

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

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



There is no Grade 4 in Volpe classification.



Normal CT Scan









CT Scan Intraventricular Hemorrhage





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







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%)







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





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





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)



Let's meet a preemie at risk for IVH

Connecticut Children's

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

UCONN HEALTH 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 1st 48 hrs...

Connecticut 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, & 2nd 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



Decreased Risk f	UCONN		
Characteristic	Significance (p-value)		HEALTH
Increasing gestational age	.01		
Preeclampsia	<.001		
Complete antenatal steroid exposure	.02	Alphabet-Aden Extremely premature No pre-eclampsia No useful antenatal steroids Yes Cesarean section	
Cesarean delivery	<.001		
White race	.01		
Sha	nkaran et al 2014	IN	iot white



Maternal Race, Demography, and Health Care Disparities Impact Risk for IVH in Preterm Neonates

Increased Risk for IVH (all)

Characteristic	Significance (p-value)
Chorioamnionitis	.01
5-min Apgar <3	< .004
Surfactant use	< .001
HFOV	< .001

Increased Risk for IVH (Faranoff & Martin, 2015)

- Prematurity
- Low birth weight
- Chorioamnionitis
- Male gender

Alphabet-Aden Every one





Maternal Race, Demography, and Health Care Disparities Impact Risk for IVH in Preterm Neonates

Race-related Risk Impact on IVH					
Race	Characteristic	Risk (+/-)	Signific (p-valu	cance le)	
African ancestry	>1 prenatal visit	decreased	.02	Alpha- Ye	Aden?
White	Multiple gestation	increased	< .001		
White	Higher maternal education	decreased	< .05		
J					

Shankaran et al., 2014



Protective Factors

- Antenatal steroids
- Maternal pre-eclampsia

Did Alphabet-Aden have these? NO





Faranoff & Martin, 2015



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"
 - Hypovolemia and Hypotension
- Hypoglycemia
- Sepsis
- Coagulopathies and Anemia



Alphabet-Aden

Yes to all



Kenner & Lott, 2014



PATHOPHYSIOLOGY (How does this happen?)

- Lack of 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





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

















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





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

IVH Diagnosis





Shah & Wusthoff, 2016



Intrapartum Interventions

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







Pathogenesis and Prevention of IVH

Connecticut Children's	Major Pathogenic Mechanism	Putative Mechanisms ^a	Risk Factors	Preventive Measures
Piac Statement:	Disturbance in Cerebral blood flow (CBF)	Fluctuation in CBF	 Suctioning and handling Hypercarbia, hypoxia, acidosis 	No routine suctioningOptimize ventilation
Bias Statement: Correlation of mechanisms w/ risk factors & preventive measures is based on available evidence &			 Asynchrony between infants and ventilator breathe 	•Synchronized ventilation by the use of assist control or synchronized mandatory ventilation modes
			•Severe RDS	Exogenous surfactant
author's speculations			 Patent ductus arteriosis 	 Indomethacin/ibuprofen
speculations	Clinics Review Articles		• Rapid infusion of NaHCO ₃	•Slow infusion over extended period
	Clinics In Perinatology	High cerebral venous pressure	 Pneumothorax, high ventilator pressure 	•Gentle ventilation
			 Prolonged labor 	 Individualized approach
		Ва	llabh. 2014	

	Major Pathogenic Mechanism	Putative Mechanisms ^a	Risk Factors	Preventive Measures
Connecticut Children's	Disturbance in CBF Clinics Review Articles	Abnormal blood pressure	 Hypotension Hypertension Sepsis Dehydration 	•As appropriate for the infant Volume infusion Vasopressors Placental transfusion
Prenatal glucocorticoids (antenatal steroids) have	Clinics In Perinatology	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
emerged as the most effective intervention to prevent IVH.	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
UCONN HEALTH	Platelet and coagulation disturbances	Hemostatic failure	Thrombocytopenia Disseminated intravascular coagulopathy	Replacement of blood products
			Ballabh.	2014



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





Optimal frequency of ETT suctioning - not yet defined



Informed decisions.

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."



Children's

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

Bruschetti et al., 2016

Low Birth Weight: < 2500 g (who.int, 2004)



Midline Head Positioning: What does the evidence support?

- Midline/neutral head positioning and HOB at 30-degree elevation for 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







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





Decreased Incidence and Severity of IVH

- Estimated 50% reduction in IVH with DCC
- DCC promotes cardiovascular stability. Increased blood volume and blood flow →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 gastroschesis, etc.
- Maternal indications: placental or umbilical cord disruption (abruption, prolapse, vasa previa, maternal hemorrhage)
- Multiple gestation?



Hemodynamic antecedents of peri/IVH in very preterm neonates

Connecticut Children's MEDICAL CENTER 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 (PaCO₂ above the low-mid 50s) might potentiate the post-ischemic reperfusion phase leading to P/IVH in 2nd & 3rd postnatal days

Noori & Seri, 2015



Hemodynamic antecedents of peri/intraventricular hemorrhage in very preterm neonates



Highlights:

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

Seminars in

FETAL & NEONATAL

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

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.

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







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







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





Antithrombin 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 neonates1982-2015: 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

- Trusted evidence. Informed decisions. Better health.
- 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

Seminars in

FETAL & NEONATAL





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





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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





Gene-environment interactions in severe IVH of

- 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





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





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