

Cryo-ROP Classification

Stage I:
Demarcation line visible between vascular and avascular retina

Avascular Retina

Demarcation Line

Vascular Retina
Cryo-ROP Classification

Stage II:
Ridge visible between vascular and avascular retina +/- “popcorn”

Stage III:
Ridge with extraretinal fibrovascular proliferation may be present at ridge or just posterior
Cryo-ROP Classification: Stage 3

Cryo-ROP Classification: Stage 3
Laser-ROP
ROP: Unfavorable outcome

![Bar chart showing different treatment outcomes for ROP.](chart.png)

- Untreated
- Cryo
- Laser
- Early Laser

---

![Image of medical professionals attending to a patient](image.png)
Weekly Rounding with Online Mentoring

Rate of Blindness after treatment

- Cryo ROP
- ETROP
- Armenia

4/4/2017
Time Line for MOH ROP Certification

- Lectures
- Pre-test
- Practical
- Remote supervised exams
- Post-test
- Certified

Facebook based diagnostic platform
Las Vegas 2007

Summerlin Hospital  Sunrise Hospital

Valley Hospital  University Medical Center

Telemedicine sites in LA
Doctors Test New Weapon Against Eye Disease

By LAYRA GROGORS

Step 2: In Los Angeles, Lee uses the OCT images to help decide whether patients need surgery — and then cuts away the scar tissue using a special endoscope, an ultrathin probe from New Jersey-based Ende Ophthalmics that lets him see beyond the iris deeper than standard per hour. If your view is not good, it’s like driving in the rain with the windshield wipers off with the same truck in front of you,” Lee said. The question is whether either of the tools helps — by diagnosing babies in trouble sooner or by im.

couldn’t see, said Lee, who presented preliminary data at a recent eye meeting. This scar tissue forms in strands that appear, in Lee’s scans, much like spider silk but pull with remarkable force. Results that doctors thought were lifting each eye.
Telesurgery Mentoring
Validation Study

Figure 5
Pretest and Posttest Results (n=31)
Patient Owned Medical Electronic Record

- Patient ID: #177
- First Name: George
- Last Name: Havens
- Mother's Name: Mary
- Father's Name: John
- Responsible Doctor: Dr. Johnson
- Birth Date: 05/06/2000
- Age: 9 months, 28 days
- Gestational Age: 28
- Weight at Birth: 850
- Blood Type: AB

Medical Card Number: 1242
Number of screenings at registration: 0
Birth Certificate Number: -
Gender: Male

Non-surgical resuscitation was performed with the use of oxygen: Yes
This infant received a blood transfusion: Yes
This infant has received or requires oxygen treatment: Yes
This infant has (or had) a suspicion of retinopathy: No
This infant has (or had) problems with breathing: Yes

Screenings performed:
- Until 04/07/2016 performed total:
  - Screenings: 16 times
  - Eye exams: 1 time
  - UPI: 0 time
  - VEP: 0 time

Until 08/04/2016 performance report:

Legend:
- Green: Passed
- Red: Failed
- Yellow: Deferred
No Margin
No Mission

3rd World

Revenue

Virtuous Circle

Outcome Data

1st World
Is This Child Dysmorphic?

Linda Marie Randolph, M.D.
Children’s Hospital Los Angeles
Division of Medical Genetics
6 April 2017
11th Annual Neonatal Nurses Conference
Disclosure

• I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider of commercial products or services discussed in this CME activity.
• I do not intend to discuss unapproved/investigative use of commercial product(s)/device(s) in my presentation.

Outline

• Dysmorphology: what is it, and why is it important?
• Pathogenetic mechanisms
• Clinical classification of birth defects
• The history: time consuming, but big payoff
• The physical: quantifying findings, paying close attention to details
• Testing
• Case studies
Dysmorphology

- Term coined by David Smith, M.D., in 1960s: “the study of abnormal form”
- R. Winter called it “aspect of clinical genetics concerned with syndrome diagnosis in children who have combination of congenital malformations and unusual facial features, often with delayed motor and cognitive development (Smithson and Winter Br J Dermatol 2004)

Dysmorphology

- Dysmorphology combines concepts, knowledge, and techniques from the fields of embryology, clinical genetics and pediatrics
- “Whenever any physician is confronted by a patient with a birth defect, he or she becomes, for the moment at least, a dysmorphologist (J. Aase 1990)”
Birth defects

- 4% of general liveborn population
- 22,000 babies in California per year
- ¼ of stillborns have major abnormalities
- This 34% accounts for 50% of total hospital charges

Pathogenetic mechanisms

- Deformation
- Disruption
- Dysplasia
- Malformation
Deformation

- Abnormalities produced by aberrant mechanical forces that distort otherwise normal structures
- Usually occur late in gestation
- Causes include uterine abnormality, oligohydramnios
- Most resolve spontaneously or are easier to repair than primary abnormalities
Disruption

- Destruction of previously normal tissue
- Caused by ischemia, hemorrhage, adhesion
Dysplasia

- Abnormal cellular organization or function within specific tissue type throughout body, resulting in structural changes
- Most due to single-gene defect
- Clinical effects continue as long as tissue continues to grow or function
Spondyloepiphyseal dysplasia congenita

Dysplasia
Cranial sutures

Normal Skull of the Newborn

Frontal Bones
Anterior Fontanelle
Sagittal Suture
Parietal Bones
Posterior Fontanelle
Occipital Bone
Lambdoid Suture

Neurofibromatosis 1—another dysplasia
Adults with neurofibromatosis type 1

Malformation

• Abnormalities caused by failure to complete formation of an embryonic process through arrest, delay or misdirection

• Intrinsic, limited to one region; involving organ system; or may produce malformation syndrome

• Suggests error took place early in gestation
Example of malformation

Down syndrome karyotype

47,XX,+21 = trisomy 21
Maternal age and trisomy 21

Clinical classification of birth defects-1

- Single-system—congenital heart defect, cleft lip, clubfoot; often multifactorial with low MZ twin concordance
- Association—several physical features that are associated in nonrandom way but link not strong enough to call a syndrome; finding prompts search for other findings
- Sequence—malformations result of cascade of events, e.g., Potter sequence
Clinical classification of birth defects-2

- Complex—developmental field complex implies insult to geographic part of developing embryo, resulting in abnormalities in adjacent structures that might be of different embryologic origin, e.g., hemifacial microsomia, Poland anomaly
Poland anomaly, aka Poland syndrome

Craniofacial microsomia (Goldenhar)
Clinical classification of birth defects-3

- Syndrome—birth defects occurring in consistent pattern; Greek, “running together”
  - Does not imply cause
  - Relies on ability of clinician to detect and interpret physical and developmental findings and to recognize patterns
  - Thousands of syndromes described

The history

- Get medical records from prenatal care, affected family members
  --Ask age of both parents, general health, outcomes of previous pregnancies
- Impaired fertility, early deaths, consanguinity
- Gestational diabetes?
- Medications, other exposures during pregnancy? Fever, infection? Prenatal diagnosis? Ultrasound findings?
The history

• Fetal growth
• Too much or too little amniotic fluid?
• Fetal movement
• Family history includes asking who is full sibling and who is half-sibling
• Pedigree
• “Is there anything I haven’t asked you that you think might be important?”
• History will be directed also by child’s presentation

The value of the history: Case report 1

• 1-y.o. female in foster care since 4 d. age; DD, low tone, dysmorphic, radial apasia and absent thumb, 1 side
• Mom had been in “institution” but was free to come and go; hx schizophrenia, bipolar d/o
• Foster mom knew no hx but called social worker, who told us of taking valproate for entire pregnancy
The physical exam

- Need to know normal to know abnormal
- Overall appearance and posture
- Measurements and graphs—use the tape measure and tables
- Head to toe, observe each detail
- Look for patterns
- Terminology

Case report 2

- You are asked to evaluate a newborn with an omphalocele
- History: pregnancy notable for polyhydramnios and enlarged placenta in 32-y.o. mom w/ no exposures
Case report 2

- BW 4200 g; microarray normal
- Mom didn’t have gestational diabetes
- Mom and dad weighed <8 lbs at birth
- Baby had hypoglycemia and polycythemia in newborn period—and enlarged tongue

Case report 2

- You note creases in lobules and small dents in backs of pinnae
- You tabulate the findings: large for gestational age, polyhydramnios, macroglossia, creases in lobules, indentations in backs of pinnae, large placenta, omphalocele
- Diagnosis that comes up: Beckwith-Wiedemann syndrome
- Read about it: does it fit?
Beckwith-Wiedemann syndrome

Case report 2

• You decide it fits
• OMIM links to www.GeneReviews.org
• Enter the name of the syndrome in Reviews box to determine whether there is a writeup about disorder
• For Beckwith-Wiedemann, there is—discusses clinical findings, management, diagnosis, differential diagnosis and testing
• Separate location on www.GeneTests.org has lists of labs and types of testing
Case report 2

- You learned from www.GeneTests.org that methylation testing is most likely test to diagnose patient with Beckwith-Wiedemann
- You find labs in the list that offer methylation testing and send specimen to lab you choose
- Result is negative—you go back to www.GeneTests.org and find next test
- Meanwhile, you perform health surveillance measures such as abdominal ultrasound, sleep apnea study, monitor for hemihyperplasia, consider craniofacial consult
- Family evaluated for features and counseled

Case report 3: Subtle features, difficult diagnosis

- Patient has mild intellectual disability, low muscle tone, poor feeding, poor weight gain
- Diagnosed with cardiomyopathy
- Prenatal and family histories negative
- Subtle dysmorphic features
Case report 3

• Chromosome testing might have been done in past: normal results
• Might have had metabolic testing for cardiomyopathy: normal or nonspecific results
• Single nucleotide polymorphism (SNP) chromosomal microarray ordered: patient has chromosome 1p36 deletion, aka monosomy 1p36: 1 in 5000 births
• Microarray tests have increased diagnostic yield to 10-20% of cases with DD/intellectual disability with dysmorphic features

More faces of 1p36 monosomy
SNP arrays

- SNP array is a type of DNA microarray used to detect polymorphisms in a population
- A SNP, a variation at a single site in DNA, is the most frequent type of variation in the genome
- There are about 10 million SNPs in the human genome
- Patient DNA is plated on a “chip”
- Array we use has 2.6 million probes which are automatically applied to search for matches and mismatches in patient DNA
- Results read by computer software showing areas of missing and extra genomic material and areas of loss of heterozygosity

SNP array in cancer specimen

![Tumor: Chronic Lymphocytic Leukemia (CLL)](image)
More on arrays vs. chromosomes

- Arrays detect everything chromosomes do except balanced translocations
- No need to order chromosomes unless suspicion of aneuploidy, for example
- Cost of chromosomes plus fluorescence in situ hybridization is comparable to microarray, and yield is much less
- Interpretation can be challenging in microarray
- Parents/patients should be informed result will be difficult to interpret and could be abnormal but not explain the patient’s presentation
- SNP array also will detect consanguinity, which can uncover a genetic cause

Single-gene disorders

- Mendelian, or single-gene, disorders aren’t usually detected by microarray unless the mutation in the gene is a duplication or deletion large enough for the microarray to detect it
- Decision as to whether to order microarray or a specific genetic test or panel of tests depends upon certainty of diagnosis, other factors
- Insurance companies do not like “panels,” so when possible we arrange reflex testing by tiers of likelihood of finding a mutation in a given gene
Whole exome sequencing

- Exons make up one percent of the genome
- These are areas where 85% of our genetic disorders are
- Whole exome sequencing sequences exons and omits introns

When the patient and parents—a trio—are sequenced in this way, the detection rate of making a diagnosis ranges from 25-40%, depending upon the lab and patient’s clinical picture

- Test is ideally reserved for those patients who have had a thorough evaluation using more conventional genetic testing, given the high price tag and difficulty analyzing huge quantities of data, but increasingly doctors are using this test earlier in process
- Informed consent by a genetic counselor is important, as genetic information that was unanticipated can be uncovered, such as a BRCA1 mutation or high risk for cardiomyopathy
Trial and error—and patience

- Sometimes a diagnosis is not reached
- Faces change over time, and new clinical findings can add to “search terms” that allow for a diagnosis
- Better not to assign a diagnosis one is unsure about
- Worthwhile to follow a patient over time and with reassessment there is opportunity to establish diagnosis—sometimes with aid of new gene discovery
- Diagnosis gives the family the information it has lacked—and tools for understanding the patient, better healthcare

References

- Jones, K.L. *Smith’s Recognizable Patterns of Human Malformation*, now in 7th ed.
Brain Injury
Current Thoughts & Controversies

Sharon Fichera RN, MSN, CNS, NNP-BC
Clinical Manager/Clinical Nurse Specialist
Newborn & Infant Critical Unit
Children’s Hospital Los Angeles

Objectives

To review the current thoughts & controversies surrounding brain injury in the newborn,:

* PIVH
* PVL
* HIE
Periventricular/Intraventricular Hemorrhage

• Primary lesion is bleeding from small vessels in the supependymal germinal matrix
  1970’s incidence was as much as 50%

• Incidence
  – 751 to 1000 grams 12%
  – 501 to 750 grams 26%

Brain anatomy
Papile’s Grading system

- Grade I – confined to the germinal matrix
- Grade II-III – extends and ruptures into the adjacent ventricular system
- Grade IV – intraparenchymal hemorrhage within the periventricular white matter
Grade I Periventricular Hemorrhage (PVH) Subependymal Germinal Matrix Hemorrhage

- Subependymal is a region that lies just under the wall of the lateral ventricle.
- The germinal matrix supports the division of glioblasts and differentiation of glial elements. This highly metabolic area is fragile network of capillaries.
- This is where the hemorrhage occurs.

Grade II PVH

- Grade II - Subependymal hemorrhage with extension into lateral ventricles without ventricular enlargement, as shown below.
Grade III PVH

- Grade III - Subependymal hemorrhage with extension into lateral ventricles with ventricular enlargement.

Periventricular Hemorrhagic Infarction (PVHI)
Old Grade IV IVH

- Periventricular Hemorrhagic Infarction (PVHI) previously classified as grade IV IVH
- Compression of the terminal vein by the GMH which can impair venous drainage causing congestion and lead to a hypoxic ischemic event in the periventricular white matter.
- GMH & PVL occur together 75% of the time
PVHI
mechanisms of vulnerability

- Vascular anatomic immaturity
- Hemodynamic factors
- Inflammatory mediators

Vascular Anatomic Features

- Venous drainage is through the terminal vein, which empties into the internal cerebral vein; this in turn empties into the vein of Galen. Blood flow changes from an anterior direction to a posterior direction from the terminal vein to the internal cerebral vein causing
  - Venous congestion
  - These are fragile thin walled, immature vessels prone to rupture

Figure 4: The principle cerebral venous vessels and sinuses.
Hemodynamic Factors
Passive cerebral pressure autoregulation

- Increases in CBF
  - Hypertension
  - Rapid volume expansion
  - Pressor treatment
  - Hypercarbia,
- Decreases in CBF
  - Hypotension
  - Hypocapnia
- Elevated Cerebral Venous pressure
  - Positive pressure ventilation
- Fluctuating CBF
  - unsynchronus ventilation

Cytokines & Inflammatory Mediators

- Many studies have suggested an association between cytokines, inflammatory mediators and the development of PIVH
Can we prevent Brain injury?

- Antenatal corticosteroids
- Magnesium
- Paralytics - NAVA?
- Indomethicin
- EPO

Epo as a Neuroprotective Agent

- We have been using Epo since 1991
- May be used in conjunction with cooling
- Or alone for the ELGANs

- May have some neuroprotective effects
Neuroprotective?

- PENUT trial
  - In the ELGAN population
- HEAL trial
  - Utilizing high dose EPO

Neuroprotective

- Anti
  - Apoptotic
  - Inflammatory
  - Excitotoxic
  - oxidant
- Protective
  - Oligodendrocyte
  - neurogenic

Promotes: neurogenesis and angiogenesis
Periventricular Leukomalacia
PVL
• Periventricular - area the area of the ventricles of the brain
• Leuko - white matter of the brain, motor cortex pathways
• Malacia - injury
• AKA - White Matter Necrosis
• Ischemic brain injury found in premature infants

PVL
• Coagulation necrosis in the cerebral white matter
• Microglial infiltration
• Astrocytic proliferation and repair
• Cyst formation - scarring
Pathways of White Matter Injury

Ischemia

Glutamate

Reperfusion

Cytokine release → Oligodendroglial Cell death ← Free radical formation

PVL Vascular Factors

- Watershed or Border zones
- Increased risk of ischemia due to loss of CBF autoregulation with the sick preemie
- Limited ability of the vessels to dilate after ischemic injury during the reperfusion phase
PVL Damage to Oligodendrocytes

• Free radical injury
  – Ischemic injury to the periventricular white matter releases free radicals that lead to cell death apoptosis of the oligodendrocytes

• Cytokines
  – Ischemia/reperfusion activates microglia, releases cytokines and other inflammatory mediators - toxic to oligodendrocytes

PVL & GMH

• The bleeding into the periventricular white matter results in a coagulation necrosis, resulting in death of the tissues responsible for manufacturing myelin
Periventricular Leukomalacia White Matter Necrosis

- A hypoxic ischemic insult to the periventricular region of the preemies brain (watershed/boarder zone)
  
  *Motor cortex pathways = Cerebral Palsy*

- PVL = HIE in a preemie

Hypoxic Ischemic Encephalopathy (HIE)

- If a hypoxic ischemic injury is severe enough to injury the brain, within 12 to 36 hours it leads to neonatal encephalopathy known as

  *Hypoxic Ischemic Encephalopathy
  HIE*
**Hypoxic Ischemic Encephalopathy (HIE)**

<table>
<thead>
<tr>
<th>Hypoxia</th>
<th>Ischemia</th>
<th>Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Oxygen</td>
<td>Decreased perfusion</td>
<td>Brain injury</td>
</tr>
</tbody>
</table>

**Asphyxia**
- Hypoxemia
- Hypercapnia
- Acidosis
Asphyxia - Incidence

- Antepartum: 20%
- Intrapartum: 30%
- Ante/intrapartum: 35%
- Postpartum: 10%
- Unknown: 5%

HIE
HIE

- Not a single event but a progressive injury/lesion
- Necrosis may occur then followed by apoptosis later

Therapeutic Hypothermia

- FDA approved devices
- Indications for use for newborns with moderate to severe HIE
  - A. 36 weeks or > with one of the following
    - Apgar score of 5 or less at 10 minutes
    - Continued need for resuscitation at 10 minutes
    - Within 60 minutes of life a pH < 7
    - Within 60 minutes of life a Base Deficit > 16
HIE

Head Cooling
Total Body Cooling

aEEG Cerebral Function Monitoring
NIRS

Areas for further research
References


McPherson RJ, Juul SE. Recent trends in erythropoietin-mediated neuroprotection. Int J Dev Neurosci. 2008;26:103-111. The historical evidence for Epo-mediated neuroprotection, and the rationale for using Epo to treat perinatal asphyxia are reviewed. [PMC free article] [PubMed]

PDA:
Controversies & Treatment Options in 2017

Shahab Noori, MD, MS CBTI
Associate Professor of Pediatrics
Division of Neonatology

PDA Dilemma
Case

- 24 week premie born via c-sec, good Apgar
- On conventional ventilator post-surfactant
- Hypotensive by end of first day
- On dopamine 15 mcg/kg/min, weaned off after hydrocortisone
Controversy ....

- Patency of the ductus arteriosus in the premature infants: is it pathologic? Should it be treated? (Laughon, Simmons, Bose. Curr Opin Pediatr 2004)
- Treatment to prevent patency of the ductus arteriosus: beneficial or harmful? (Bose and Laughon. J Pediatr 2006)
- Patent ductus arteriosus: lack of evidence for common treatments (Bose and Laughon. Arch Dis Child 2007)
- Evidence for active closure of patent ductus arteriosus in very preterm infants (Knight & Laughon. J Pediatr 2008)
- Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? (Benitz. J Perinatol 2010)
- Patent ductus arteriosus in the preterm infant: to treat or not to treat? (Noori. J Perinatol 2010)
- Preterm patent ductus arteriosus: Should we treat it? (Evans. J Paediatr & Child Health 2012)

Reasons for Controversy

- Little evidence from RCT
- Failure of prophylactic indomethacin to improve neurodevelopmental outcome
- Side effects of medication
- High incidence of spontaneous closure

We need to be selective in deciding which PDA deserves treatment
Defining hemodynamically significant PDA:

Vulnerability: gestational age

Functional Closure of DA is Impaired in Extremely Preterm Infants

- Thin muscular layer in DA (poor intrinsic tone)\(^1\)
- Balance of vasoconstrictors and dilators favors patency\(^1,2\)
- Low O\(_2\) saturation target may favor patency\(^3\)

\[^{1}\text{Hermes-DeSantis & Clyman. J Perinatol. 2006; 26:S14-8}\]
\[^{2}\text{Hamrick & Hansmann. Pediatrics 2010; 125:1020-30}\]
\[^{3}\text{Noori et al. J Perinatol. 2009; 29:553–557}\]
Anatomical Closure of DA is Impaired in Extremely Preterm Infants

Inability to induce profound hypoxia in muscle media (trigger for remodeling)
- Underdeveloped vasa vasorum
- Thin-walled DA

Time of Spontaneous Closure of DA in ELBW infants

42 (34%) of studied subjects permanently closed their PDA
Excluding babies with a BW<500g and GA ≤24 (n=33), death <36 hr (n=8), death within 10 days (n=10) and others.

Mean GA:
Spontaneous closure 27 wk
No spontaneous closure 25.6 w

Koch et al. Pediatrics 2006;117:1113-21
In addition to higher vulnerability, we need to consider 23, 24 and 25 weeker to be at greatest risk for failure of spontaneous closure and have lower threshold to treat.

73% of survivors past 72 hours with PDA closed their ductus spontaneously

Rolland et al. Arch Dis Child 2015

In addition to higher vulnerability, we need to consider 23, 24 and 25 weeker to be at greatest risk for failure of spontaneous closure and have lower threshold to treat.
Defining hemodynamically significant PDA:

Vulnerability: chronological age

Case

A 24 wk premie has normal BP and CRT and acceptable acid-base balance on a ventilator at about 12h after birth. PDA is 3 mm with almost completely L-R shunt.

Do you treat the PDA?
Middle Cerebral Artery Flow Doppler

Case 1
MV 7.05 cm/s

Normal
MV 12.7 cm/s

Do you treat the PDA?

Organ Vulnerability Varies Depending on Chronological Age

<table>
<thead>
<tr>
<th>IVH</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Days - Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary Hemorrhage</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What Determine the Degree of Symptomatology of PDA?

- Size and direction of shunt
- Duration of patency of ductus arteriosus
- Extent of steal phenomena
- Adequacy of compensatory mechanisms

Echocardiographic Indicators of hsPDA

- Shunt size
  - Diameter
  - Flow pattern

- Volume overload
  - LA/Ao
  - LVO
  - LPA

- Pulmonary overflow

- Systemic hypoperfusion
  - Desc aorta flow
  - Organ flow
Echocardiographic Assessment of Hemodynamic significance

Ductal View

- Pulmonary artery
- Right Pulm. artery
- Left Pulm. artery
- Desc. Aorta
- PDA
Echocardiographic Assessment of Hemodynamic significance

Estimating Ductal Diameter

PDA Flow Pattern

Growing
Pulsatile
Closing

Associated with hsPDA

Pulmonary hypertension

Su et al. Archives of Disease in Childhood 1997;77:F36–F40
• LA/Ao ratio may be normal in the presence of large hsPDA if there is a large PFO.

Left Pulmonary Artery Doppler

- 34 wk  no PDA at 4 day
- 33 wk  large bidirectional PDA at 2 h
- 33 wk  small L-R PDA at 18 h
- 24 wk  large L-R PDA at 21 day

End diastolic velocity > 20 cm/s associated with hsPDA
Renal Artery

Normal

Abnormal
Conservative Management

- Impact of no treatment not fully known
- Medication less effective
- Little data on increasing PEEP and Fluid restriction
- Increased mortality
Effect of PEEP on PDA shunt flow

- n=16
- Median GA 26 weeks (range 23-30)
- Age 6 days (2-71).
- Baseline PEEP= 5 cmH₂O changed to 2 and 8.

PEEP 8: median LVO/SVC and LVO ↓ by ~13% and ~8%, respectively.
Decrease in PDA shunt vs. reduction in venous return.
No change in cerebral oxygenation, SPO₂ and FiO₂


Fluid Restriction in Preterm Infants with PDA

- No effect on PDA or respiratory parameters
- Evidence of decrease systemic flow

n=18, 24-31 wk (mean 24.8), >10 days old, failed 2 courses of ibuprofen, from 145±15 to 108±10.

Increased Mortality Rate in VLBW infant ≤ 29 wk with Persistent vs. Closed Ductus

8-fold increase in mortality if ductus remained open*

* adjusted for initial disease severity, perinatal factors and pathologies associated with death


Table 1: Increased outcomes characteristics of neonates born between 26 and 28 weeks' GA with PDA and without PDA

<table>
<thead>
<tr>
<th></th>
<th>PDA</th>
<th>Without PDA</th>
<th>p &lt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>46</td>
<td>51</td>
<td>NS</td>
</tr>
<tr>
<td>Birthweight, g (mean ± SD)</td>
<td>980 ± 204</td>
<td>1090 ± 214</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Head circumference (cm, mean ± SD)</td>
<td>35 ± 2</td>
<td>36 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GA, weeks (mean ± SD)</td>
<td>27 ± 2</td>
<td>28 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC, 10³/μl (mean ± SD)</td>
<td>10 ± 3</td>
<td>9 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Inborn, %</td>
<td>79</td>
<td>91</td>
<td>NS</td>
</tr>
<tr>
<td>Antenatal steroids, %</td>
<td>67</td>
<td>78</td>
<td>NS</td>
</tr>
<tr>
<td>Full antenatal steroids, %</td>
<td>30</td>
<td>32</td>
<td>0.006</td>
</tr>
<tr>
<td>Parental optician, %</td>
<td>24</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>Early-onset infection, %</td>
<td>23</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Cesarean section, %</td>
<td>32</td>
<td>37</td>
<td>NS</td>
</tr>
<tr>
<td>Day 1–day 2 fluid balance, ml/kg (mean ± SD)</td>
<td>101 ± 19</td>
<td>101 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>Day 3–day 10 fluid balance, ml/kg (mean ± SD)</td>
<td>133 ± 29</td>
<td>156 ± 33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>21</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Sepsis, %</td>
<td>0.2</td>
<td>44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of intubation, median (range)</td>
<td>10 (5–71)</td>
<td>6 (8–40)</td>
<td>NS</td>
</tr>
<tr>
<td>Steroid pretreatment, %</td>
<td>47</td>
<td>16</td>
<td>0.01</td>
</tr>
<tr>
<td>Postnatal steroids, %</td>
<td>49</td>
<td>23</td>
<td>0.02</td>
</tr>
<tr>
<td>Necrotizing enterocolitis stage III-IV, %</td>
<td>12</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Intraventricular hemorrhage grade II, %</td>
<td>28</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Intraventricular hemorrhage grade III–IV, %</td>
<td>10</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Parenteral nutrition, %</td>
<td>6</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Luminous lesions, %</td>
<td>48</td>
<td>49</td>
<td>NS</td>
</tr>
<tr>
<td>Fetal distress scoring, %</td>
<td>15</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Intubation, %</td>
<td>38</td>
<td>16</td>
<td>0.07</td>
</tr>
<tr>
<td>Gestation, weeks (range)</td>
<td>31 (1–30)</td>
<td>34 (28–39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day of oral feeding, mean ± SD</td>
<td>7 ± 2</td>
<td>10 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight at 36 weeks, g, mean ± SD</td>
<td>1060 ± 325</td>
<td>1972 ± 596</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CA = gestational age; PDA = patent ductus arteriosus; PAP = postnatal age; NS = non-significant; PA = postarterial age. The units for GA are completed weeks.

Authors' CONCLUSION:
This study adds further evidence that persistent patent ductus arteriosus has no significant effect on mortality and morbidity in VLBW infants born at ≥ 25 weeks' gestational age.

Mortality 21% vs. 9% p=NS

Mortality 21% vs. 9% p=0.05

Pharmacological Treatment
### COX Inhibitor Treatment Strategies

<table>
<thead>
<tr>
<th>Stage of Symptomatology</th>
<th>Closure of PDA</th>
<th>LVH &amp; Pulm. Hem</th>
<th>Ligation</th>
<th>Unnecessary Rx</th>
<th>Risk of NEC</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis (first 12-24 hour)</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-symptomatic (echo-based)</td>
<td>++++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early symptomatic (hemodynamic symptoms)</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late symptomatic (early signs of organ failure)</td>
<td>+++</td>
<td></td>
<td></td>
<td>?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very late (heart failure)</td>
<td>++</td>
<td></td>
<td></td>
<td>++</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

**Phospholipids**

- Ibuprofen
- Indomethacin
- Acetaminophen

**Arachidonic Acid**

- COX
- PGG₂
- PGH₂

**PGH₂ Complex**

- PGE₂
- PG₁₂
- TXA₂

**Allegaert 2013**
## Indomethacin vs. Ibuprofen vs. Acetaminophen

<table>
<thead>
<tr>
<th></th>
<th>Indomethacin</th>
<th>Ibuprofen</th>
<th>Paracetamol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective in closing PDA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes?</td>
</tr>
<tr>
<td>Decrease risk of IVH*</td>
<td>Yes</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td>Improve long-term outcome</td>
<td>No?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Decrease risk of NEC</td>
<td>No</td>
<td>Yes?</td>
<td>?</td>
</tr>
<tr>
<td>Increase risk of Pulmonary hypertension*</td>
<td>No</td>
<td>Yes?</td>
<td>?</td>
</tr>
<tr>
<td>Transient renal side effect</td>
<td>++++</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Displace bilirubin from albumin</td>
<td>+</td>
<td>+++</td>
<td>?</td>
</tr>
</tbody>
</table>

* When given as prophylaxis

**Ligation**
Immediate Deleterious Effects of Surgical Closure

• Major complication (rare)
• Vocal cord paralysis (5.2 - 67%)\textsuperscript{1,2}
• Hypotension (10-30%)\textsuperscript{3-5}
• Myocardial dysfunction\textsuperscript{4-6}
• Respiratory deterioration\textsuperscript{7}


Myocardial Dysfunction after PDA Ligation

Pre-Ligation

Post-Ligation
Possible Causes of Hemodynamic Instability after Ligation

- Decrease LVO (≠ more than expected from decrease in preload)
- Subtle deterioration in myocardial function (worsening MPI)
- Likely other mechanisms also involved (e.g. vasodilatation) ? Adrenal insufficiency
Change in Hemodynamic Parameters at 8 hours Post-ligation

- Significant increase in the incidence of “decreased LV performance”
  Defined as either:
  a) left ventricular output <170 ml/kg/min
  b) fractional shortening <25%
  c) systolic blood pressure less than 3rd percentile


Hypotension Following PDA Ligation: the Role of Adrenal Hormones

- Prospective
- n=95
- mean GA ~ 26 weeks
- 45% hypotension
- 15% catecholamine-resistant hypotension

- Compared to normotension, post-op cortisol level higher in mild-moderate but lower in catecholamine-resistant hypotension
- No increase in cortisol precursors (inadequate adrenal stimulation)
- Neither baseline nor post-stimulation cortisol prior to ligation were predictive catecholamine-resistant hypotension

Catecholamine-resistant Hypotension and Myocardial Performance Following PDA Ligation
(prospective, n=45, mean GA 25.5 weeks)

<table>
<thead>
<tr>
<th>Part A</th>
<th>Part B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normotension</strong></td>
<td><strong>Hypotension</strong></td>
</tr>
<tr>
<td>No Hypotension (n=27)</td>
<td>Hypotension (all types) (n=18)</td>
</tr>
<tr>
<td>LVO (mL/kg/min)</td>
<td>240±58</td>
</tr>
<tr>
<td>LVO &lt; 150 mL/kg/min (%)</td>
<td>8</td>
</tr>
<tr>
<td>Shortening fraction ≤25% (%)</td>
<td>15</td>
</tr>
<tr>
<td>MPI</td>
<td>0.42±0.12</td>
</tr>
<tr>
<td>NP&lt;2 (%)</td>
<td>11</td>
</tr>
<tr>
<td>UKEDD (cm kg⁻¹)</td>
<td>1.32±0.37</td>
</tr>
<tr>
<td>LA/AVO</td>
<td>1.31±0.34</td>
</tr>
<tr>
<td>SVR (mm Hg L⁻¹ kg⁻¹ min⁻¹)</td>
<td>167±74</td>
</tr>
<tr>
<td>Mean rate (beats/min⁻¹)</td>
<td>155±13</td>
</tr>
<tr>
<td>Stroke volume (mL/kg⁻¹)</td>
<td>1.36±0.42</td>
</tr>
<tr>
<td>VO₂/c (mm Hg·L⁻¹·s⁻¹)</td>
<td>1.24±0.20</td>
</tr>
<tr>
<td>Wall stress (g cm⁻²)</td>
<td>31±19</td>
</tr>
<tr>
<td>Cortisol (ng/mL) median (interquartile range)</td>
<td>24 (10-54)</td>
</tr>
</tbody>
</table>

Catecholamine-resistant hypotension:

- No association with decreased preload, shortening fraction or ventricular output.
- Lower SVR and postoperative cortisol level


Ligation and Long-term Outcome

Poor neurodevelopment:

- Association rather than cause-and-effect
- Possible causes:
  - Adverse hemodynamic effects of long standing ductal shunting
  - Disease severity or same underlying pathology causing both patency of the ductus and poor outcome

Bronchopulmonary dysplasia:

- Possible cause-and-effect
  - 2 fold increase

Noori S. Pros and Cons of PDA Ligation. Semin Perinatol 2012
Device Closures

Weight: >1.5 – 2 kg
PDA size and shape
GA: ??
Heparin
Device complications: blocking LPA or aorta

Amplatzer Vascular Plug II
Amplatzer Vascular Plug IV

Amplatzer Vascular Plug IV Occlusion Device

Summary (1)

• Controversy over management of PDA should not result in dismissal of its adverse hemodynamic effect

• Full impact of conservative management on outcome is unknown; concerns regarding increased mortality and morbidity remain.

• Treatment should be individualized based on the vulnerability of the given patient and population

Summary (2)

• Hemodynamic significance of PDA should be interpreted by considering gestational and chronological age, vulnerability of organs at risk for overflow (lung) and hypoperfusion (brain, guts, kidneys)

• Assessment of multiple echocardiographic indices with organ blood flow Doppler are helpful in evaluating hemodynamic significance of PDA

• Tylenol and device closure should be considered before PDA ligation
Overview

- Congenital Bowel Obstruction
- Acquired Bowel Obstruction
Congenital Bowel Obstruction

- Malrotation
- Hirschsprung’s Disease
- Imperforate Anus
- Hernias
  - Inguinal
  - Umbilical
  - Meconium ileus

Acquired Bowel Obstruction

- Adhesions
- Pyloric Stenosis
- Intussusception
- Hernias - Incisional
- Hernias – Internal
- Constipation/Obstipation
Intestinal atresia

- Incidence
  - Duodenal: 1:2500 live births
  - Jejuno-ileal: 1:1000 live births
  - Others: pyloric, colonic

- Presentation
  - Bilious emesis within 24 hours
  - Abdominal distention
  - May or may not pass stool

- Workup
  - KUB
  - Contrast enema
  - ? UGI study

Atresia

- Initial Management
  - NGT, IVF

- Operative

- Concerns
  - Multiple atresias
  - Anastomotic stricture
  - Proximal limb stasis
Tracheo-esophageal fistula / esophageal atresia

- Pre-op – workup and evaluation
  - Radiograph
  - Echocardiogram
  - Side of arch
  - Renal USG
  - Anorectal evaluation
  - Genetic
- Pre-op stability
  - Respiratory
  - Abdominal

**Fig. 1**

<table>
<thead>
<tr>
<th></th>
<th>a.</th>
<th>b.</th>
<th>c.</th>
<th>d.</th>
<th>e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Literature</td>
<td>6%</td>
<td>1%</td>
<td>80%</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Mammotoh</td>
<td>20%</td>
<td>1%</td>
<td>70%</td>
<td>1%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**TEF**

- Bronchoscopy
  - Location of fistula
- Intubation
  - Placement of ETT
- OGT/NGT placement
TEF

- Intra-op considerations
  - Ventilation pressures
  - Fistula management
    - ETT placement
    - Fogarty
    - G-tube placement
    - Needle decompression
  - OGT – NG feeding tube conversion
- Post-op issues
  - NGT – critical tube
  - ETT – ventilation, handbagging
  - Re-intubation
- Anesthesia
  - Epidural?
  - Post-op extubation?

Malrotation

- Incidence
  - Autopsy: 0.5-1% of total population
  - With clinical symptoms: 1:6000 to 25,000
  - Presentation: BILIOUS EMESIS
    - 50-75% symptomatic in first month of life
    - 90% symptomatic before 1 year of age
- Diagnosis
  - KUB: NO!!!!
  - BE: not reliable
  - UGI - NOW!
Malrotation

- Treatment
- Emergent operative repair: Ladd's Procedure

- Post-op concerns
- Prolonged ileus

- Long term concerns
- Can still have midgut volvulus after Ladd's procedure!!

Hirschsprung's Disease

- Incidence
  - 1:5000 newborns
  - 70-80% male

- Presentation
  - No stool in first 48 hours of life
  - Abdominal Distention
  - Enterocolitis, sepsis

- Workup
  - KUB - consistent with distal bowel obstruction
  - Contrast enema - transition point
  - Bedside suction rectal biopsy
  - Ganglia, ACE
Hirschsprung’s Disease

- Treatment
  - Irrigation
  - Leveling colostomy
  - Primary pullthrough
  - Laparoscopic biopsy

- Long term concerns
  - Constipation
  - Enterocolitis

Imperforate Anus

- Incidence
  - 1:4000 to 5000 newborns

- Presentation
  - Spectrum of disease
  - Anterior displaced anus
  - Boys: urethral fistula
  - Girls: vestibular fistula

- Workup
  - Physical examination
**Imperforate anus**

- **Treatment**
  - Dilation vs. Operative repair (immediate vs. delayed)
  - Colostomy and mucous fistula creation for high fistula/cloaca
- **Long term concerns**
  - Constipation
  - Stricture

**Hernias - Umbilical/Inguinal**

- **Incidence:**
  - Umbilical - true incidence unknown since many resolve spontaneously (race, prematurity)
  - Inguinal - Approximately 1-5%, M:F (8:1-10:1), prematurity
- **Presentation**
  - Vomiting
  - Hard, firm, tender lump in groin
  - Distended abdomen
Hernias

- **Diagnosis**
  - Physical exam, KUB, USG

- **Treatment**
  - Immediate reduction
  - Timing of operative repair

- **Concerns**
  - Recurrence

Acquired Bowel Obstruction
Adhesions

- Presentation
  - History of previous abdominal surgery
  - History of NEC
  - Vomiting
  - No BM

- Diagnosis: KUB, CT Scan

---

Adhesions

- Treatment
  - NGT
  - NPO
  - IVF
  - Serial exams
  - Serial KUB
  - Exploratory laparotomy if conservative management fails

- Concerns
  - Recurrence
Pyloric stenosis

- Incidence
  - 1-3:1000 births
  - 4:1 (M:F)
  - More common in Caucasians, rare in Asians
  - Erythromycin

- Presentation
  - 3-8 weeks of age
  - Non-bilious, non-bloody, projectile emesis

- Diagnosis
  - Physical exam
  - USG (>3mm thick and 14mm long – think pi)
  - UGI
  - Electrolytes (low Cl, high HCO3, low K)
  - Paradoxical aciduria

Pyloric Stenosis

- Treatment
  - IVF
  - Normal saline bolus (20 cc/kg)
  - ½ normal saline maintenance
  - Never ¼ saline
  - Pyloromyotomy

- Concerns
  - Correct electrolytes (Cl >100, CO2 <30)
Necrotizing Enterocolitis

- Diffuse infectious process of the intestine
- Unclear etiology
  - Formula feeds
  - Prematurity
  - NSAIDS (Indocin)
  - Steroids
- Presentation
  - Bloody stool, bloody emesis (NGT)
  - Abdominal distention
  - Sepsis / instability

NEC

- Acute disease
  - Perforation
  - Non-perforated disease
- Chronic
  - Stricture, bowel obstruction
  - Feeding intolerance
- Workup
  - KUB
  - Contrast studies
    - Contrast enema
    - UGI with SBFT
Baby with Bowel Obstruction

- Stop feeds
- Exam
- Plain films of the abdomen
  - Two views
- Gastric decompression
  - Biggest tube possible
  - OG vs NG

- Etiology of obstruction
  - Additional studies

- Operation
  - Stability of child
  - Suspected diagnosis