Intraventricular Hemorrhage Prevention in Neonates

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OBJECTIVES

• Learners will be able to identify at least 3 structures in the anatomy of the neonatal brain

• Learners will be able to list the criteria for intraventricular hemorrhage grading, noting the difference between Volpe and Papile grading systems

• Learners will be able to identify at least 3 bedside practices in intraventricular hemorrhage prevention in neonates

• Learners will be able to identify at least 1 area of future research
What is IVH?  

GRADING PAPILE VS VOLPE

<table>
<thead>
<tr>
<th>GRADE</th>
<th>Papile Grading system</th>
<th>Volpe Grading system</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Subependymal hemorrhage w/ minimal or no IVH</td>
<td>Germinal Matrix</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemorrhage &lt; 10% IVH</td>
</tr>
<tr>
<td>2</td>
<td>IVH without Ventricular dilatation</td>
<td>IVH 10-50%</td>
</tr>
<tr>
<td>3</td>
<td>Enlargement of the ventricles secondary to distension with blood</td>
<td>IVH &gt;50% with lateral ventricle dilatation</td>
</tr>
<tr>
<td>4</td>
<td>Extension of hemorrhage into the parenchyma along with IVH and enlargement</td>
<td></td>
</tr>
</tbody>
</table>

There is no Grade 4 in Volpe classification.
Normal CT Scan
CT Scan Intraventricular Hemorrhage

Grade I

Grade II

Grade III

Grade IV
Just How Big is this Problem?
Prevalence of IVH in VLBWs

• Intraventricular hemorrhage (IVH): The most common CNS complication of preterm birth

• Despite advances in neonatal intensive care, the incidence of Gr 3-4 IVH has changed little over the past 2 decades (Stoll, 2010) [NICHD Neonatal Research Network]

• IVH occurs in 25-30% of VLBWs (Bruschetti et al., 2016 [Cochrane Neonatal Group]; Christian et al., 2016)

• Nationally, ~15% of all VLBWs have Gr 3-4 IVH (Aden, 2013)
Incidence & Prevalence of Sequela

• > 3600 new cases/yr of significant cognitive impairment are former preterm infants w/ IVH
  [US Census Bureau & NICHD Neonatal Research Network]

• 50-75% of IVH survivors develop cognitive Impairment, cerebral palsy, &/or hydrocephalus (Aden, 2013; Ballahb, 2014)

• ~25% of nondisabled survivors develop psychiatric disorders & problems with executive function (Ballahb, 2014)
Outcomes based on Volpe Grading

- Small hemorrhage (Grade 1):
  - Major neurodevelopmental disability 10%

- Moderate hemorrhage (Grade 2):
  - Major neurodevelopmental disability 40%,
  - Mortality rate 10%

- Severe hemorrhage (Grade 3):
  - Major neurodevelopmental disability 80%
  - Mortality rate 50%
  - Hydrocephalus common in survivors

Adcock, 2016
Trends in hospitalization of preemies with IVH & hydrocephalus in the US, 2000-2010

**Objective:** Describe current trends in hospitalization of infants with post-hemorrhagic hydrocephalus (PHH)

[used Nationwide Inpatient Sample (NIS) and Kids’ Inpatient Database (KID)]

- n=147,823 infants w/ IVH
  - Gr 1 (1%), Gr 2 (4%), Gr 3 (25%) & Gr 4 (28%)

- 38% of PHH required permanent VP-shunts

- 9% = hydrocephalus (~ 13,000 infants)

- Mortality (during birth hospitalization):
  - Gr 1 (4%), Gr 2 (10%), Gr 3 (18%), & Gr 4 (40%)

Christian et al., 2016
Trends in hospitalization of preterm infants with IVH & hydrocephalus in the US, 2000-2010

• Findings:
  LOS & adjusted inpatient cost trending up:
  • IVH: 49 days & $201,578 in 2000 -> 56 days & $353,554 in 2010
    15 day average ↑ & > $150,000 ↑
  • PHH: 59 days & $260,077 in 2000 -> 70 days & $495,697 in 2010
    11 day average ↑ & > $230,000 ↑

• Conclusion:
  • IVH rates ↑ despite preterm birth rate ↓
  • Severity of sequela correlated w/ IVH grade
  • Incidence of PHH in preterm has remained stable at 8-10%
  • Hospital cost has progressively increased

Christian et al., 2016
Timing of Onset

• 50% occur by 24 hours of life

• 80% occur by 48 hours of life

• 90% occur by 72 hours of life

• By 7 days of life, 99.5% have occurred

• 20-40% have hemorrhage progression over 3 to 5 days

Verklan & Walden, 2015
A Preemie Problem

• IVH is uncommon in term infants

• Why?
  • The germinal matrix begins to involute after 34 wks postconceptional age -> vulnerability decreases, but not totally eliminated
  • By 36 wks gestation, the germinal matrix has involuted in most infants (some residual may persist)

Adcock, 2013
Let’s meet a preemie at risk for IVH

Alphabet-Aden’s mother:
29 y.o. G1 P0, negative serologies, unknown GBS

- Black, single, late to prenatal care, high school grad, working at Walmart when premature (24 3/7wk) spontaneous onset of labor & vaginal bleeding

- Presented to small community hospital single dose of celestone 20 min PTD

- Fetal jeopardy = double footling breech & decels

Unable to place epidural -> general anesthesia -> STAT C section w/ difficult extraction
• Alphabet-Aden emerged pale, limp, w/out resp effort -> “hot potato hand-off” -> PPV x 15 min up to 100% O2-> intubated on 3rd attempt

• Apgars 2-4- 6. Wt 750g
  Venous cord gas 7.2/-10
  Arterial cord gas 7.01/-14

• Emergent low lying UVC for saline bolus

• Curosurf @ 45 min w/ transport team

• UAC & central UVC placed

• In ambulance hypotensive -> NS bolus #2 & dopamine. Legs so ecchymotic unable to evaluate perfusion of toes, but needed continuous BP monitoring...
The 1\textsuperscript{st} 48 hrs...

Exam remarkable for left eye fused, Coarse breath sounds bilaterally, Grade II/VI systolic murmur, Pulses +1 of 4 x 4, significant edema & bruising of legs

- Non-shifted CBC but Hct 33.7 & platelet ct 138K -> Transfused PRBC 15 ml/kg -> Hct 40
- DOL-2 platelet ct declined to 87K, coagulopathy -> pulmonary hemorrhage -> HFOV
- FFP 10ml/kg, Platelet transfusion 10ml/kg, PRBC 15 ml/kg, & 2\textsuperscript{nd} Curosurf
- Cranial ultrasound: bilateral Grade 4 IVH
- Placenta pathology + chorioamnionitis

Extension of hemorrhage into the parenchyma along with IVH and enlargement
Maternal Race, Demography, and Health Care Disparities Impact Risk for Intraventricular Hemorrhage in Preterm Neonates

- **Objectives**: Determine if risk factors associated with grade 2-4 IVH differ between African ancestry and white infants

- Intervention group (n=579): Inborn, AGA infants w/ BWt 500-1250 g, at least 1 dose of antenatal steroids enrolled in 24 NICUs

- Control group (n=532): Controls matched to cases for site, race, BWt range & had 2 normal ultrasounds read centrally

- **Conclusion**: Risk for IVH differs between African ancestry and white infants, possibly attributable to both race and health care disparities

  Shankaran et al., 2014
### Decreased Risk for IVH (all)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Significance (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing gestational age</td>
<td>.01</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Complete antenatal steroid exposure</td>
<td>.02</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White race</td>
<td>.01</td>
</tr>
</tbody>
</table>

Shankaran et al., 2014
Maternal Race, Demography, and Health Care Disparities Impact Risk for IVH in Preterm Neonates

### Increased Risk for IVH (all)

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<tr>
<th>Characteristic</th>
<th>Significance (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorioamnionitis</td>
<td>.01</td>
</tr>
<tr>
<td>5-min Apgar &lt;3</td>
<td>&lt; .004</td>
</tr>
<tr>
<td>Surfactant use</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>HFOV</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Increased Risk for IVH (Faranoff & Martin, 2015)
- Prematurity
- Low birth weight
- Chorioamnionitis
- Male gender

Alphabet-Aden
Every one

Shankaran et al., 2014
# Maternal Race, Demography, and Health Care Disparities Impact Risk for IVH in Preterm Neonates

## Race-related Risk Impact on IVH

<table>
<thead>
<tr>
<th>Race</th>
<th>Characteristic</th>
<th>Risk (+/-)</th>
<th>Significance (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>African ancestry</td>
<td>&gt;1 prenatal visit</td>
<td>decreased</td>
<td>.02</td>
</tr>
<tr>
<td>White</td>
<td>Multiple gestation</td>
<td>increased</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>White</td>
<td>Higher maternal education</td>
<td>decreased</td>
<td>&lt; .05</td>
</tr>
</tbody>
</table>

Shankaran et al., 2014
Protective Factors

- Antenatal steroids
- Maternal pre-eclampsia

Did Alphabet-Aden have these? NO
Intra partum Factors

- Maternal transport vs. Neonatal transport
- Mode of delivery
  - Cesarean
  - Vaginal birth
- Delayed cord clamping
- Birth asphyxia

Alphabet-Aden

Neonatal transport – bad
Cesarean - good
Birth asphyxia - bad
No delayed cord clamping - bad

Fanaroff & Martin, 2015
Neonatal Factors

- Respiratory:
  - Mechanical ventilation, asynchronous ventilation
  - Pneumothorax
  - Hypercarbia & Hypocarbia
  - Acidosis
  - Hypoxemia

Kenner & Lott, 2014
Neonatal Factors cont’d.

- Cardiovascular
  - Impaired autoregulation
  - Immature brain “pressure passive”
  - Hypovolemic and Hypotension
- Hypoglycemia
- Sepsis
- Coagulopathies and Anemia

Kenner & Lott, 2014
PATHOPHYSIOLOGY (How does this happen?)

• Lack of cerebral blood flow (CBF) auto regulation causes a pressure passive state

• The highly vascularized germinal matrix lacks a supporting basement membrane which puts the fragile, immature blood vessels at risk for bleeding.

• Pathologic fluctuations in the cerebral blood flow from RDS, Pneumothorax, PDA, Hypothermia etc. places the preterm infant at risk

• Isolated hypertension associated with seizures, intubations & suctioning also predisposes these babies to IVH

Owens, 2005
PATHOPHYSIOLOGY cont’d.

• The occurrence of preterm IVH is greatly associated with the immaturity of the germinal matrix of the lateral ventricles

• The cortical neuronal and glial cell precursors develop from the germinal matrix and the adjacent ventricular germinal zone during the late 2nd and 3rd trimester

• This ependymal germinal matrix is highly vascularized region with arterial supply from the anterior and the middle cerebral arteries and the anterior choroidal vessels

• Bleeding in this region, thus may be confined to the germinal matrix or it may rupture into either lateral ventricles and may thereby become a unilateral or bilateral IVH

Owens, 2005
Grade 1 IVH
(Blood in GM only)
Grade 2 IVH
(Blood in LV without ventriculomegaly)
Grade 3 IVH
(Blood in LV with ventriculomegaly)

- Blood on Arachnoid Villi
- OBLITERATIVE ARACHNOIDITIS

- Slowly Evolving Hydrocephalus
- Germinal Matrix
- Choroid Plexus
- Blood
Grade 3 IVH
(Blood in LV with ventriculomegaly)

Rapidly Progressive Hydrocephalus

Ventriculomegaly

Large IVH

Obstruction at Foramen of Monro

3rd

GM SEH

Occipital Horn

Luschka Magendie

4th

Arachnoid Villi

Germinal Matrix

Choroid Plexus

Blood
Grade 4 IVH
(Periventricular Hemorrhagic Infarction)
Presentation

- **Silent**: presentation in 25-50% of infants
  - Full fontanel
  - Decreasing HCT

- **Saltatory**: most common, develops over hours to days: nonspecific findings
  - Hypotonia
  - Change in general movements

- **Catastrophic**: sudden deterioration in status
  - Apnea
  - Hypotension
  - Acidosis
IVH Diagnosis

- Cranial ultrasound
  - At 7 to 14 days
  - Repeat at 36-40 weeks postmenstrual age

Shah & Wusthoff, 2016
Intrapartum Interventions

- Prevent premature birth
- Maternal transport
- Experienced resuscitation team
- Maintain neutral thermal environment
- Avoid head down positions

Adcock, 2016
## Pathogenesis and Prevention of IVH

<table>
<thead>
<tr>
<th>Major Pathogenic Mechanism</th>
<th>Putative Mechanisms</th>
<th>Risk Factors</th>
<th>Preventive Measures</th>
</tr>
</thead>
</table>
| Disturbance in Cerebral blood flow (CBF) | Fluctuation in CBF | • Suctioning and handling  
• Hypercarbia, hypoxia, acidosis | • No routine suctioning  
• Optimize ventilation |
|                            |                     | • Asynchrony between infants and ventilator breathe | • Synchronized ventilation by the use of assist control or synchronized mandatory ventilation modes |
|                            |                     | • Severe RDS | Exogenous surfactant |
|                            |                     | • Patent ductus arteriosis | • Indomethacin/ibuprofen |
|                            |                     | • Rapid infusion of NaHCO₃ | • Slow infusion over extended period |
| High cerebral venous pressure |                     | • Pneumothorax, high ventilator pressure | • Gentle ventilation |
|                            |                     | • Prolonged labor | • Individualized approach |

**Bias Statement:**
Correlation of mechanisms w/ risk factors & preventive measures is based on available evidence & author’s speculations.

**Ballabh, 2014**
<table>
<thead>
<tr>
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<th>Putative Mechanisms</th>
<th>Risk Factors</th>
<th>Preventive Measures</th>
</tr>
</thead>
</table>
| Disturbance in CBF        | Abnormal blood pressure | •Hypotension  
•Hypertension  
•Sepsis  
•Dehydration | •As appropriate for the infant  
Volume infusion  
Vasopressors  
Placental transfusion |
|                            | Pressure passive circulation | Extreme prematurity and low birth weight (<1000 g)  
Clinically unstable resulting from respiratory compromise, sepsis, or other reasons | •As appropriate for the infant  
Gentle vent, midline position  
Good O2/CO2 exchange  
Fluid/electrolyte balance  
Thermoregulation, antibiotics |
| Inherent fragility of germinal matrix vasculature | Might be worsened by an inflammatory injury to the blood-brain-barrier | Hypoxic ischemic insult  
Sepsis | Prenatal GCs stabilize the microvasculature by increasing:  
1. Contractile pericyte coverage of veins & capillaries  
2. Protein expression in astrocytes (nerve cells)  
3. Fibronectin (cell adhesion molecule) in basal lamina |
| Platelet and coagulation disturbances | Hemostatic failure | Thrombocytopenia  
Disseminated intravascular coagulopathy | Replacement of blood products |
Neuroprotective Care

• Appropriate respiratory support
  • Noninvasive SpO2 and CO2 monitoring

• Avoid rapid IV flushes
  • UAC, UVC sampling

• Midline head positioning

• HOB flat or slightly elevated
  • Diaper changes

• Suction only when required

Kaspar & Rubarth, 2016
Frequency of ETT suctioning for the prevention of respiratory morbidity in ventilated newborns

Optimal frequency of ETT suctioning - not yet defined

1. scheduled ETT suctioning versus prn
2. More vs less frequent ETT suctioning

- 1980-2015: Single RCT (n=97 LBW)
  - high risk of bias, small, old study (1987-1988)
  - Secondary outcome: IVH

- No difference in IVH between groups (RR 1.12, 95% CI 0.44 to 2.85)

- Conclusion: “There was insufficient evidence to identify the ideal frequency of ETT suctioning in ventilated neonates.”

- Future research: Effects of suctioning frequency on very preterm infant’s lungs & brains

Bruschetti et al., 2016
Midline Head Positioning: What does the evidence support?

- Midline/neutral head positioning and HOB at 30-degree elevation for the first 72 hours of life in infants < 32 weeks gestation to prevent alterations in cerebral blood flow
  - Significant decrease in tissue Hgb index and tissue oxygenation index during head rotation < 26 weeks gestation infants
  - Significant increase in cerebral blood volume (CBV) during 90 degree head rotation < 1200 gm infants
  - Jugular blood flow was decreased with 90 degree head rotation
  - Significant increase in CBV with head tilted down
- No adverse consequences identified

Malusky & Donze, 2011
Midline Head Positioning?
Midline Head Positioning
Delayed Cord Clamping (DCC)

- As much as 30% of NB blood supply remains in placenta with immediate cord clamping

- Placental transfusion via DCC (2-5 minutes) can yield 83-110 ml of blood (24-32ml/kg)

- Benefits: ↑ blood volume, ↓ need for transfusion, ↓ anemia, ↓ rates of sepsis and necrotizing enterocolitis

AND

Scheans, 2013
Decreased Incidence and Severity of IVH

- Estimated 50% reduction in IVH with DCC
- DCC promotes cardiovascular stability. Increased blood volume and blood flow $\Rightarrow$ improved tissue perfusion and oxygenation

Scheans, 2013
DCC Recommendations

Delay cord clamping for 30-60 seconds, with newborn held at or below level of the uterus/placenta

- Apgar timing, drying/placing in sterile warming bag, suctioning, stimulating may all occur as needed during DCC

- **Contraindications:**
  - Fetal indications: anomalies that need immediate care: congenital diaphragmatic hernia, possibly gastroschisis, etc.
  - Maternal indications: placental or umbilical cord disruption (abruption, prolapse, vasa previa, maternal hemorrhage)
  - Multiple gestation?

Scheans, 2013
Hemodynamic antecedents of peri/IVH in very preterm neonates

Practice points

Low cardiac output predisposes very preterm brain to ischemia immediately after birth.

Adaptation to clamped cord & perfused lungs -> improved myocardial function
Systemic & CBF improve. CBF regulation occurs 2nd & 3rd postnatal days

Placental transfusion (delayed cord clamping or cord milking) can reduce the risk of cerebral hypoperfusion and subsequent hypoperfusion–reperfusion injuries

Permissive hypercarbia (PaCO$_2$ above the low–mid 50s) might potentiate the post-ischemic reperfusion phase leading to P/IVH in 2nd & 3rd postnatal days

Noori & Seri, 2015
Conclusions:

These findings suggest initial cerebral hypoperfusion followed by a period of reperfusion before the occurrence of IVH. Decrease in CBF during and after the development of P/IVH. Shaded area represents the period when P/IVH occurred.

Highlights:

1. Cerebral tissue oxygen saturation (rSO2) was stable in no P/IVH group (black boxes), but fluctuated in P/IVH group (clear diamonds).

2. Cerebral fractional oxygen extraction (CFOE) was stable in no P/IVH (black boxes), but fluctuated in P/IVH (clear diamonds).

Noori & Seri, 2015
Comfort Measures

- Pain and Stress: may impede venous return, increasing cerebral blood volume
  - Swaddling, boundaries, preemie hugs
  - Minimal stimulation
  - Quiet, dark environment
  - Routine procedures

Kenner & Lott, 2014
Prophylactic indomethacin infusion increases fractional cerebral oxygen extraction in ELBW neonates

- **Background:** Previous studies found indomethacin given in the first 6 hr of life reduces the incidence of severe IVH in VLBW neonates & decreases CBF, suggesting a decrease in cerebral oxygen delivery.

- **Intervention:** n=27 ELBW neonates < 30 weeks = slow indomethacin infusion for IVH prophylaxis.

- **Result:** Fractional cerebral oxygen extraction increased from baseline after indomethacin from

- **Conclusion:** Fractional cerebral oxygen extraction ↑ 9% from 0.23±0.11 to 0.25±0.10 (P=0.034) w/ indomethacin 0.1 mg kg⁻¹ given over 1 to 2 h.

- **Clinical implications:** This small increase in oxygen extraction likely represents decreased cerebral perfusion -> may be harmful to the developing brain.

Garner, Miller, & Burchfield, 2012
Among VLBWs is RBC transfusion an independent risk factor for subsequently developing a severe IVH?

5 yr retrospective study
VLBWs w/out IVH on initial report -> Gr 3-4 w/ subsequent imaging

• N=54 cases crossmatched (1:2) for confounders
  • initial pH, sepsis, ventilation, coag studies, or proportion w/ severe thrombocytopenia

• Results: w/ normal head u/s = more likely to get RBC transfx (p < 0.001)

• 94% case sequence: No IVH -> RBC transfusion -> severe IVH

• Logistic regression: each subsequent RBC transfusion during 1st week doubled the risk of a severe IVH (ea transfx ↗ RR, 2.02; 95% CI, 1.54-3.33)

• Sensitivity analysis: Hct/ Hgb level prior to transfusion not significant

• Conclusion: RBC transfusions given before IVH are independent risk factor for developing a severe IVH

Baer, 2011
Antithrombinin for the prevention of IVH in very preterm infants

- IVH assumed venous origin: trigger may be intrinsic thromboses in GM
- Antithrombin (glycoprotein from liver): major plasma inhibitor of thrombin
  - controls blood coagulation
  - VLBWs = low antithrombin thus increased risk of IVH in first hrs post-birth
- **Objective:** Does prophylactic antithrombin administration (w/in 1st 24 hrs) reduce incidence of GM-IVH in very preterm neonates 1982-2015: 2 RCTs met criteria (combined n=182) < 32 wks, any birth wt
- **Conclusion:** “use of antithrombin does not reduce the risks of bleeding in the brain, mortality or any other relevant outcomes in very preterm neonates when compared to placebo”

Bruschetti et al., 2016

Extremely preterm: < 28 wks / Very preterm: 28 to < 32 wks (who.int, 2016)
Heparin for the prevention of IVH in preterm infants

- IVH assumed venous origin: trigger may be intrinsic thromboses in GM
- Heparin activates antithrombin & promotes thrombin inactivation
  - VLBWs = low antithrombin thus increased risk of IVH in first hrs post-birth
- **Objective:** Does prophylactic heparin reduce incidence of GM-IVH in very preterm neonates
- 1980-2015: 2 RCTs met criteria (combined n=155) – secondary outcomes
- Both trials compared low-dose heparinized solution to same solution unheparinized in very preterm newborns requiring umbilical catheters
  - No trials specifically used heparin for purpose of lowering risk of germinal matrix-IVH
- **Conclusion:** “The use of heparin does not reduce the risks of bleeding in the brain, mortality or any other relevant outcomes in very preterm neonates when compared to solution without heparin”

Bruschetti et al., 2016

Preterm: < 37 wks (who.int, 2016)
Hemodynamic antecedents of peri/intraventricular hemorrhage in very preterm neonates

Research directions

Role of cardiac dysfunction & PDA shunting in cerebral hypoperfusion in immediate postnatal period

Mechanisms of beneficial hemodynamic effects of DCC

Best approach to enhancing placental transfusion & identify population that benefits most

Role of hemodynamic & cerebral oxygenation monitoring in assessing adequacy of CBF & oxygenation

Noori & Seri, 2015
IVH in term neonates with HIE: a comparison study neonates treated with vs without hypothermia

- Hypothermia as prevention for IVH
- Small study of term infants only (n=61)
- Demonstrated IVH is uncommon in term infants with HIE
- But was more prevalent in those treated with hypothermia than controls.
- How does temperature stability affect the cerebral vasculature of the very preterm neonate?
- Are there databases that can retrospectively compare infants with unstable temperature trends

Gorelick et al., 2016
Candidate Gene Analysis: Severe IVH in Inborn Preterm Neonates

- IVH: disorder of complex etiology
- Analyzed genotypes for 7 genes (224 inborn preterm neonates w/ Gr 3-4 IVH (all = antenatal steroids & BWt 500-1250g)
  - Compared w/ 389 matched controls
  - 24 universities participated: entered data into secure online database at Yale
- **Objective:** Investigate previously published genetic risk factors for Gr 3-4 IVH in a cohort of inborn AGA preterm neonates
  - Included 11 polymorphic genetic variants in 9 genes
- Only methylenetetrahydrofolate reductase was more prevalent in cases of IVH
  - 1298A > C variant for MTHFR yielded equivocal results emphasizing the need for more comprehensive genetic strategies

Aden et al., 2013
Gene–environment interactions in severe IVH of preterm neonates

- Genome-wide association studies / whole-exome sequencing data to promote understanding of genetic contributions to IVH through RCTs.
  - Might include delivery mode trials for fetuses
- Current preclinical genetic studies & clinical candidate gene reports suggest multiple genes & interactive environmental factors associated w/ IVH w/ small effect sizes
- These common variants have small-to-moderate effects on disease risk
- Individual risk variants not necessary nor sufficient to produce disease
- Development of a large-scale neonatal genomic medicine network w/ infrastructural capacity for an accessible database of sequence variants & phenotypic associations w/ a framework for defining & cataloging clinically actionable variants
- Identification of genes & pathways underlying IVH may promote development of prenatal diagnostics and/or preventive therapeutics

Ment et al., 2014
Neuroendoscopic lavage for the treatment of IVH & hydrocephalus in neonates

**Background:** Neonatal IVH may evolve into posthemorrhagic hydrocephalus (PHH) & cause neurodevelopmental impairment

- **Objective:** Evaluate safety & efficacy of endoscopic surgical approach to remove intraventricular hematomas
- **Intervention:** 19 neonates w/ PHH had neuroendoscopic lavage to remove intraventricular blood remnants
- **Control:** 10 neonates were treated conventionally
  - initially w/ temporary CSF diversion via lumbar punctures, a ventricular access device, or an external ventricular drain
- **Results:** S/p endoscopic lavage, 11 (58%) of 19 patients required a later shunt insertion, as compared with 100% of infants treated conventionally (p < 0.05)
  - Endoscopic lavage was associated with fewer numbers of overall necessary procedures (median 2 vs 3.5 per patient, respectively; p = 0.08), significantly fewer infections (2 vs 5 patients, respectively; p < 0.05), or supratentorial multiloculated hydrocephalus (0 vs 4 patients, respectively; p < 0.01
- **Conclusion:** Demonstrated feasibility & safety of Tx of PHH by neuroendoscopic lavage for neonates w/ IVH

Schulz et al., 2014
Former VLBW 26 weeker now a robust, healthy 1 year old

used with permission from Luke's mom
Resources


Resources


Resources


Resources


Resources


Resources (Google Images)

- Crying baby in hand. Retrieved from https://s-media-cache-ak0.pinimg.com/564x/6d/fa/cc/6dfacca421b3070baec08379f1306de0.jpg
- Houston we have a problem baby. Retrieved from http://images.memes.com/meme/912369
Resources (Google Images)


• CCMC critical transport ambulance. Retrieved from https://www.amrpulse.com/img/content/7-2Slider/connecticutChildrens.jpg

• Intubated micropreemie with umbi-lines. Retrieved from http://i.dailymail.co.uk/i/pix/2013/08/12/article-2390517-1B4234BB000005DC-51_634x453.jpg


• Intubated preemie under plastic. Retrieved from https://s-media-cache-ak0.pinimg.com/736x/30/c8/01/30c801360c5878fb9e9cd9b579b51cc2.jpg

• Intubated preemie holding finger. Retrieved from http://i.imgur.com/8YBKi10.jpg

• Germinal matrix cartoon. Retrieved from https://image.slidesharecdn.com/braininjuryinpreterminfants
Resources (Google Images)

• Grade I IVH cartoon. Retrieved from https://image.slidesharecdn.com/braininjuryinpreterms
• Grade II IVH cartoon. Retrieved from https://image.slidesharecdn.com/braininjuryinpreterms
• Grade III IVH cartoon. Retrieved from https://image.slidesharecdn.com/braininjuryinpreterms
• Grade IV cartoon. Retrieved from https://image.slidesharecdn.com/braininjuryinpreterms
Resources (Google Images)


• Preterm infant with non-midline positioned head. Retrieved from https://s-media-cache-ak0.pinimg.com/564x/e6/28/0c/e6280cd753c46e35d8ac97aca9980fe6.jpg

• Preterm infant with midline positioning. Retrieved from https://s-media-cache-ak0.pinimg.com/736x/e5/09/ef/e509ef30dde6afc7819a07c3d46148c7.jpg

• Delayed cord clamping comparison. Retrieved from aimsireland.ie


• Blood flow diagram heart to lungs. Retrieved from https://i.ytimg.com/vi/Kj8xI3Qzmb8/hqdefault.jpg


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