Thomas Lancaster, MD

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

Protecting our Tiniest Humans: Primum Non Nocere

Thomas M. Lancaster, MD
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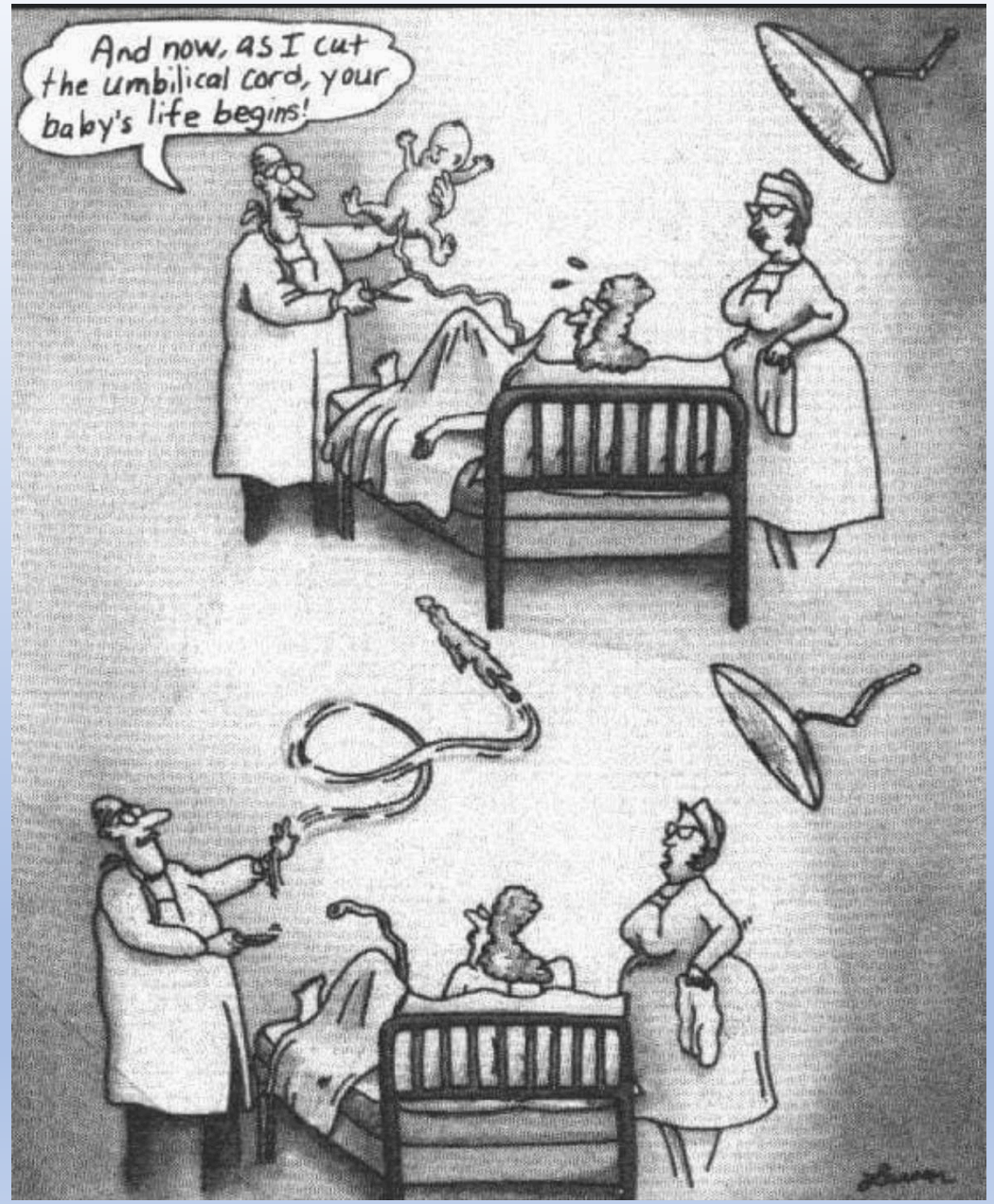
Medical Director, NICU OPRMC and NCCN

Disclosure

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



Objectives

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

Impact of preterm birth on brain outcomes

Magnitude of the Problem

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

In the U.S. –

- **57,000 infants born yearly**
- **90+% survive**
- **of survivors, 5 - 10% later exhibit "cerebral palsy", and 25 - 50%, cognitive/behavioral deficits.**

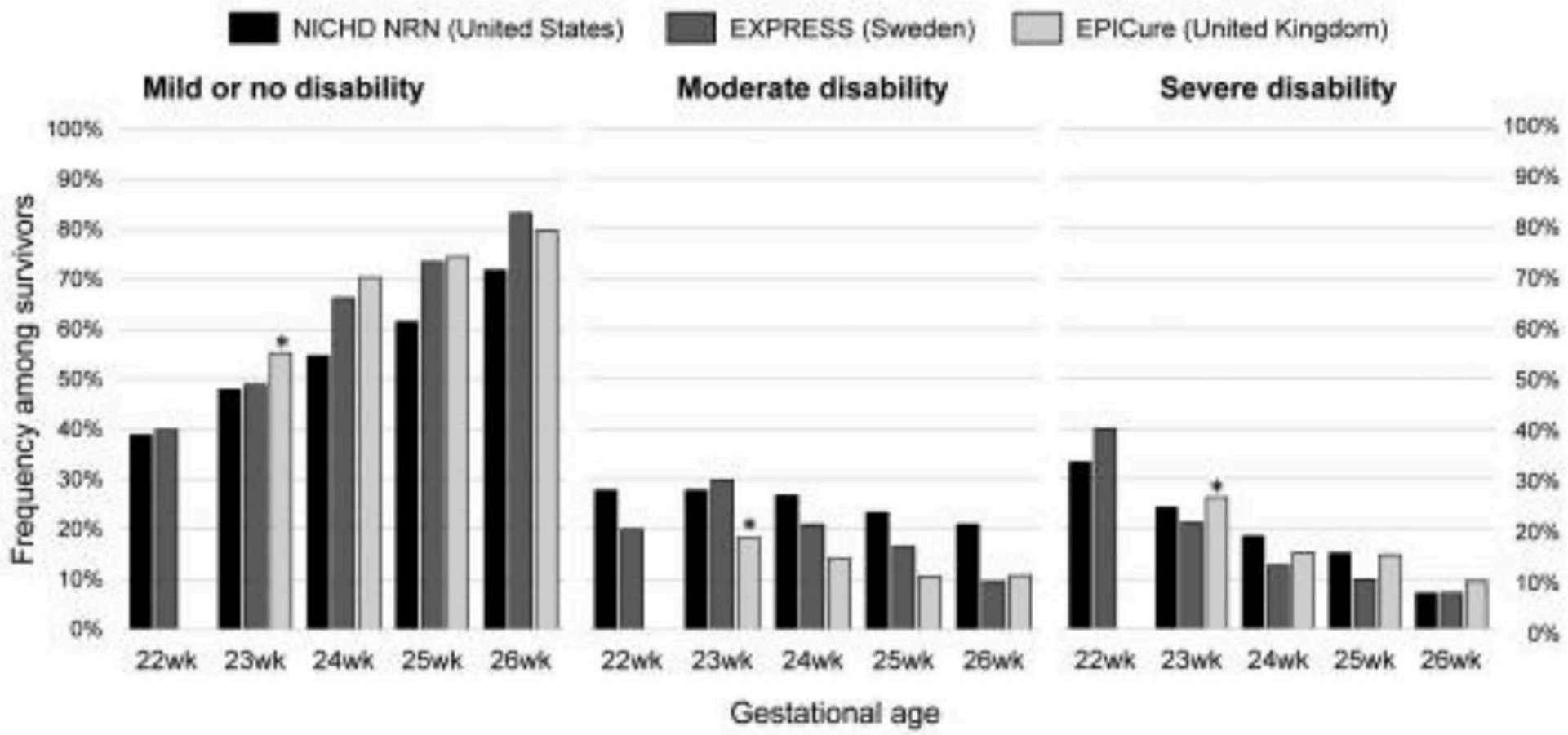
Long Term Outcome for Very Preterm Infants

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

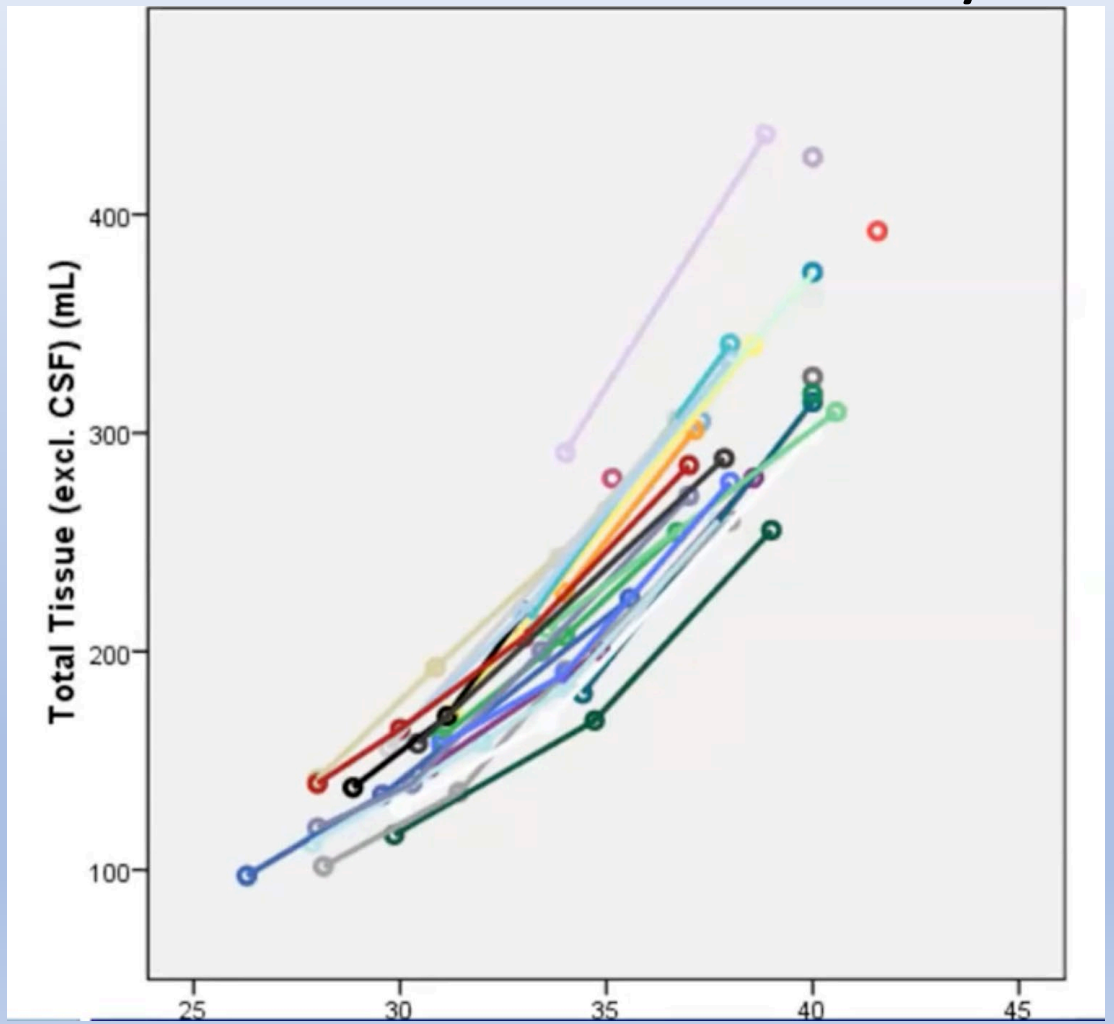
> 25% of children requiring educational assistance

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

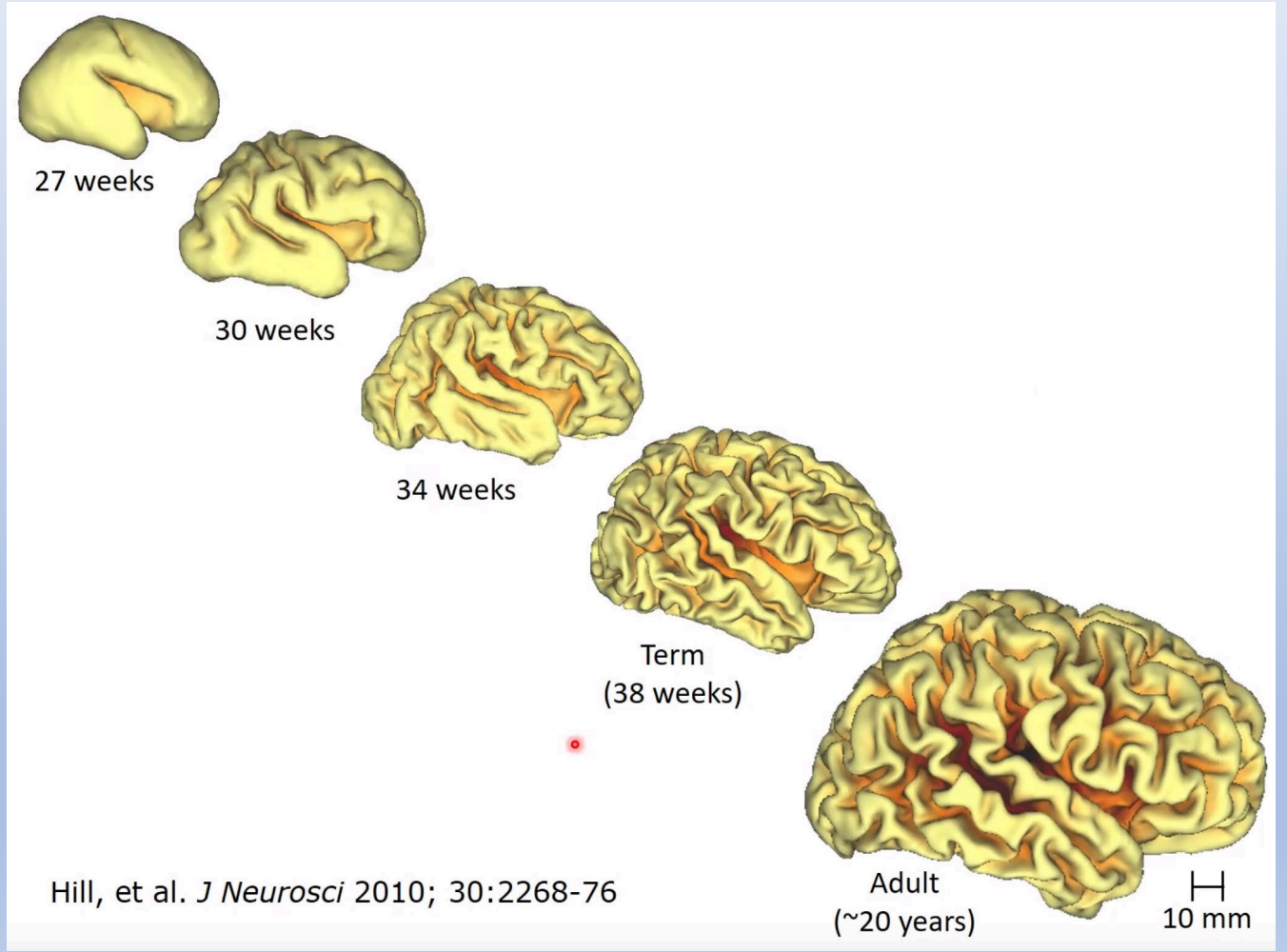
Outcomes at 2 years



Fetal brain growth accelerated compared to newborn and beyond

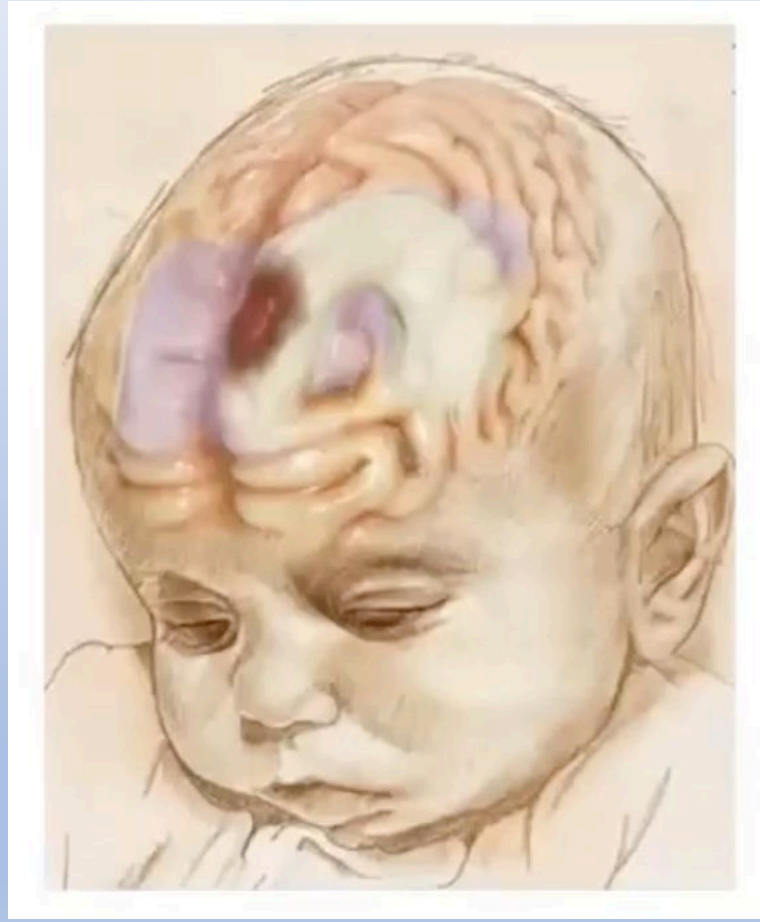


Mathews, et al. 2018



Brain injury in VLBW comes in many forms:

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



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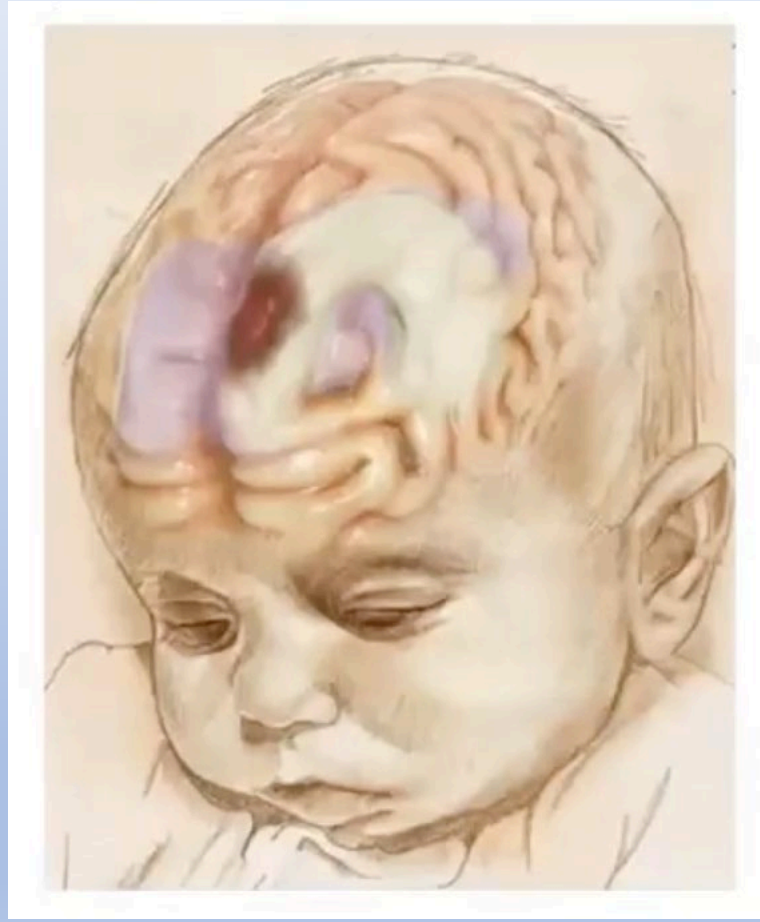

Regional description of preterm brain injury

Region	Disorder	cUS	MRI	Neuropathology	Clinical outcome including Neurodevelopmental Disability (NDD)
Germinal Matrix	GMH-IVH I-II	+/-	+	Germinal matrix vasculature rupture into ventricle.	Inconsistent outcomes related to higher risk with more immature infants
	IVH III - PHVI	+	+	Large IVH +/- PHVD. Complicated by parenchymal venous hemorrhagic infarction	Relates to severity with large IVH, PHVD and parenchymal involvement increasing risk of NDD
	PHVD	+	+	Hydrocephalus complicating IVH.	Increased risk for NDD that may be improved by appropriate intervention
White Matter	Cystic Injury	+	+	Cystic periventricular lesions now rare <5%	Increased risk of cerebral palsy with diplegia
	PWMLs	+/-	+	Glial scars in periventricular region	Increased risk of motor disability if PLIC involved. Number and placement may impact outcome
	Loss of WM volume	-/+	+	Loss of axons and oligodendroglia	Increased risk for cognitive and behavioral disorders
	Impaired myelination	-	+	Impaired maturation of oligodendroglia	Increased risk of delayed motor development, clumsiness and mild NDD
Cerebellum	Large CBH	+	+	Hemorrhagic +/- ischemic injury	Increased risk of NDD, language impairment and autism
	Moderate and Punctate CBH	-	+	Focal cerebellar microvascular rupture	Not yet fully defined – mild to no risk for NDD
Cortex	Encephalopathy	-/+	-/+	Impaired cortical neuronal (dendritic) development	Increased risk for NDD in cognition and behavior
	Focal stroke			Ischemic arterial infarct	PLIC involvement increased risk for CP

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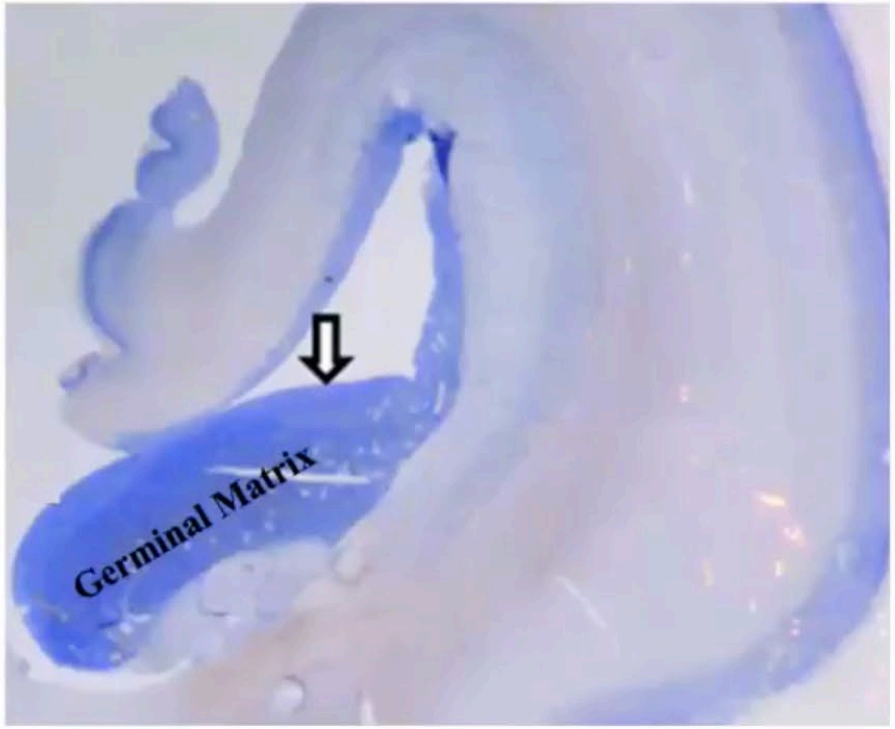
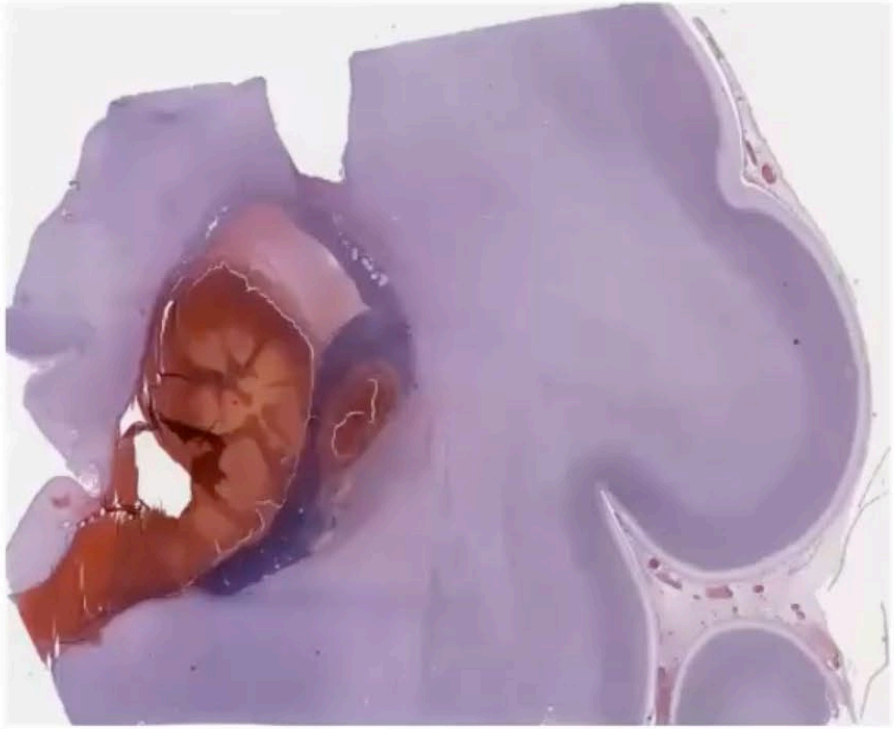
Germinal matrix: An immature and highly vascular structure



Internal and external disturbances



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

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

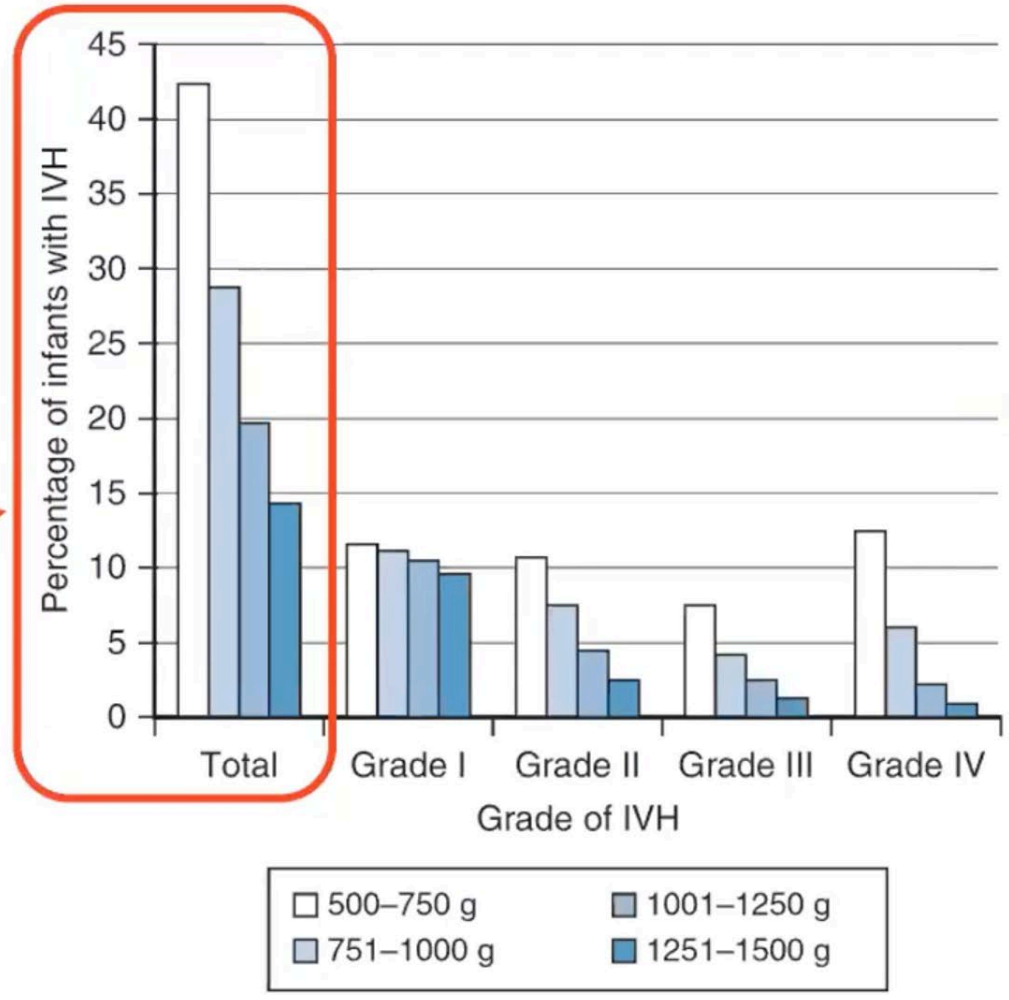
Figure: Adapted from Ballabh P. Pediatr Res, 2010

Figure: Courtesy of Dr. Harris Brent from Georgetown University

Incidence overall is trending down in preterm population

- 1970-80's: 40-50%
- Overall incidence ≈ 20%
- Severe IVH: 5-10%
- Gestational age
- Birth weight

} Close association



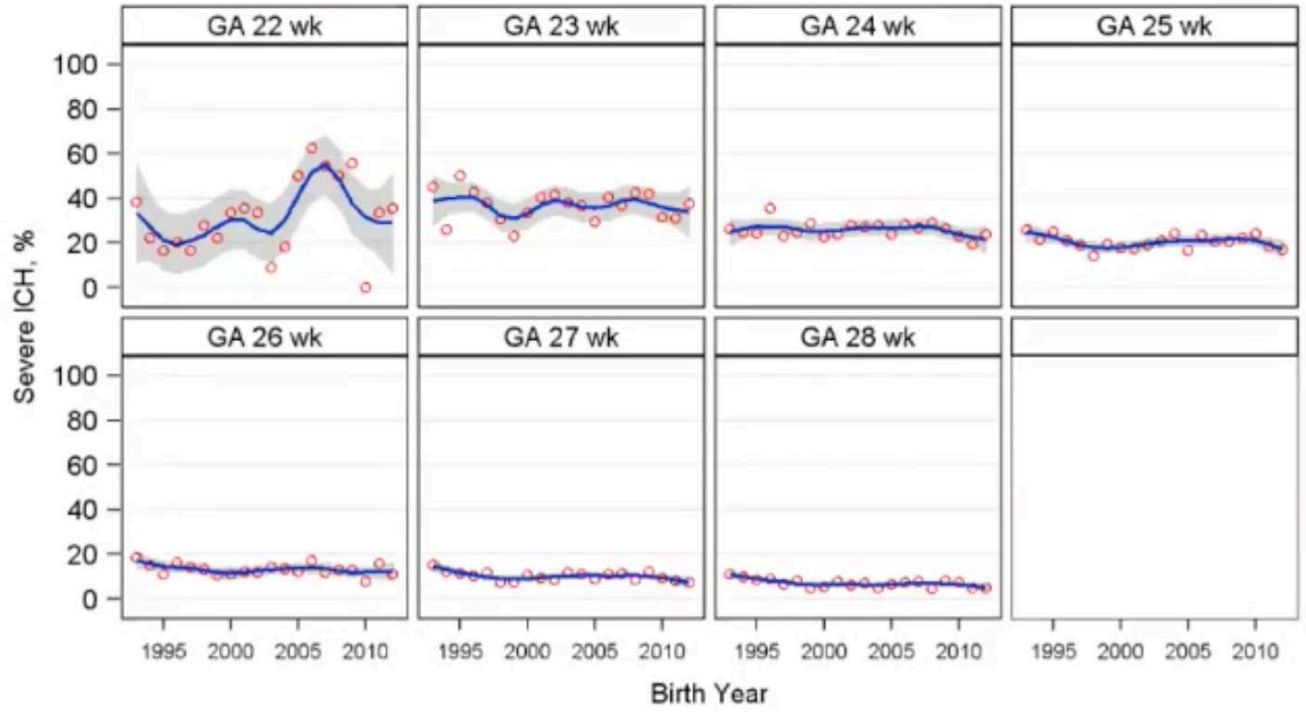
Handley SC et al. J Pediatr, 2018
Cizmeci MN et al. J Pediatr, 2019
Shankaran S et al. J Pediatr, 2020
Yeo KT et al. Arch Dis Child Fetal Neonatal Ed, 2020

Figure: Volpe's Neurology of the Newborn, 2017. p 640

Incidence of IVH in very preterm infants unchanged

- Prospective registry of 34,646 infants 22-28 weeks EGA at 26 Neonatal Research Network centers from 1993-2012
  - Survival increased for infants ≥ 23 weeks (varied by age)
  - Reduction in intracranial hemorrhage for infants 26-28 weeks EGA, but not 22-25 weeks
    - Antenatal steroids increased 24% → 87%
    - Intubation decreased 80% → 65%

Stoll B.J. et al. JAMA 314(10): 1039-51, 2015.



Grading Systems of GMH-IVH

- First classification by Papile et al. 1978
- Volpe classification
  - Joseph Volpe, 1989
  - ***Recommended classification***
- A recent classification
  - EurUS.Brain Group, 2020

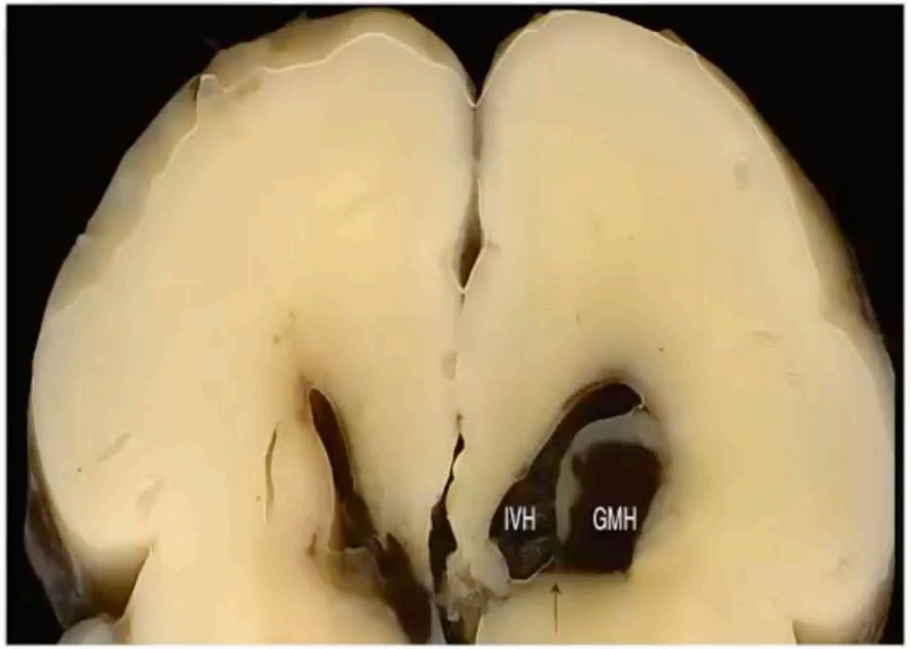


Figure from: Parodi A et al. Pediatr Res, 2020

Papile LA et al. J Pediatr, 1978
Volpe JJ. Ann Neurol, 1989
Parodi A et al. Pediatr Res, 2020

Grading Intraventricular Hemorrhage

Papile*		Volpe†	
Grade	Description	Grade	Description
Grade 1	Germinal matrix hemorrhage	Grade I	Germinal matrix hemorrhage with no or minimal hemorrhage
Grade 2	Blood within but not distending ventricular system	Grade II	IVH (10–50% of ventricular area)
Grade 3	Blood filling and distending ventricular system	Grade III	IVH (>50% of ventricular area; usually distends ventricle)
Grade 4	Parenchymal involvement of hemorrhage	Severe + periventricular hemorrhagic infarction	Grade III IVH with periventricular hemorrhagic infarction

* (Data from Papile LS, Burstein J, Burstein R. Incidence and evolution of the subependymal intraventricular hemorrhage: A study of infants with weights less than 1500 grams. J Pediatr 1978;92:529.)
† (Data from Volpe JJ. Neurology of the newborn, 3rd edn. Philadelphia: WB Saunders, 1995:424–428.)

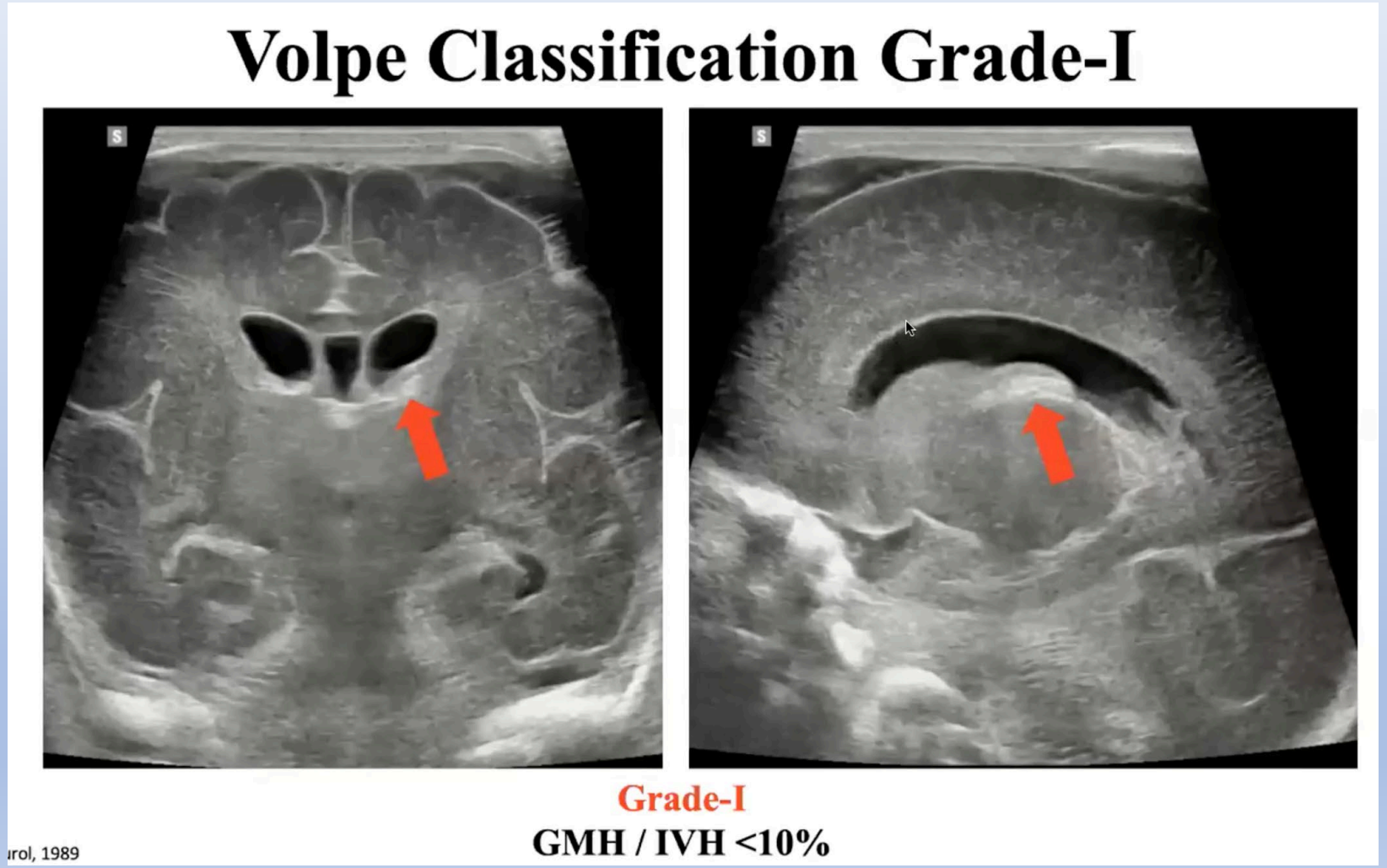
Grade I

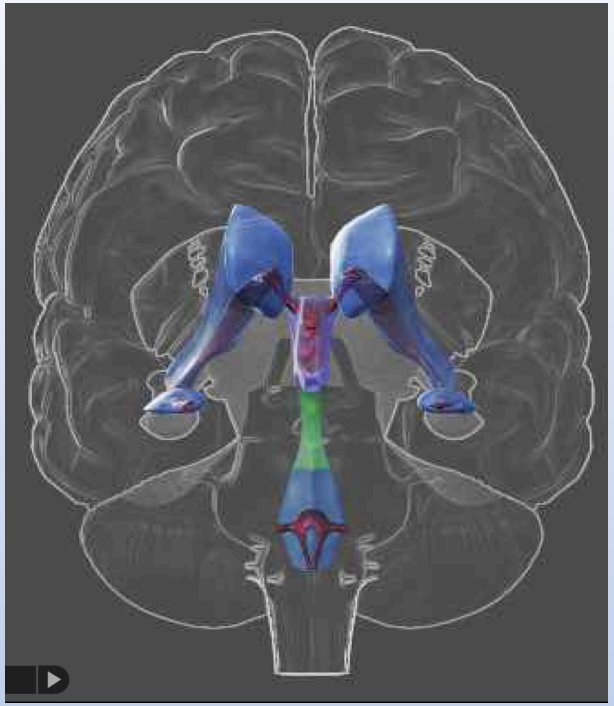
Grade II

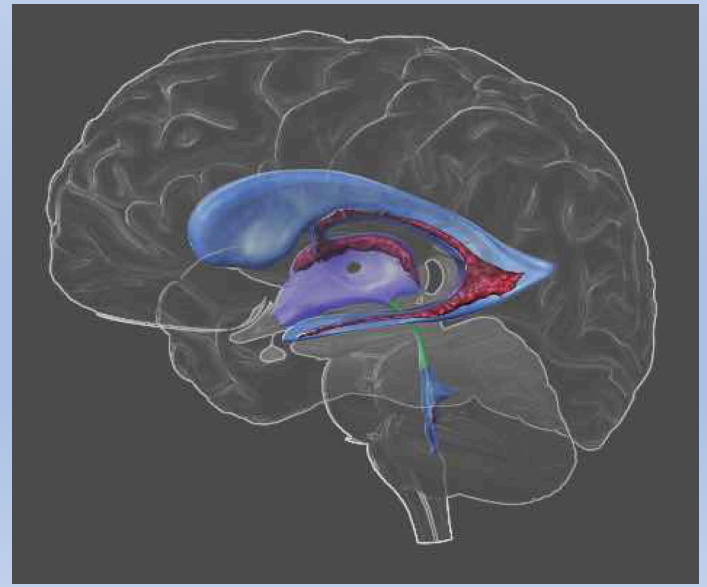
Grade III

Grade IV
Grade III with PHI

Grade I IVH

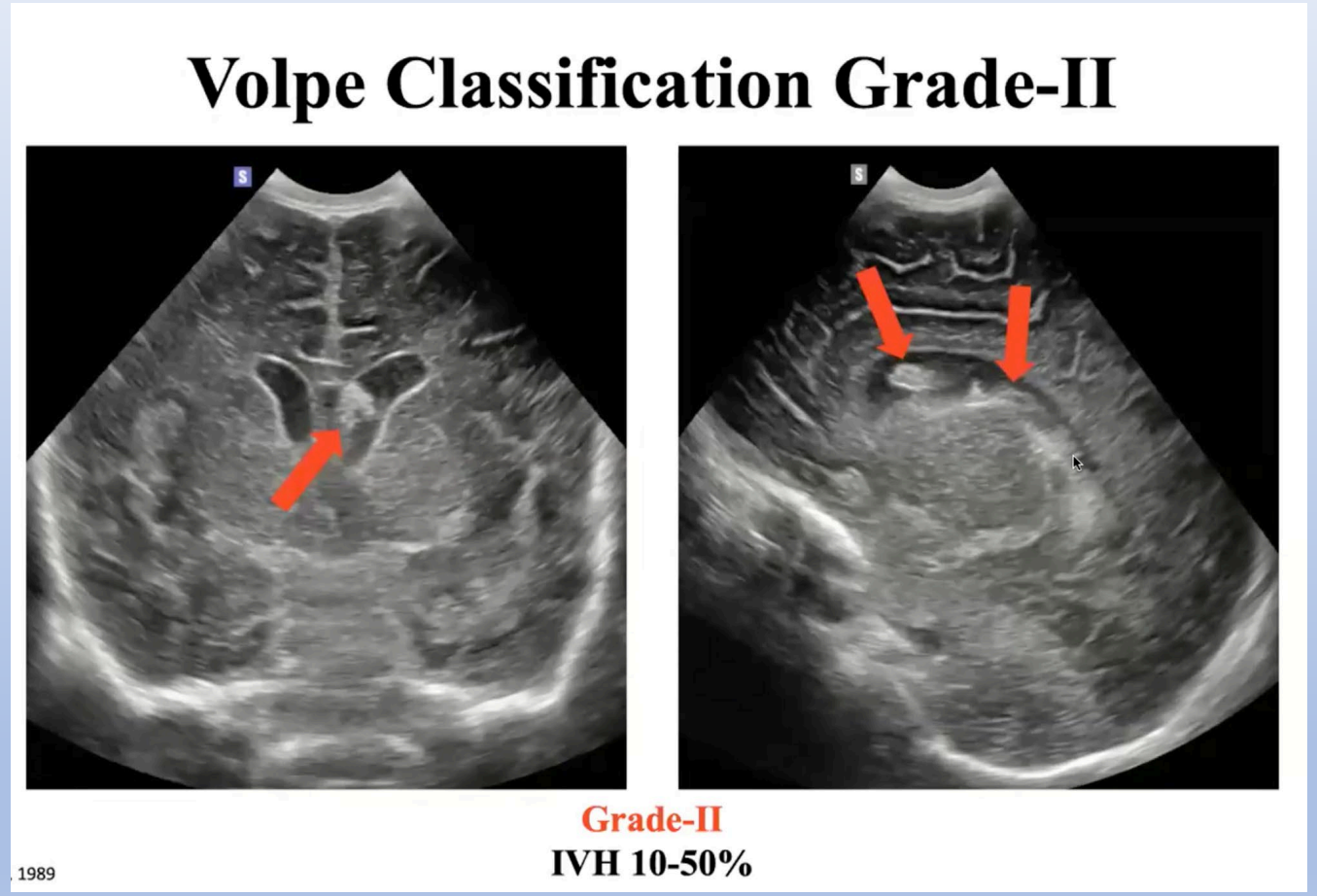


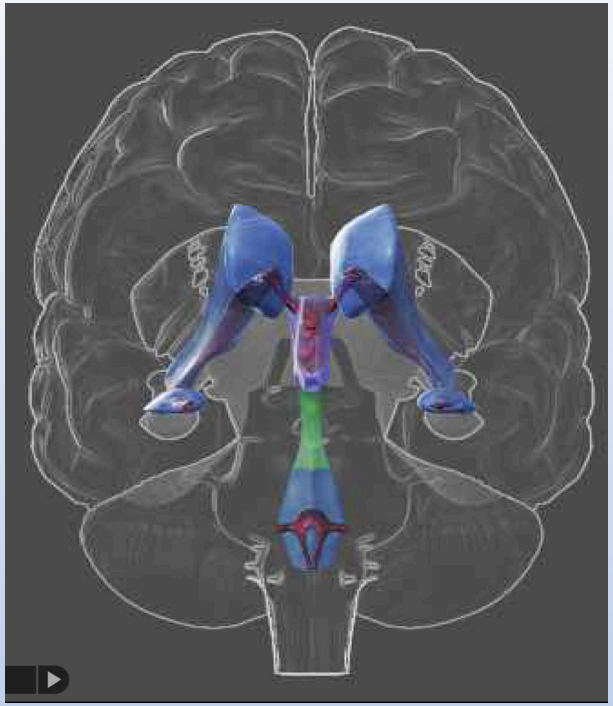


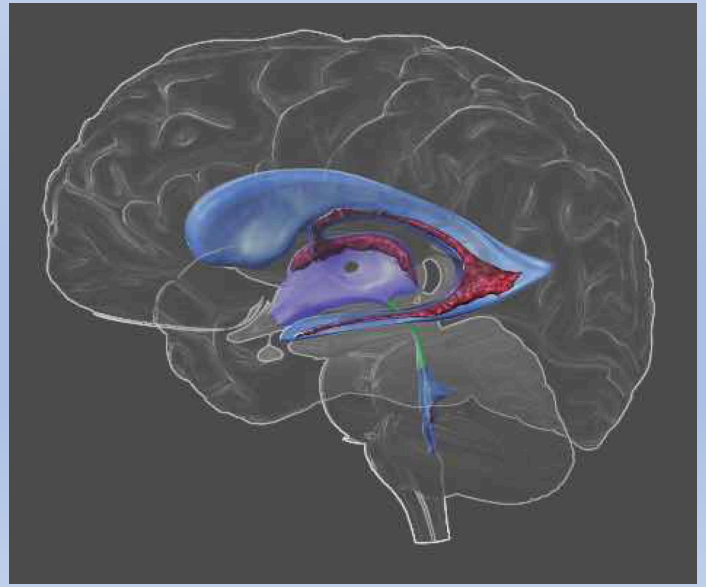


Volpe J., Ann. Neurol. 1989

Grade II IVH

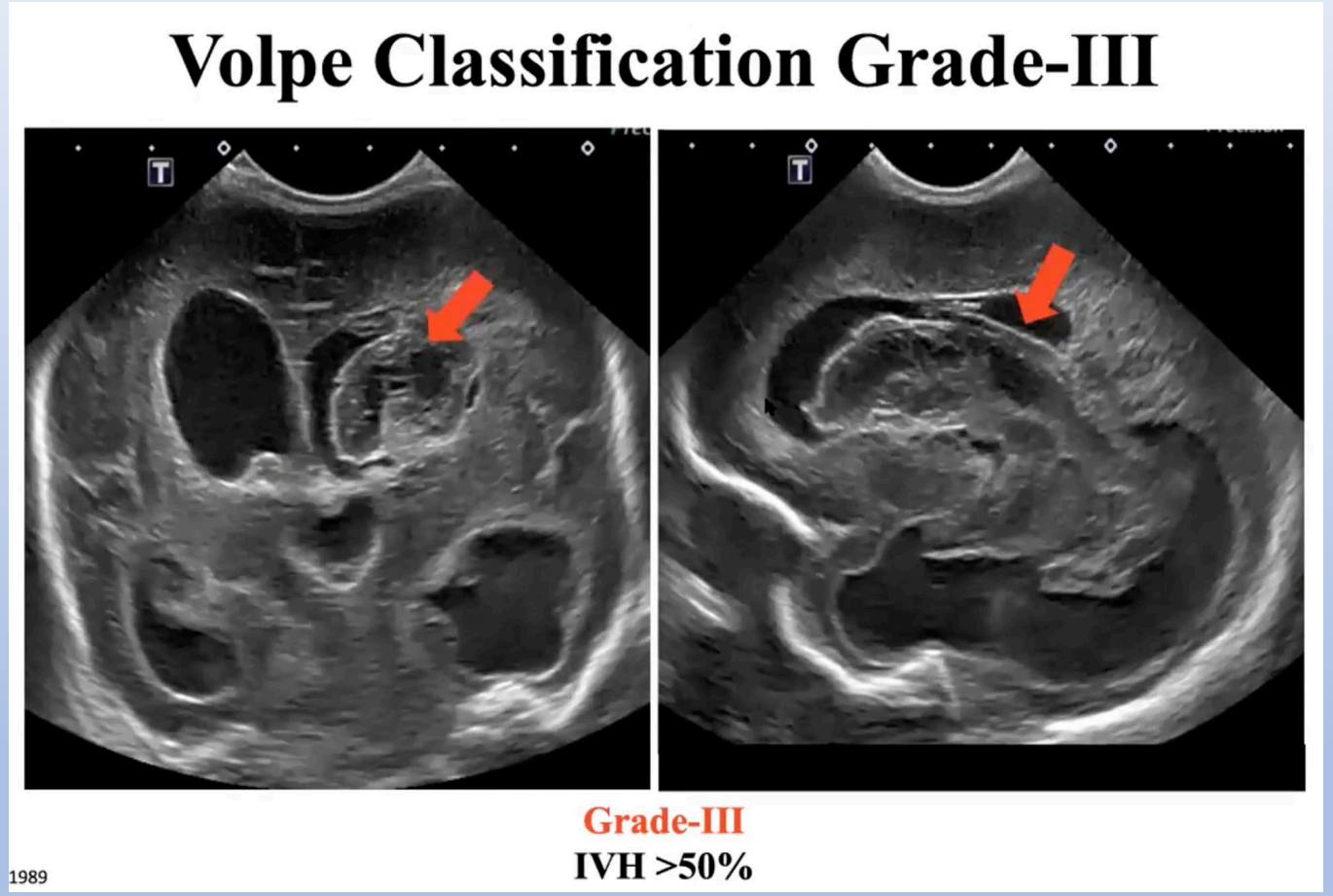


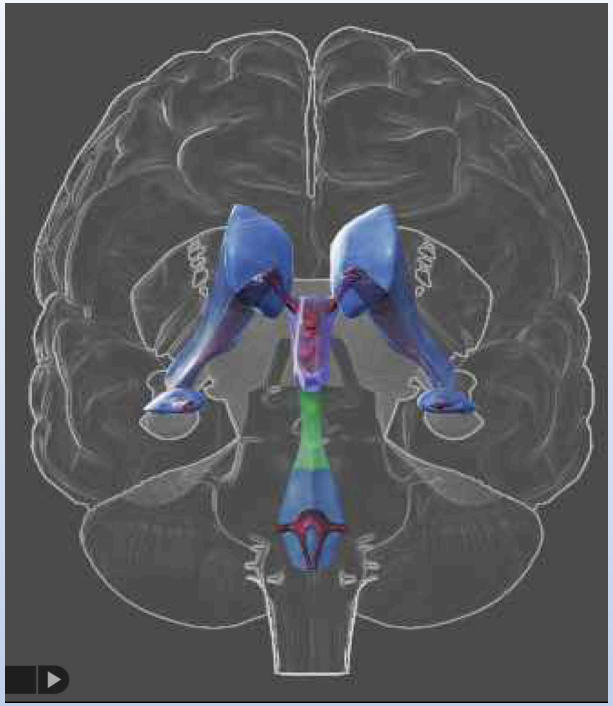


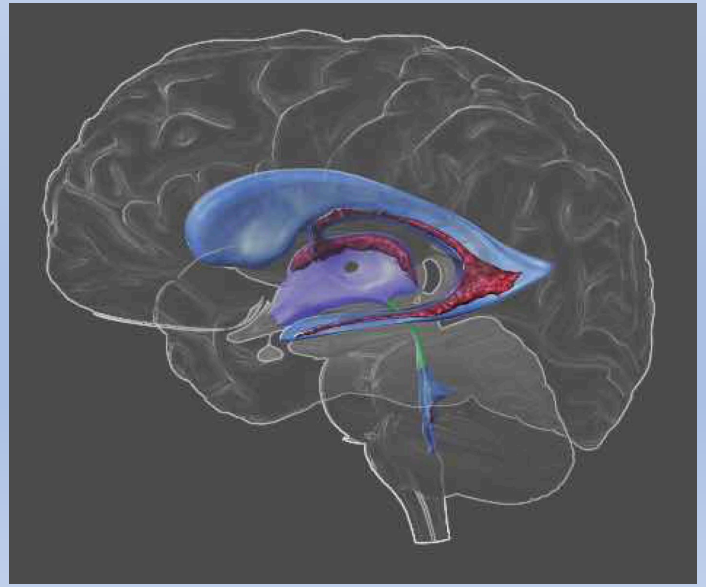


Volpe J., Ann. Neurol. 1989

Grade III IVH

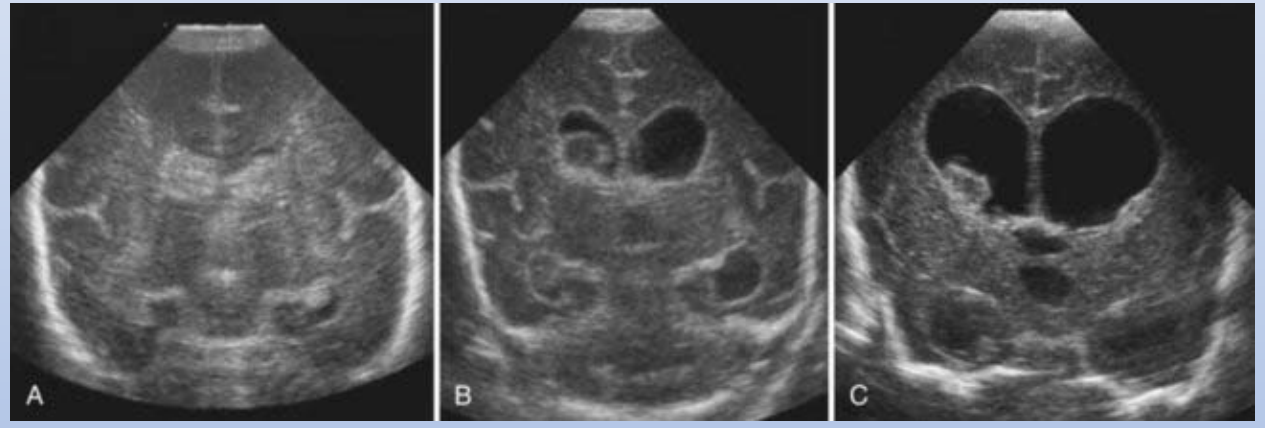






Volpe J., Ann. Neurol. 1989

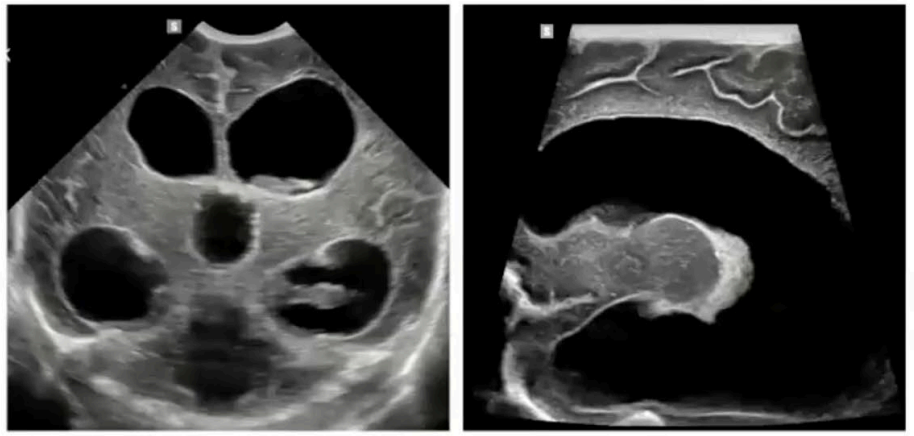
Large GMH-IHV are at risk of developing PHVD



PHVD onset is typically 7-14 days following GMH-IVH

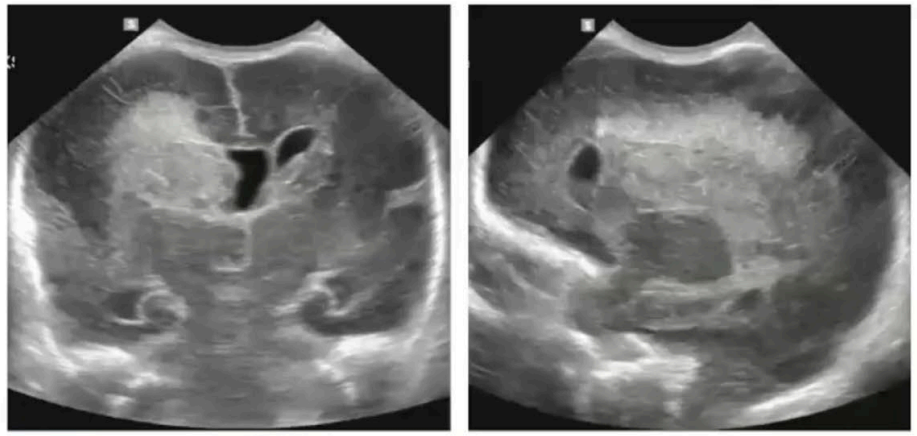
PVHD and PVHI – Most severe complications of IVH

Ventricular Dilatation and Parenchymal Hemorrhage



Post-hemorrhagic Ventricular Dilatation (PHVD)

= Ventricular dilatation following GMH-IVH

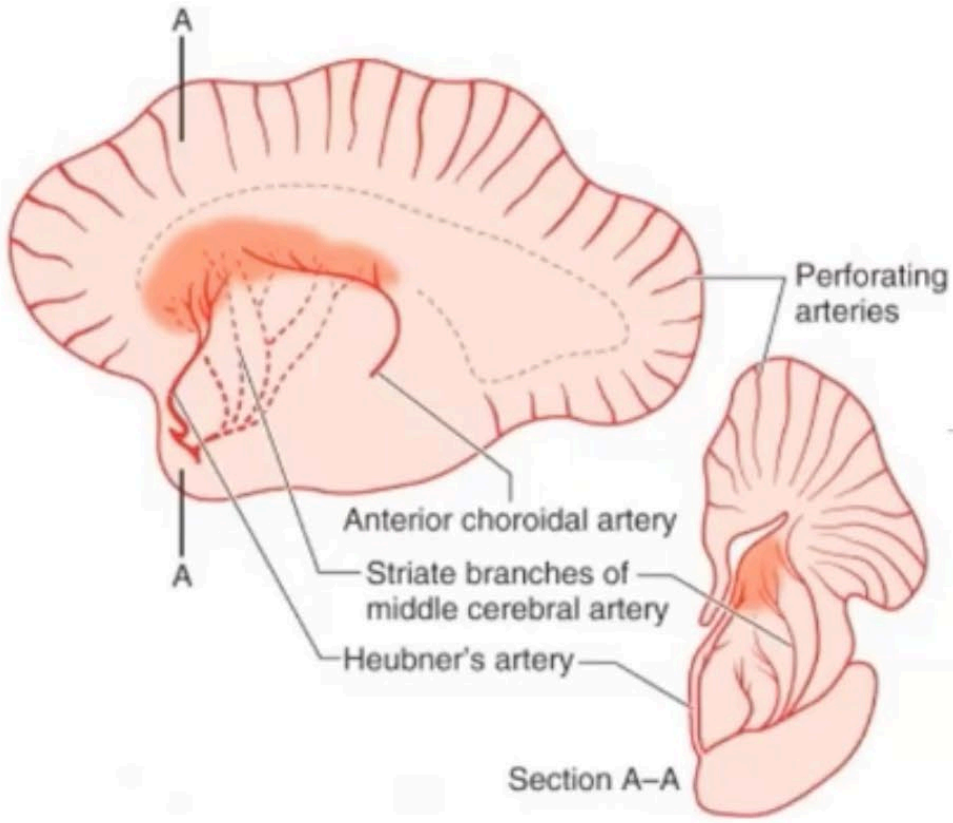


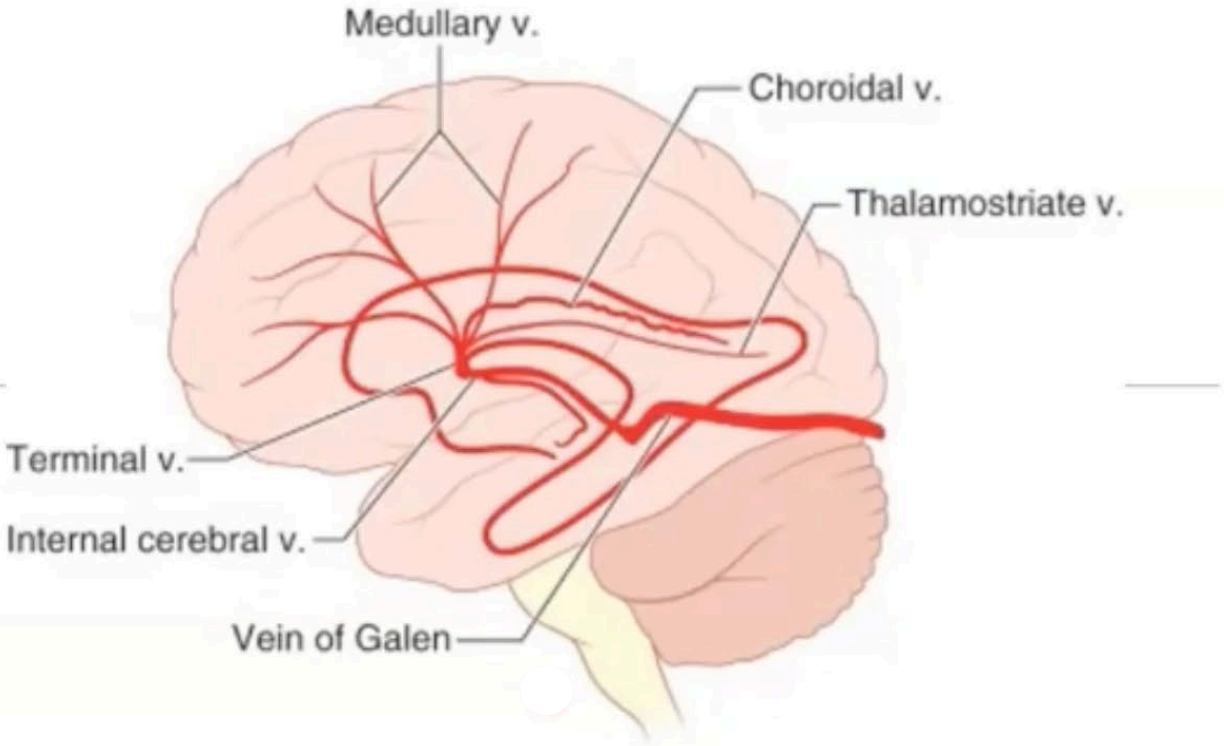
Periventricular Hemorrhagic Infarction (PVHI)

= Parenchymal hemorrhage following GMH-IVH

Equivalent of Papile Grade-IV

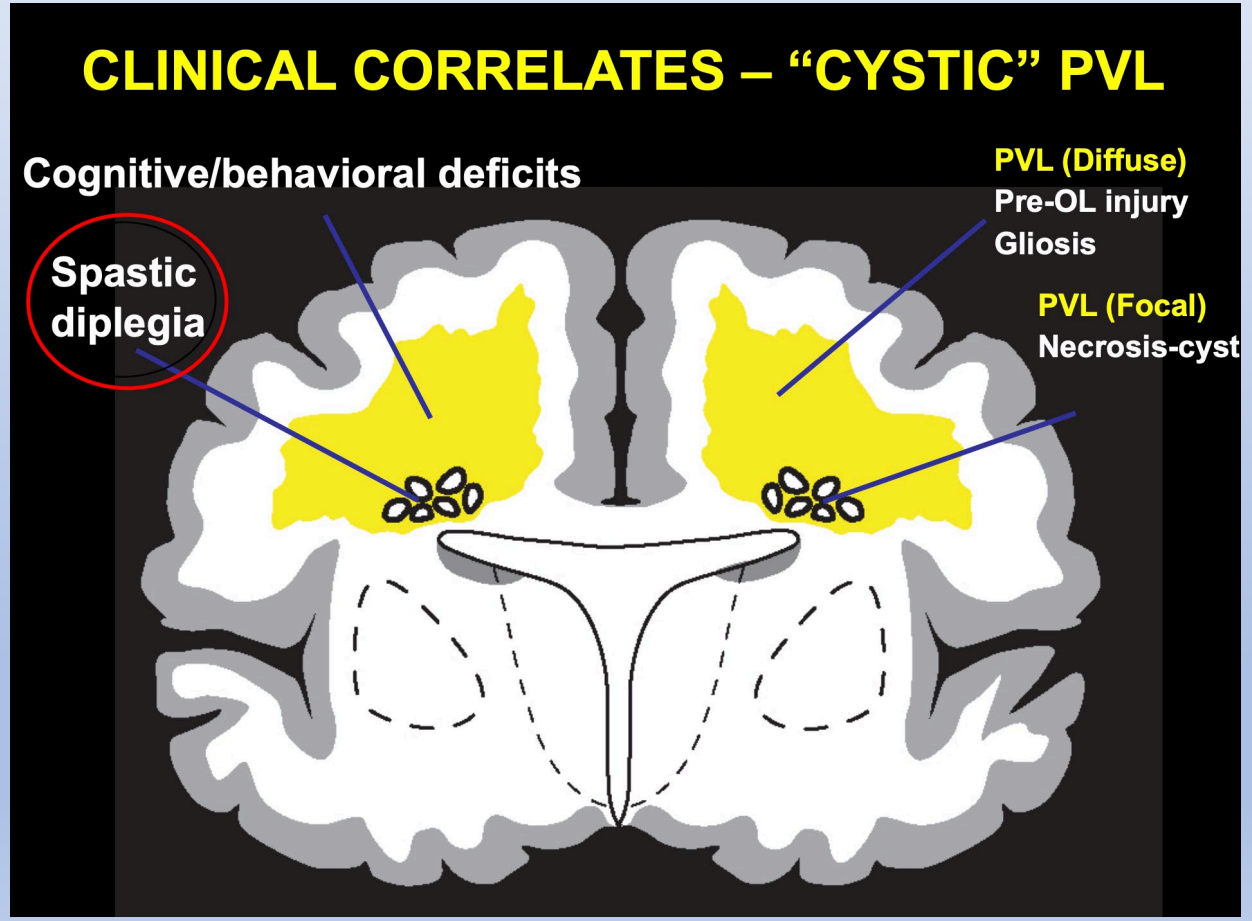
Acute/early preterm brain injury

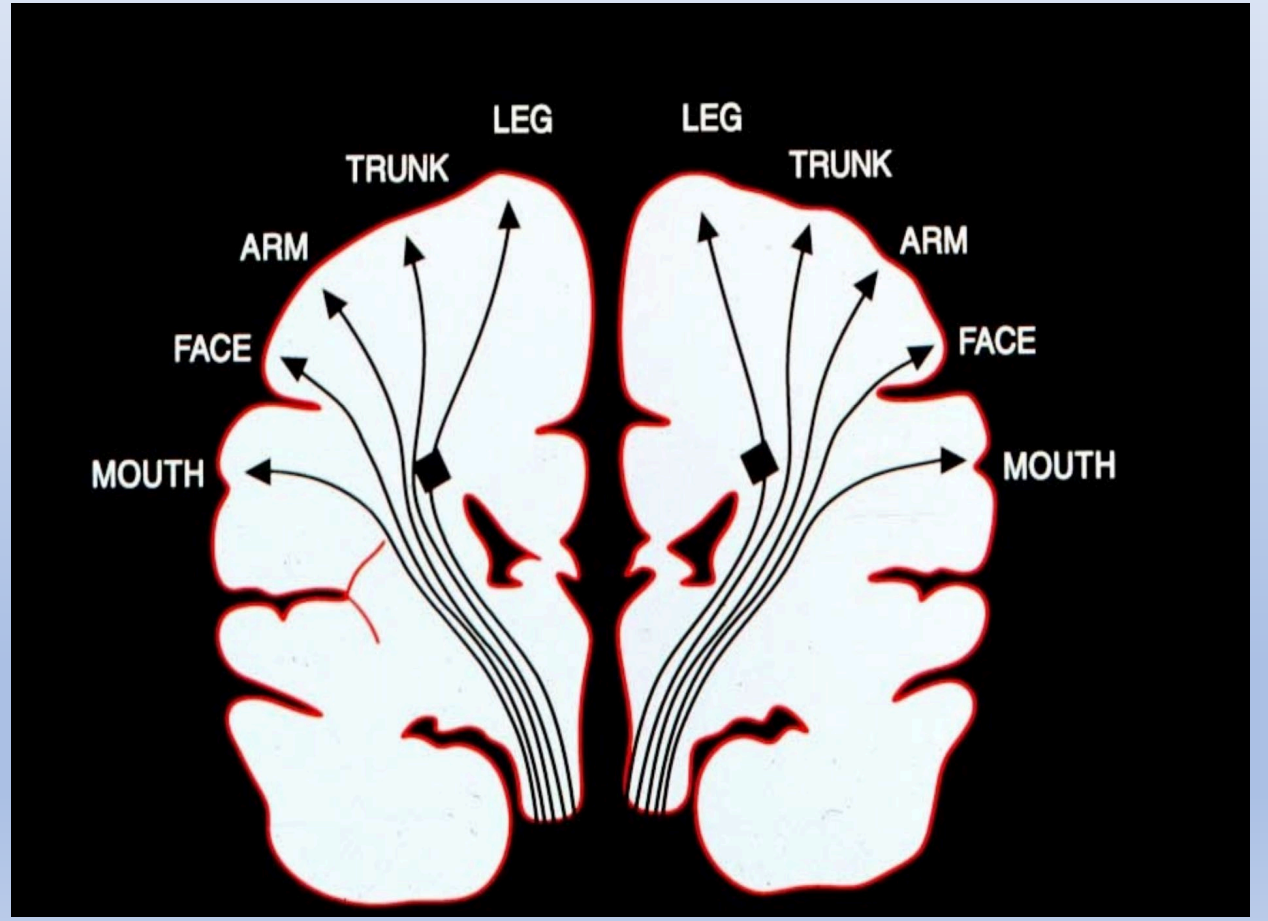




Hambleton G, Wigglesworth JS. Origin of intraventricular haemorrhage in the preterm infant. *Arch Dis Child* . 1976;51:651–659.)

Most common injury leads to spastic diplegia





Outcomes of babies <28 weeks for IVH, PHVD and PVHI

Early Neurodevelopmental Outcomes

Bolisetty et al. n=1472 infants <28 wk

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

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

Bolisetty S et al. Pediatrics, 2014
Payne A H et al. JAMA Pediatrics, 2013

Outcomes in ELGAN for IVH and PHVD

Extreme Preterms, NICHD Data 2020

n=4216 infants <26 wk

At 18-26 months CA	Normal cUS	IVH only	PHVD
Normal Outcomes	57%	51%	27%
Cerebral palsy	9%	13%	43%
Deafness	2%	2%	5%
Blindness	1%	1%	6%
ND Disability	14%	18%	47%

- Impairments more common in infants with PHVD
- Outcomes worse in PHVD requiring surgical intervention

Shankaran S et al. J Pediatr, 2020

High mortality and morbidity for PVHI

Outcomes of PVHI in the Current Era

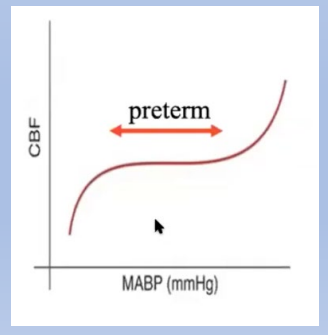
- Mortality: 40%
  - Death/severe disability: 58%
- Cerebral palsy: 42%
  - Almost all hemiparetic
  - Majority independently walking
- Improved outcomes
  - Attributed to perinatal care

Table II. Sonographic characteristics and outcome of included very preterm infants with PVHI

Cognitive outcome	
Normal (mean ± 1 SD)	48 (65)
Subclinical range (−1 and −2 SD)	17 (23)
Clinical range (<−2 SD)	9 (12)
Motor outcome	
Normal (mean ± 1 SD)	51 (69)
Subclinical range (−1 and −2 SD)	8 (11)
Clinical range (<−2 SD)	15 (20)
GMFCS scores	
Level I	18 (58)
Level II	7 (23)
Level III	3 (10)
Level IV	2 (6)
Level V	1 (3)

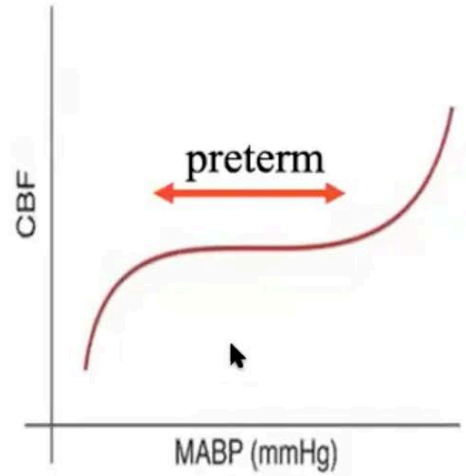
Influences on IVH and morbidities in VLBW infants

- Immature autoregulation
- Chorioamnionitis
- Outborn and transport
- Cord Milking vs DCC
- Antenatal steroids
- Mg prophylaxis
- Gentle noninvasive support
- Skin to skin

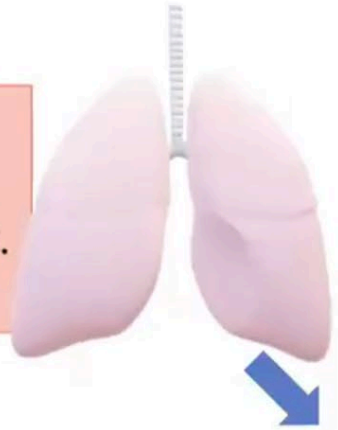


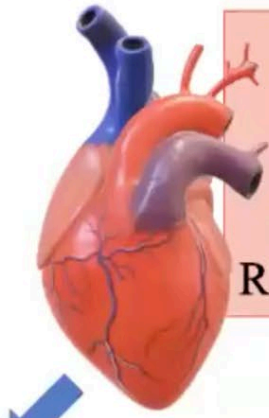
Immature Autoregulation

Narrow regulatory control window

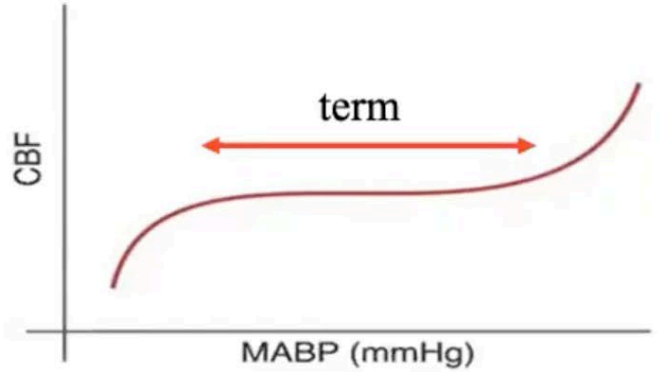


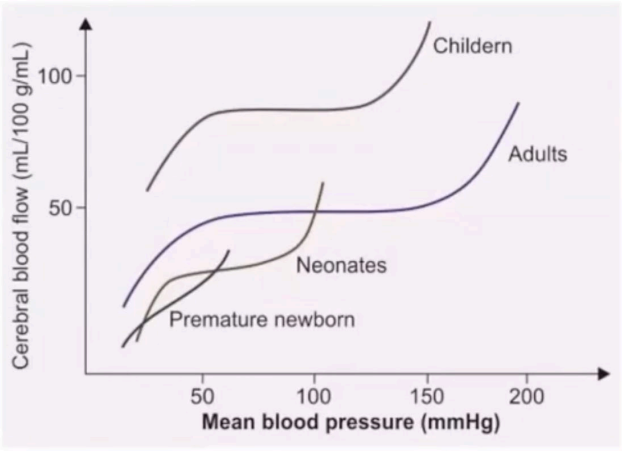
Severe RDS
Intubation
Mechanical vent.
Pneumothorax





Hypotension
hsPDA
Fluid boluses
Inotropes
RBC transfusions





GMH-IVH

Increased pCO_2
Sodium imbalance
Glucose imbalance

Leijser LM & de Vries LS. Handbook of Clinical Neurology, 2019
El-Dib M et al. J Pediatr, 2020

ORIGINAL ARTICLE

Check for updates

Early inotropes use is associated with higher risk of death and/or severe brain injury in extremely premature infants

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

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

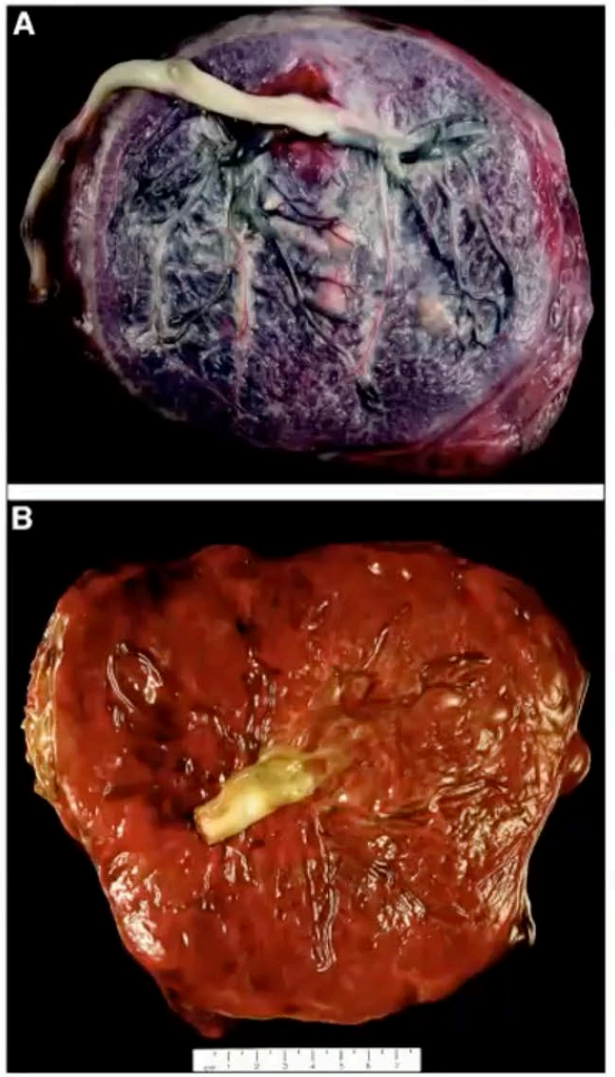
Table 3. Dopamine, dobutamine, and normal saline use and short-term neurological outcomes adjusted for confounding factors.[a]

	Early Dopamine use			Early Dobutamine use			Saline boluses		
Outcomes	AOR	95% CI	*p* value	AOR	95% CI	*p* value	AOR	95% CI	*p* value
Death and/or severe brain injury	2.3	1.1–4.8	.02	2.8	1.3–5.9	.008	2.6	1.3–4.9	.005
Severe brain injury	2.2	0.97–5.1	.06	2.6	1.1–6.2	.03	2.7	1.2–5.7	.01
IVH of any grade	1.5	0.8–2.9	.2	2	1.04–3.9	.02	2.7	1.6–4.6	<.001

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

Chorioamnionitis

- *Induces inflammation & infection*
- Meta-analysis, 85 studies, n=13,432
  - **Increase in IVH**
  - RR: 1.88 (1.61-2.19)
- **Increase in all grades of IVH**
- Controversial results for histologic chorioamnionitis



Reilly SD & Faye-Petersen OM. NeoReviews, 2008
Villamor-Martinez E et al. Front Physiol, 2018
Bierstone D et al. JAMA Pediatrics, 2018

Transport of the Preterm Infant

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

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

  - **Increase in severe IVH**
  - aOR: 1.44 (1.22-1.70)

Mohamed MA et al. Arch Dis Child Fetal Neonatal Ed, 2010
Amer R et al. J Pediatr, 2018
Shipley L et al. Pediatr Crit Care Med, 2019
Goswami I et al. Early Hum Dev, 2020

Delivery Room Resuscitation

- *Mechanical trauma*
- *Oxidative stress, hemodynamic fluctuations*

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

} additional risk

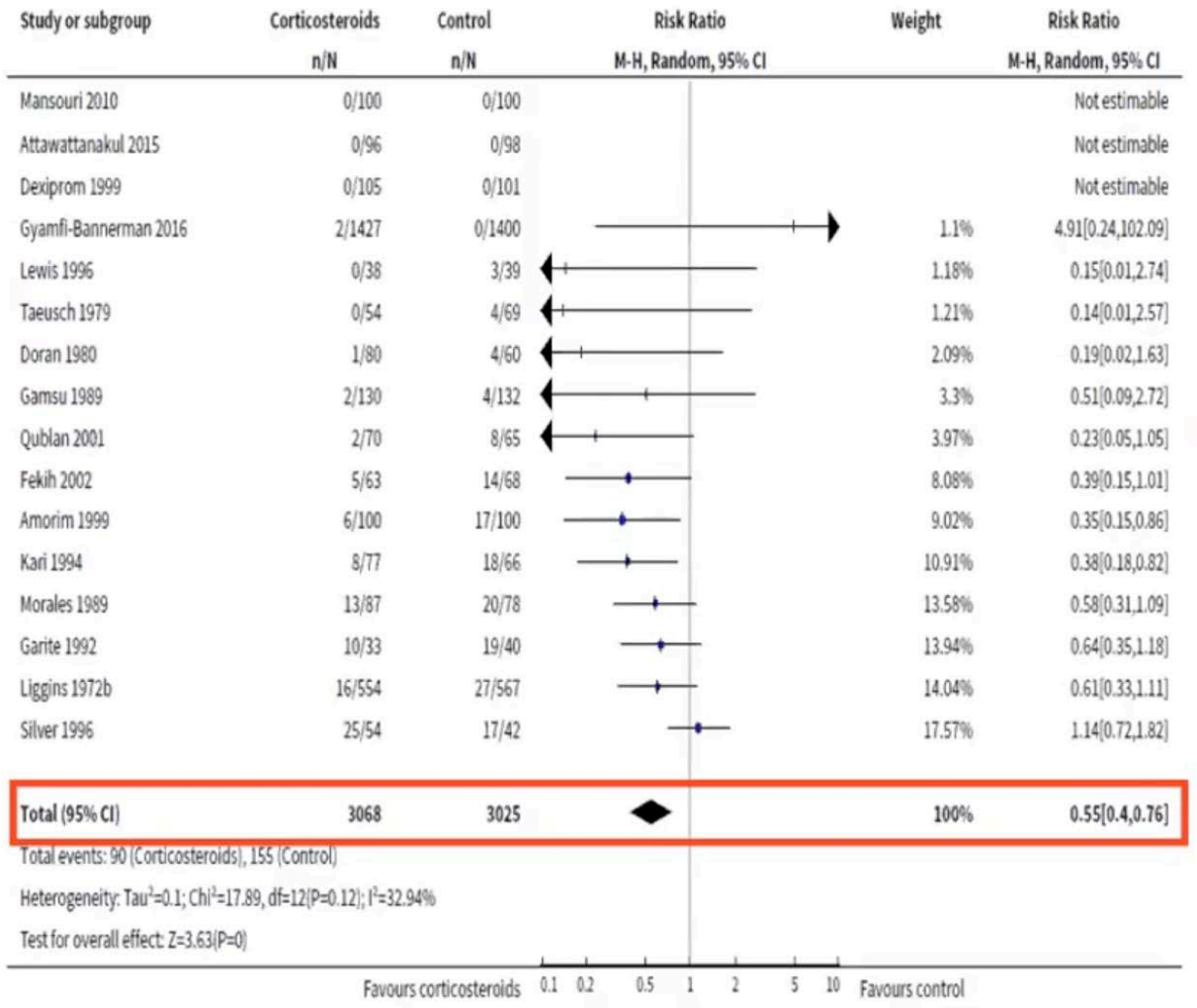
Handley SC et al. J Perinatol, 2015
Lu H et al. J Stroke Cerebrovasc Dis, 2016
Sauer CW et al. J Pediatr, 2016
Arnon S et al. J Perinatol, 2017
Oei JL et al. Pediatrics, 2017

Antenatal Steroids

Single most effective antenatal intervention

- *Induction of maturation*
- *Hemodynamic stabilization*
- *Improved respiratory status*

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



Roberts D et al. Cochrane Database Syst Rev, 2017

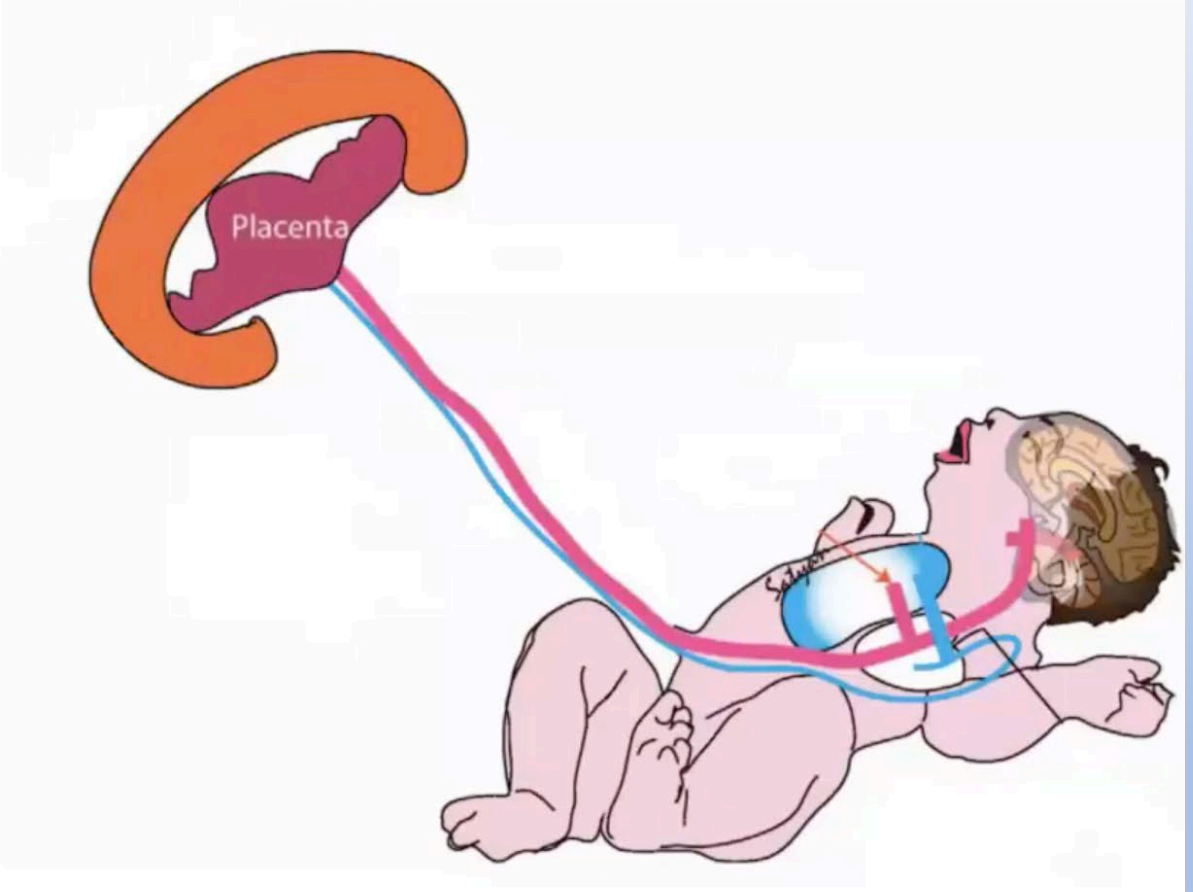
Delayed Cord Clamping

A common delivery room practice

- *Hemodynamic stability*
- *Less inotrope, RBC transfusions*

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

- No decrease in severe IVH



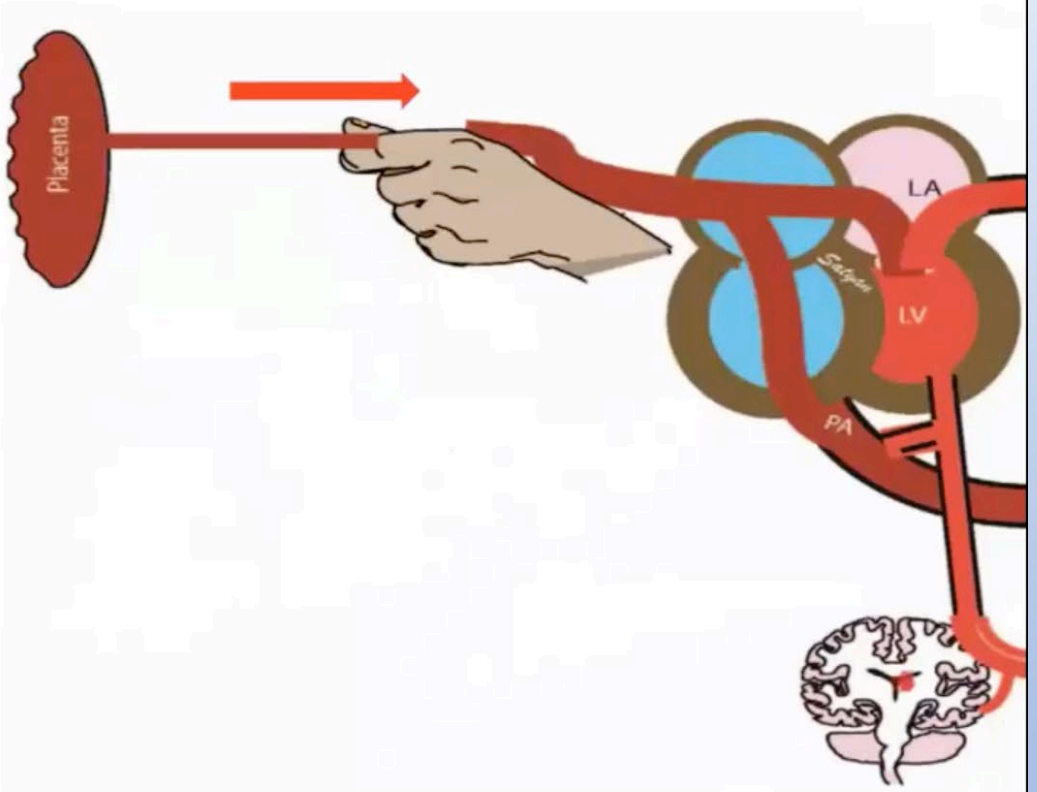
Katheria AC et al. J Perinatol, 2016
Rabe H et al. Cochrane Database Syst Rev, 2019

Figure adapted from Illustrative Neonatology by Satyan with permission

Cord Milking

Regarded as an alternative: A friend or a foe?

- First meta-analysis, 7 studies, n=501
  - **Decrease in IVH**
  - RR:0.62 (0.41-0.93)
- Recent RCT, n=474 infants
  - **Increase in severe IVH <27 wk**
  - **Trial prematurely terminated**
- Later meta-analysis, 19 studies, n=2014
  - **Increase in severe IVH**
  - RR:1.95 (1.01-3.76)

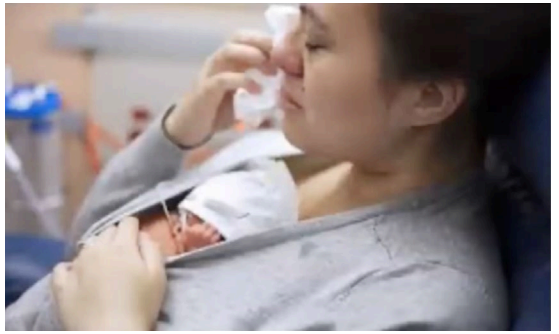


Al-Wassia H et al. JAMA Pediatr, 2015
Katheria AC et al. J Perinatol, 2016
Katheria AC et al. JAMA, 2019
Balasubramanian H et al. Arch Dis Fetal Neonatal Ed, 2019

Figure adapted from Illustrative Neonatology by Satyan with permission

Maternal-Preterm Skin-to-Skin Contact Enhances Child Physiologic Organization and Cognitive Control Across the First 10 Years of Life

Ruth Feldman, Zehava Rosenthal, and Arthur I. Eidelman



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

Gentle Care & Non-Invasive NICU Practices

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

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

Klebermass-Schrehof K et al. Neonatology, 2013
Klingenberg C et al. Cochrane Syst Database, 2017
Mian Q. Arch Dis Child Fetal Neonatal Ed, 2018
De Bijl-Marcus K et al. Neonatology, 2017
Romantsik O et al. Cochrane Database Syst Rev, 2017
Kochan M et al. J Perinatol, 2018
De Bijl-Marcus K et al. Arch Dis Fetal Neonat Ed, 2019
Figure from: Aguar M et al. NeoReviews, 2014

Original research

Neonatal care bundles are associated with a reduction in the incidence of intraventricular haemorrhage in preterm infants: a multicentre cohort study

Karen de Bijl-Marcus,[1] Annemieke Johanna Brouwe
Floris Groenendaal,[1] Gerda van Wezel-Meijler[3]

Position Statement

Neuroprotection from acute brain injury in preterm infants

Michelle Ryan, Thierry Lacaze-Masmonteil, Khorshid Mohammad

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

Original Article

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

Prashanth Murthy, MD [a], Hussein Zein, MD [a], Sumesh Thomas, MD [a], James N. Scott, MD [b], Ayman Abou Mehrem, MD [a], Michael J. Esser, MD [a], Abhay Lodha, MD [a], Cathy Metcalfe, RN [a], Derek Kowal, RT [a], Leigh Irvine, MN [a], Jillian Scotland, RN [a], Lara Leijser, MD [a], Khorshid Mohammad, MD [a,*]

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TABLE 2.
Pre-NPC and Post-NPC Implementations and Interventions in the Study Population

Characteristics		Pre-NPC Bundle (n = 301)	Post-NPC, Bundle (n = 364)	*P* Value
Hemodynamic management	Inotrope use in the first 72 hours	71 (23.6)	25 (6.9)	<0.001
	Normal saline boluses	112 (37.2)	68 (18.7)	<0.001
	Medical treatment of PDA	115 (38.9)	157 (43.3)	0.25
	Surgical ligation of PDA	30 (10)	24 (6.6)	0.12
	Timing of PDA treatment In the first 72 hours	32 (10.6)	32 (8.8)	0.29
	After 72 hours	88 (29.2)	125 (34.4)	
	DCC	77 (25.8)	229 (64.3)	<0.001
Respiratory management	Any hypercapnia >60 mm Hg in the first 72 hours	116 (38.5)	124 (34.1)	0.26
	Any hypocapnia <35 mm Hg in the first 72 hours	132 (43.9)	126 (34.6)	0.017
	Extubating success (total = 202, 106 before and 96 after the bundle)	83 (78.3)	81 (84.4)	0.27
	Pneumothorax	14 (4.7)	6 (1.7)	0.02
	Remained intubated for the first 72 hours	142 (47.2)	152 (41.8)	<0.001
	Extubation attempt within first 72 hours	107 (35.5)	96 (26.4)	
	Not intubated	52 (17.3)	116 (31.9)	
Impact of minimal handling	Use of opioids (fentanyl or morphine)	57 (18.9)	25 (6.9)	<0.001

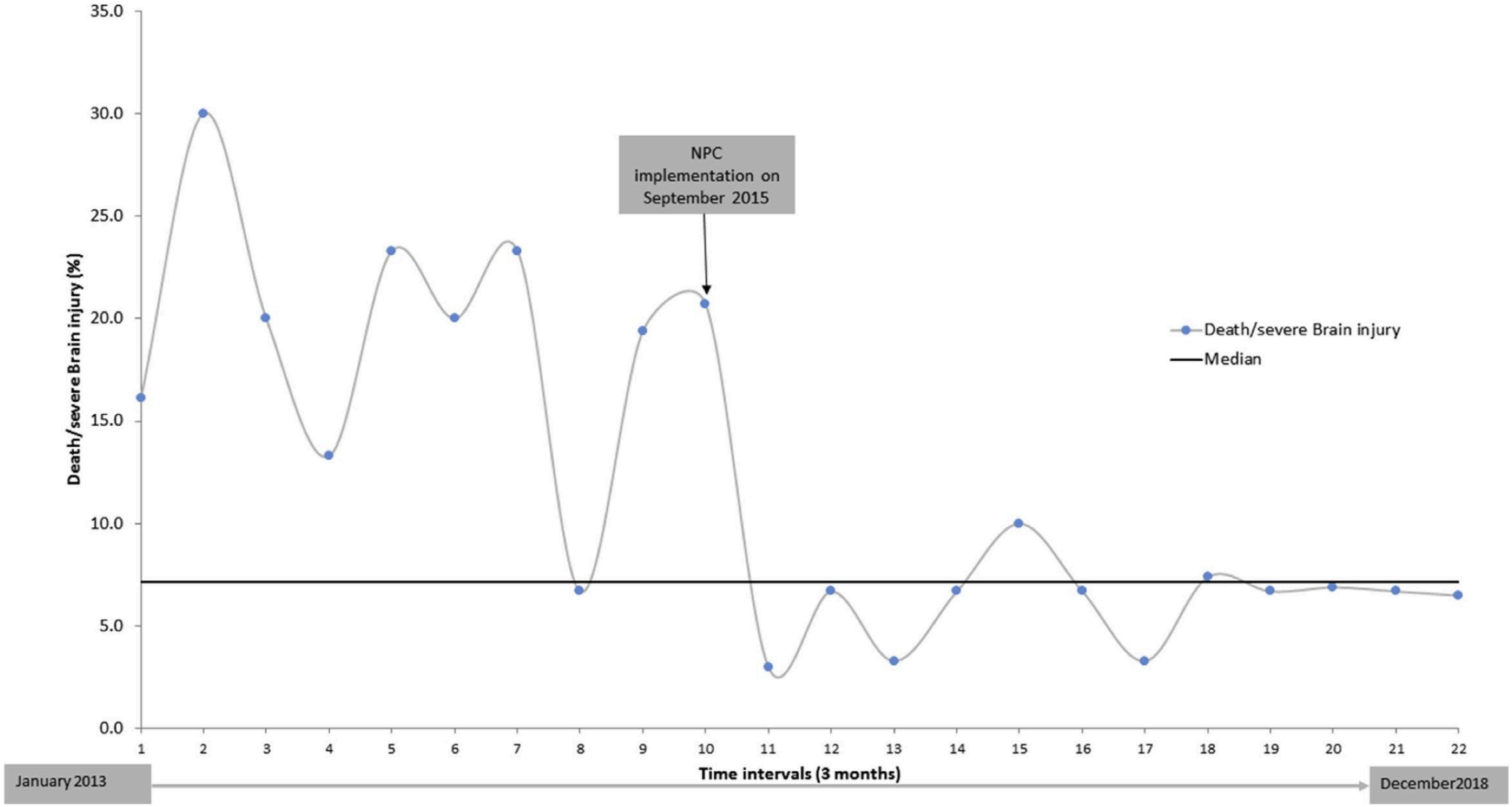


FIGURE 2. Run chart before and after the implementation of the NPC bundle. The color version of this figure is available in the online edition.

	Born Jan 1, 2013 to Sep 20, 2015 (n=342)	Born Sep 21, 2015 to Dec 31, 2018 (n=401)	p-value*
Died before age 21 months	38 (11.1%)	28 (7.0%)	0.049
Milder or severe disability:			
CP (any severity)	19/284 (6.7%)	11/344 (3.2%)	0.041
Visual impairment or blindness	7/287 (2.4%)	7/349 (2.0%)	0.711
Hearing impairment or deafness	3/286 (1.0%)	1/347 (0.3%)	0.333
Cognitive delay <85	54/248 (21.8%)	35/215 (16.3%)	0.135
Any milder or severe disability	69/251 (27.5%)	46/218 (21.1%)	0.109
Severe disability:			
CP GMFCS 3-5	4/284 (1.4%)	2/344 (0.6%)	0.418
Bilateral blindness	3/287 (1.0%)	1/349 (0.3%)	0.332
Bilateral deafness	0/286 (0.0%)	1/347 (0.3%)	>0.999
Cognitive score <70	21/248 (8.5%)	4/215 (1.9%)	0.002
Any severe disability	22/251 (8.8%)	7/218 (3.2%)	0.013
Death or any severe disability	60/289 (20.8%)	35/246 (14.2%)	0.049
Bayley III Outcomes:			
Motor score <85	63/192 (32.8%)	59/190 (31.1%)	0.712
Language score <85	79/186 (42.5%)	64/170 (37.6%)	0.354
Cognitive score <85	54/248 (21.8%)	35/215 (16.3%)	0.135
Any motor, language, or cognitive <85	113/190 (59.5%)	101/183 (55.2%)	0.403

SickKids

Brain Care Bundle by NICU Nurses

Brain Care Recommendations: Postnatal Interventions Infants < 30 weeks AND < 72 hours of age		
	Action	**Rationale**
Achieve and Maintain Normothermia	Aim to prevent hypothermia (<36 °C) and hyperthermia (>38 °C) Use heat provision measures with close monitoring and documentation eg polyethylene plastic bag on blankets for infants ≤ 28 weeks, chemical warming mattress	Hypothermia associated with a higher risk of IVH (Miller et al 2011)
Maintain Neutral/Midline Head Positioning	**Advise referral center of these practices** • Avoid prone positioning • Maintain neutral/midline head position in sidelying or supine • Maintain neutral/midline head position during handling and procedures • Turn infant as a unit • Head of bed elevated 30 degrees after NICU admission • Complete x-rays with head of bed elevated ◦ X-ray completion a 2 person procedure	Turning infant's head to the side affects jugular venous return and may affect intracranial pressure and cerebral blood flow Tilting the head up and down in preterm infants alters cerebral blood volume (Pichler et al, 2001) ICP lower with HOB elevated 30 degrees (Goldberg et al, 1983)

SickKids Guidelines on Bundle Care by Nurses

SickKids

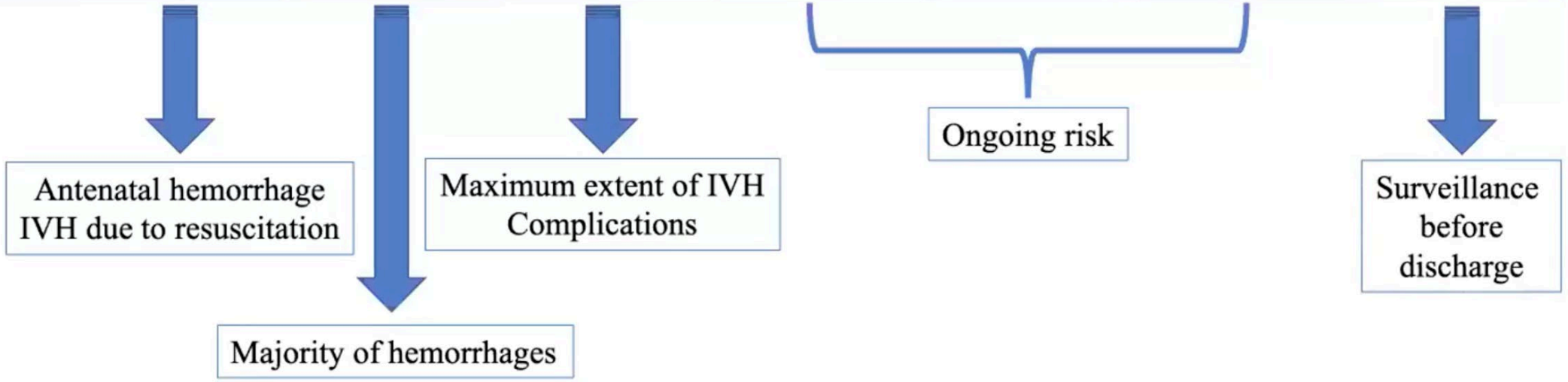
Brain Care Bundle by NICU Nurses

Brain Care Recommendations: Postnatal Interventions Infants < 30 weeks AND < 72 hours of age		
Action		**Rationale**
Gentle Diaper Changes	▪ Slightly raise buttocks to change diaper ▪ Avoid lifting legs ▪ **Infants < 1000 grams:** open diaper for 4 days to minimize groin irritation and potential skin breakdown	Minimize fluctuations in cerebral blood flow since cerebral circulatory changes demonstrated with diaper changes, specifically abrupt changes in venous return and cardiac preload with elevation of lower extremities (Limperopoulos et al, 2008)
Gentle Care	▪ Minimal and gentle handling ▪ Care by nurses with expertise in VLBW infant care To facilitate expertise, co-care/training with an experienced nurse should be facilitated ▪ Gently weigh and change under sheet once daily A 2 person procedure for 72 hours ▪ Avoid changing bedsheet for 72 hours A 2 person procedure if required before 72 hours ▪ Provide nesting and containment **Minimize Light:** Prevent constant exposure to light Cover isolette No direct light in infants' eyes **Minimize Noise:** Mute alarms swiftly Do not place objects on isolette Speak softly at bedside	Prevent agitation and manoeuvres that may fluctuate cerebral blood flow

SickKids Guidelines on Bundle Care by Nurses

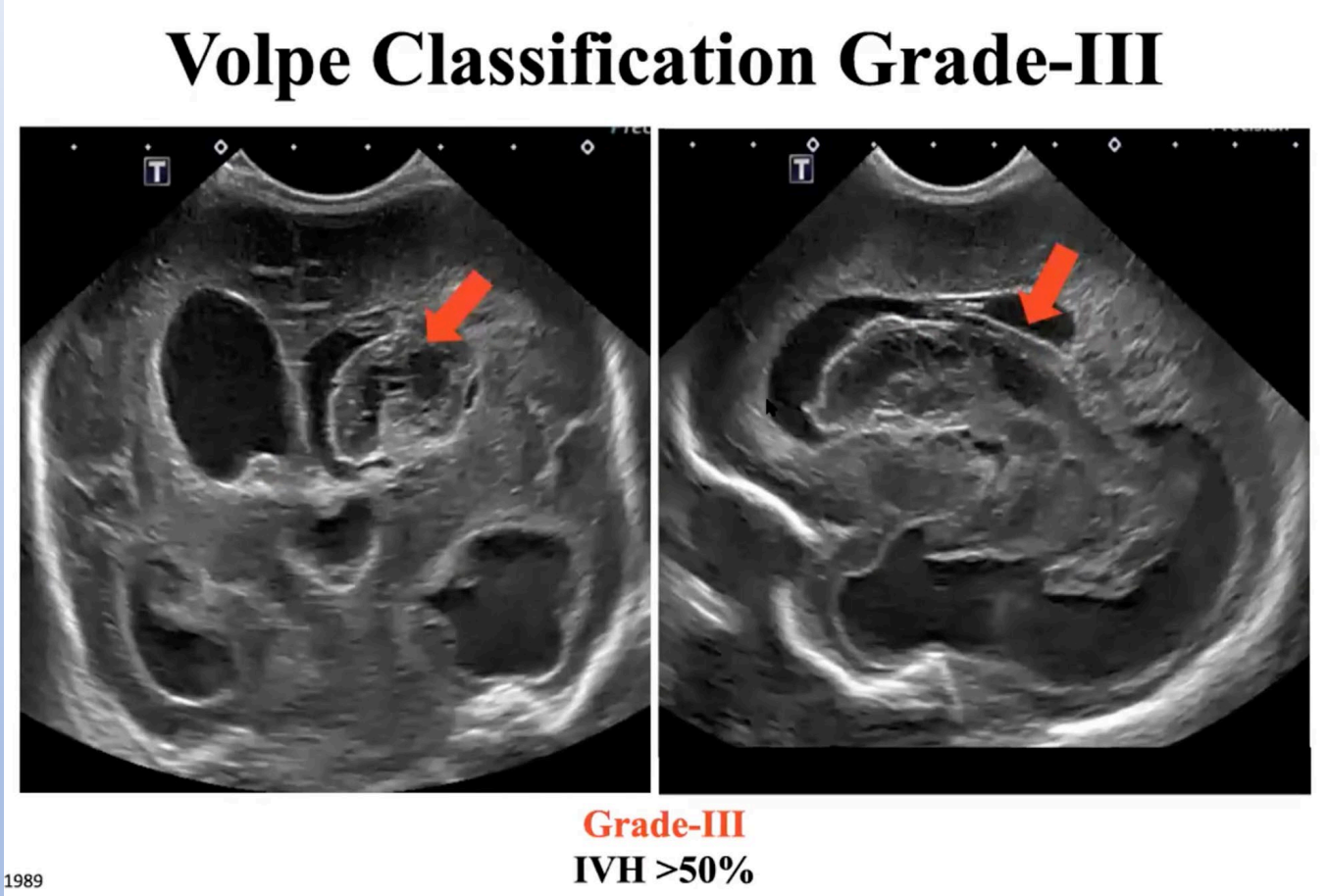
EurUS.Brain Group's Recommendations, 2020

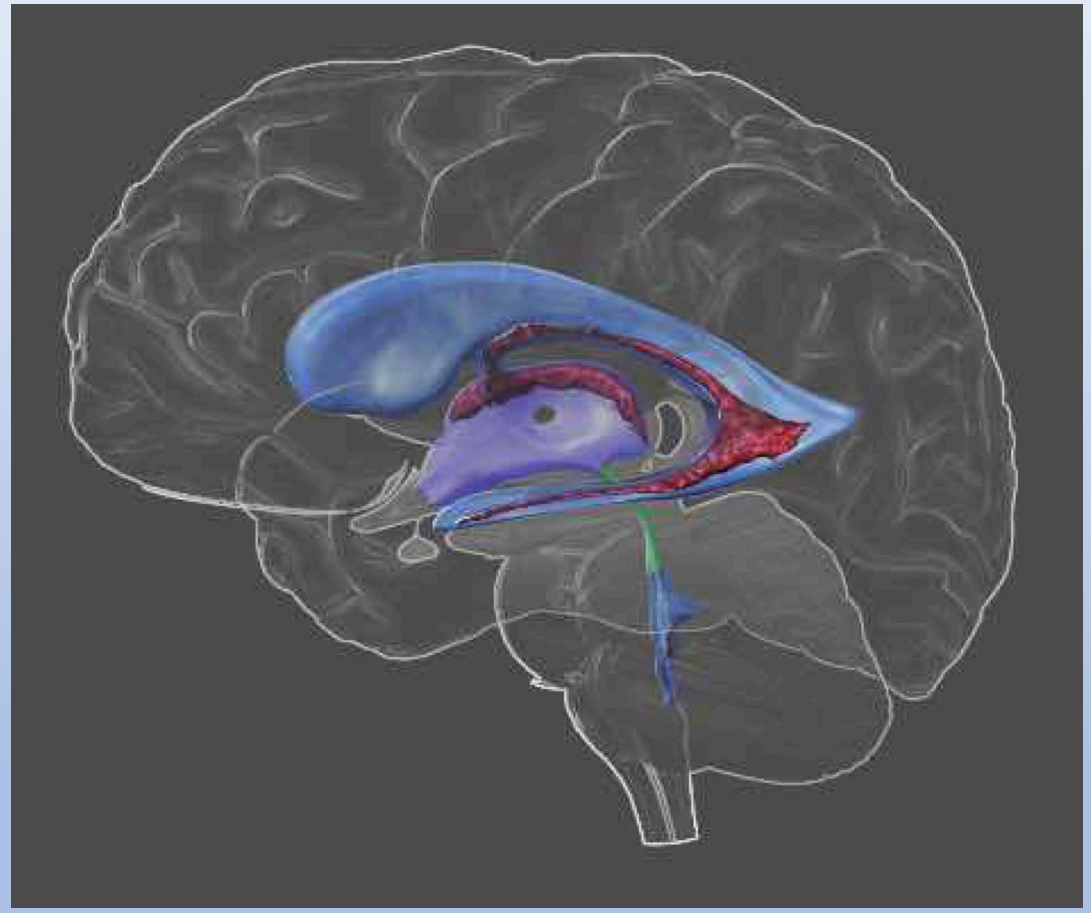
	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	Later Scans
<28 weeks	+	+	+	+	+	+	Every other week until term
≥28 weeks	+	+	+	+		+	At 6 weeks and at term



Dudink J et al. Pediatr Res, 2020
Parodi A et al. Pediatr Res, 2020

Grade III IVH

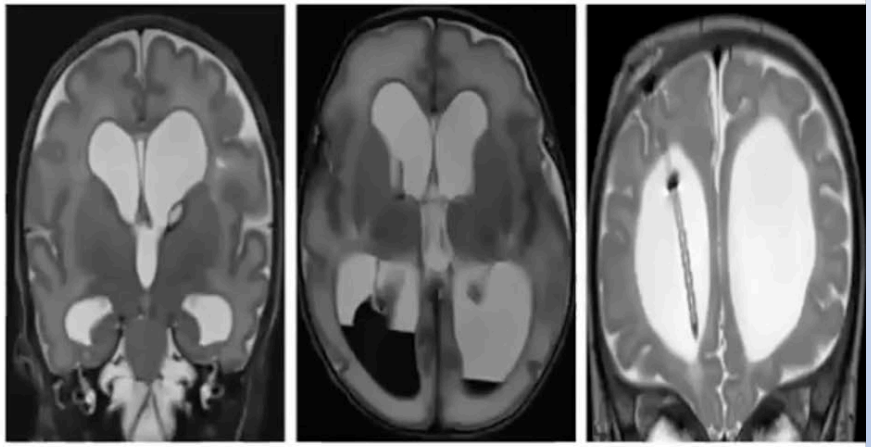




Volpe J., Ann. Neurol. 1989

Post-hemorrhagic Ventricular Dilatation (PHVD)

- Ventricular dilatation following GMH-IVH

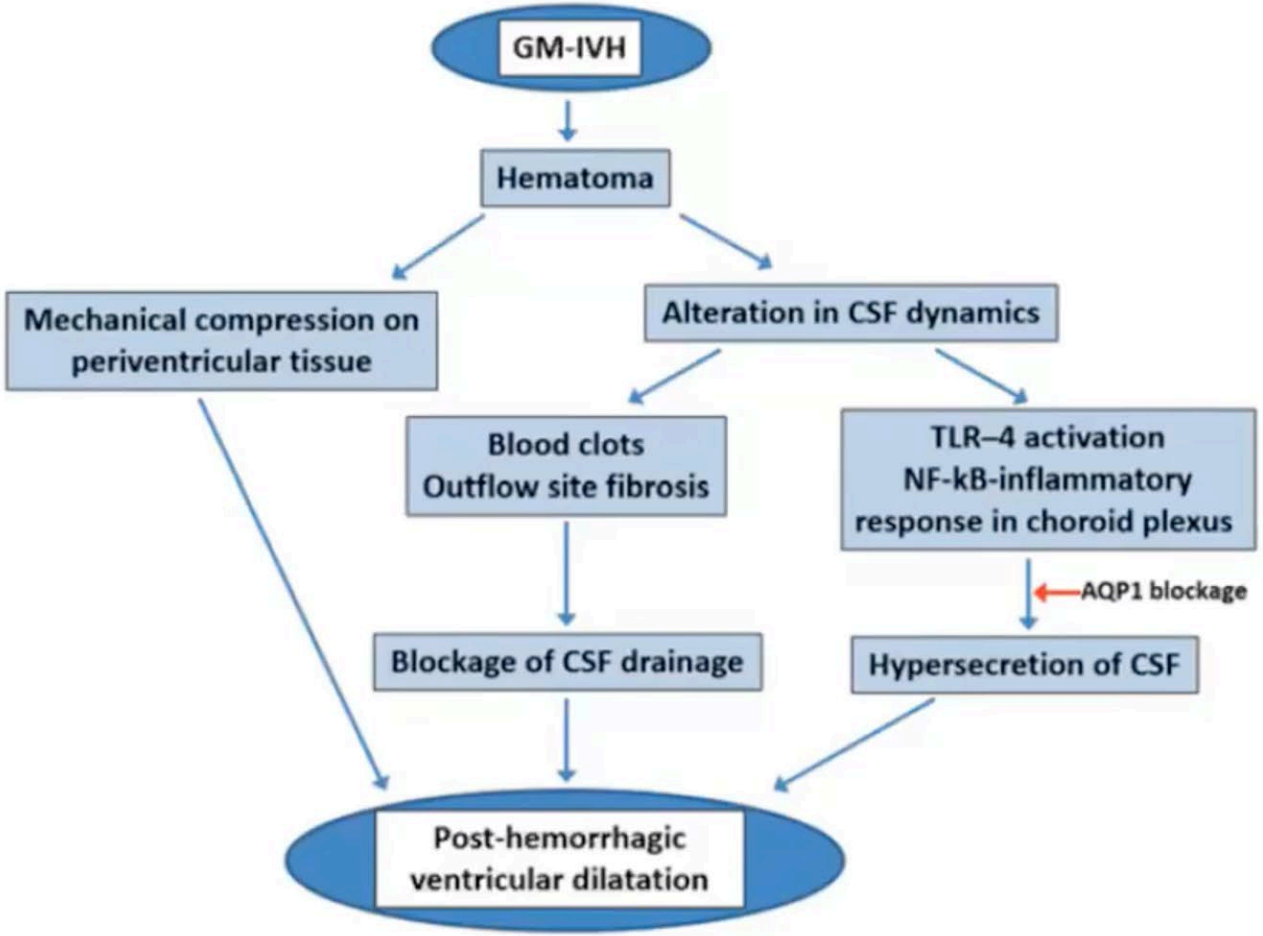


- Umbrella term that includes
  - Acute
  - Chronic stages
- Hydrocephalus (=chronic stage) also falls under this umbrella

El-Dib M et al. J Pediatr, 2020

Why Do Ventricles Enlarge?

Current pathophysiologic mechanisms



Karimy JK et al. Nat Med, 2017
Romantsik O et al. Neoreviews, 2019

Can we reduce morbidity assoc with PHVD?

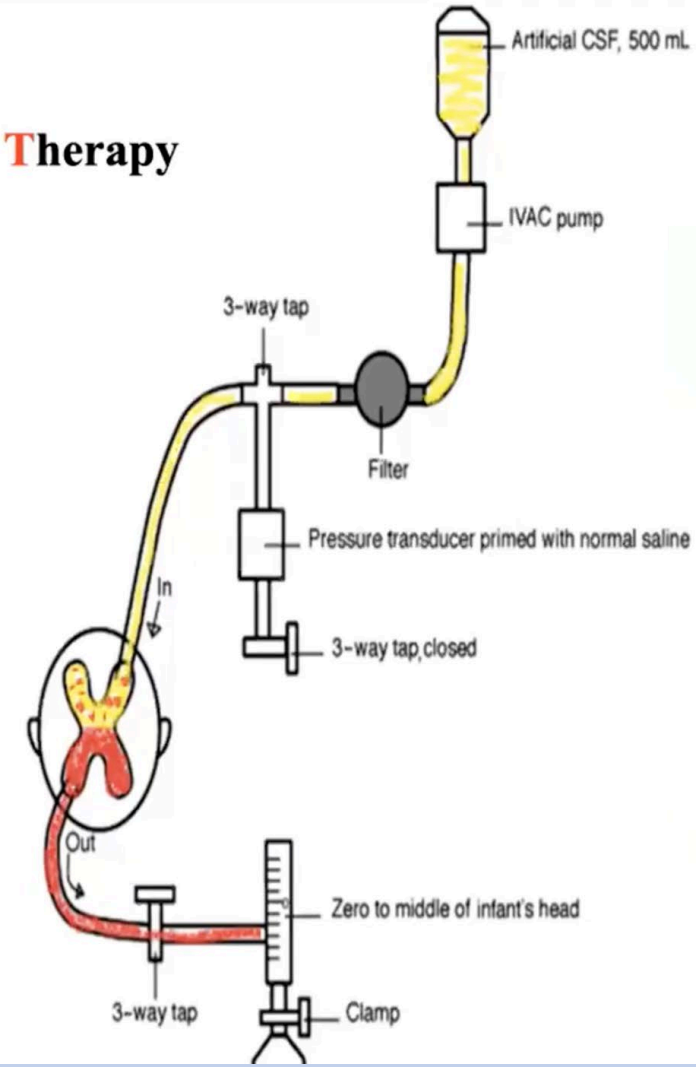
DRIFT Trial

Drainage, Irrigation, Fibrinolytic Therapy

- DRIFT (n=34) vs Standard treatment (n=36)
- VP-shunt
  - 38% vs 39%
- Mortality/VP-shunt
  - 44% vs 50%

Non-significant

- **Stopped early → secondary hemorrhage**
  - 35% vs 8%



Whitelaw A et al. Pediatrics, 2003
Whitelaw A et al. Pediatrics, 2007
Figure adapted from Whitelaw A et al. Pediatrics, 2003

Balance in Favor of Early Intervention?

- Invasive
- Early surgery and anesthesia
- Risk of infection

- Preserved white matter volume
- Fewer VP shunts
- Improved outcomes

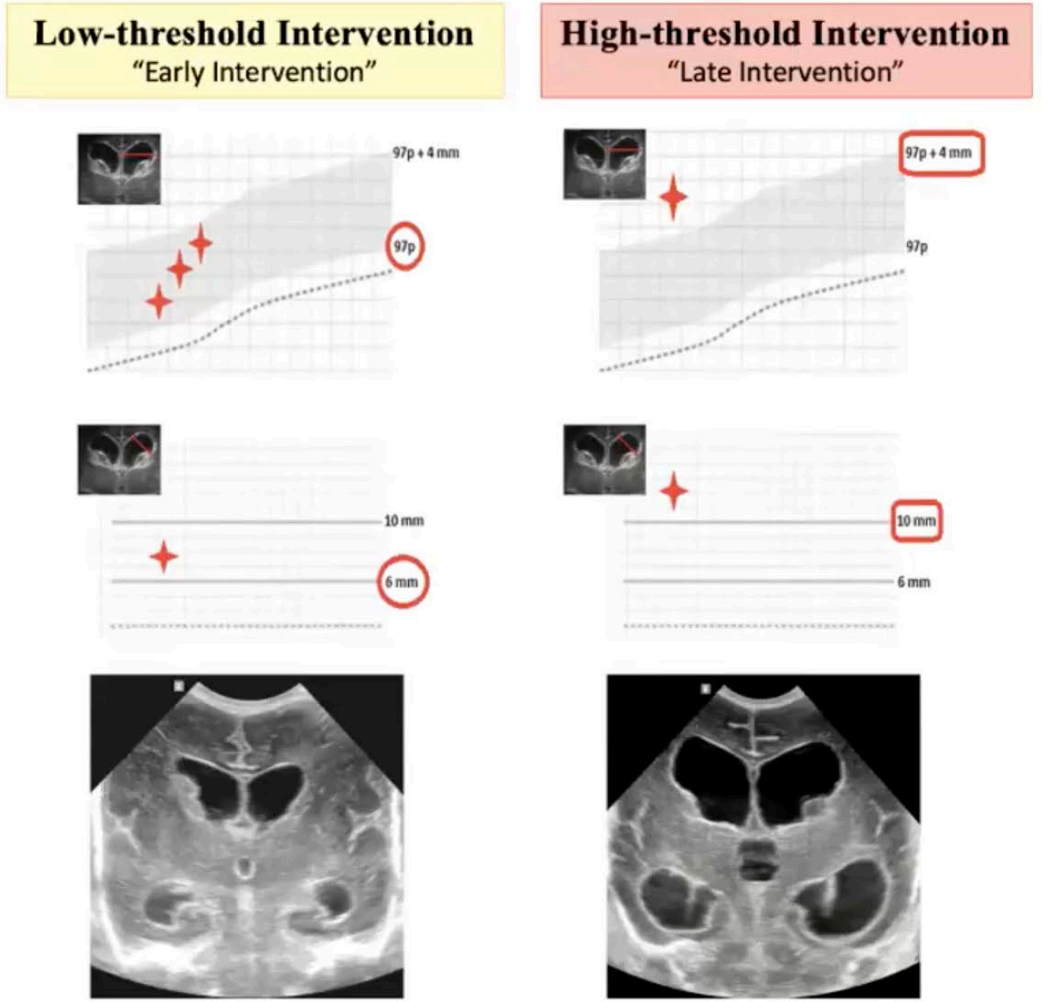
The ELVIS Trial

Early vs Late Ventricular Intervention Study

- RCT, 2006-2016
- 6 countries, 14 centers

- n=126 infants <34 wk
- Ultrasonographic criteria used

- Primary outcome: Death/VP-shunt



De Vries LS et al. Arch Dis Child Fetal Neonatal Ed, 2019

DRIFT vs. ELVIS

2-year outcomes	DRIFT	ELVIS early	ELVIS late
Cognitive score			
Normal range	23%	78%	71%
< -1 SD	26%	16%	16%
< -2 SD	51%	6%	13%
Motor score			
Normal range	12%	61%	64%
< -1 SD	15%	29%	15%
< -2 SD	73%	10%	21%

Comparison with Previous Studies

Trial	Intervention	ND Impairment (%)
Ventriculomegaly Trial Group *Arch Dis Child Fetal Neonatal Ed, 1994*	High-threshold Increased ICP signs	49 47
Kennedy et al. Acetazolamide Trial *Pediatrics, 2001*	Increased ICP signs	66
Whitelaw et al. DRIFT Trial *Pediatrics, 2010*	DRIFT High-threshold	46 58
Leijser et al. *Neurology, 2018*	Low-threshold Increased ICP signs	5 52
ELVIS Trial *de Vries LS et al. Arch Dis Child Fetal Neonat Ed, 2019* *Cizmeci MN et al. J Pediatr, 2019* *Cizmeci MN et al. J Pediatr, 2020*	Low-threshold High-threshold	10 20

- *Intervening earlier is associated with more favorable outcomes*

How should we approach PHVD?

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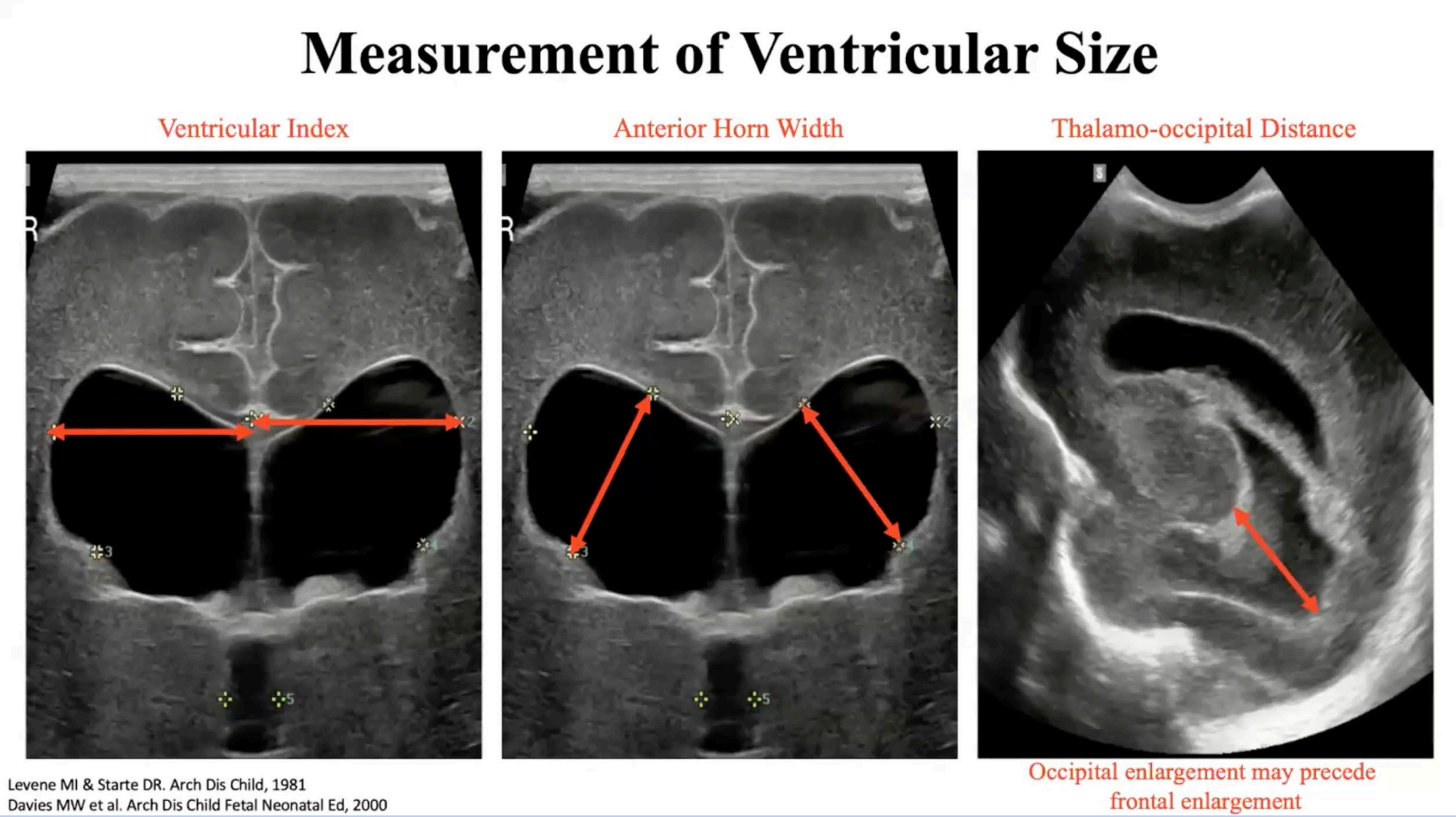
MEDICAL PROGRESS

Management of Post-hemorrhagic Ventricular Dilatation in the Infant Born Preterm

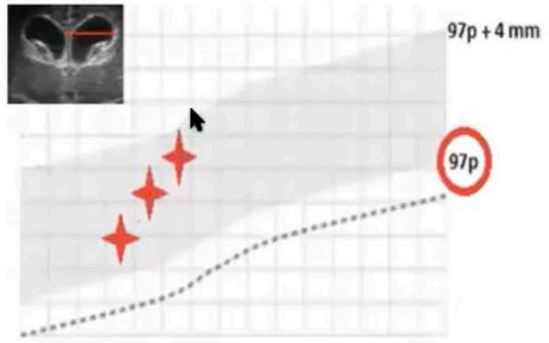
Mohamed El-Dib, MD[1], David D. Limbrick, Jr, MD, PhD[2], Terrie Inder, MBCHB, MD[1], Andrew Whitelaw, MD[3], Abhaya V. Kulkarni, MD, PhD[4], Benjamin Warf, MD[5], Joseph J. Volpe, MD[1,6], and Linda S. de Vries, MD, PhD[7,8]

Standardized approach to CUS evaluation for PHVD to guide management

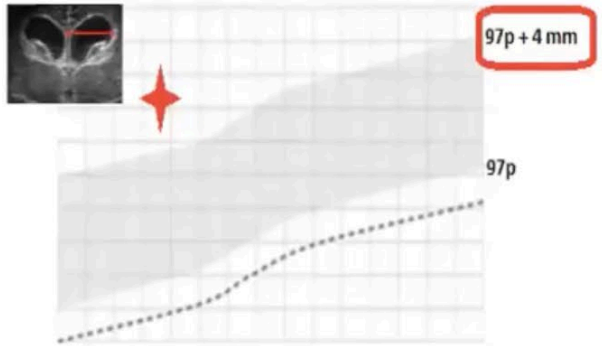


Timing of Lumbar Punctures

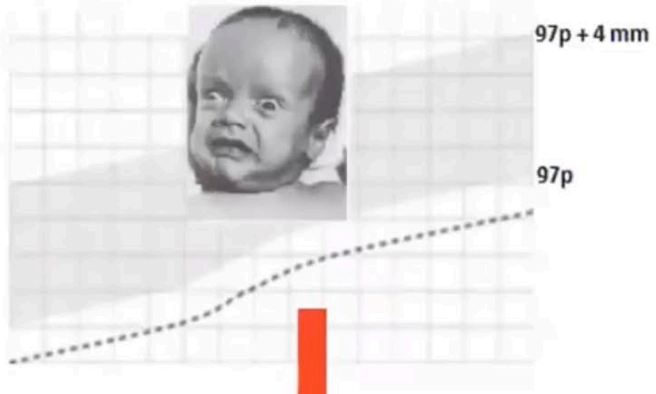
Low-threshold Intervention
"Early Intervention"



High-threshold Intervention
"Late Intervention"



Waiting for Clinical Signs
"Very Late Intervention"



Increase in head circumference > 2 cm/wk

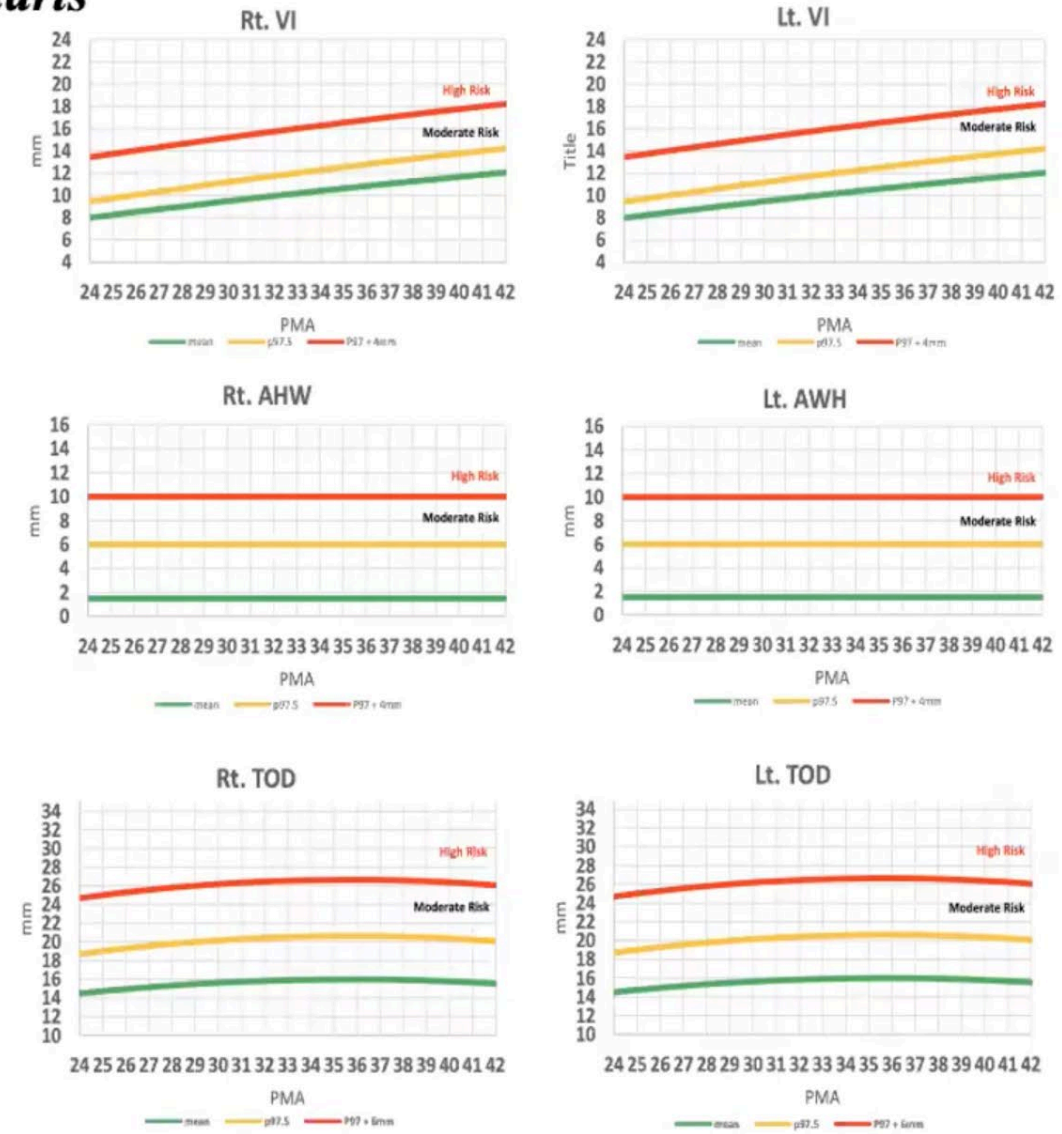
Bulging fontanelle

Separated sutures

Where to Plot?

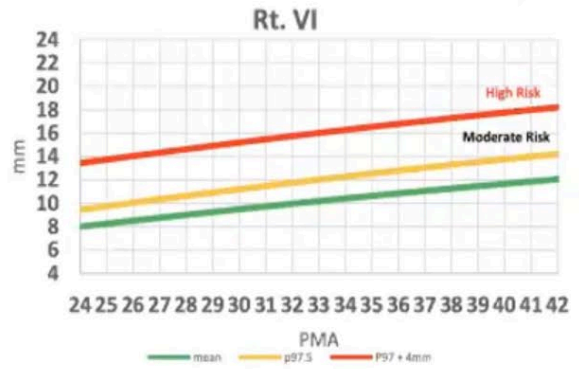
New Reference Charts

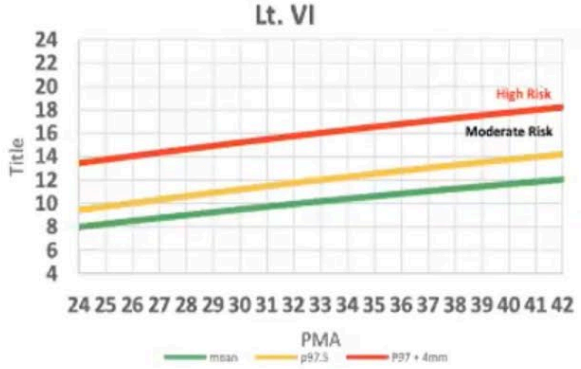
- Charts by Levene, 1981
  - Starts from 27 wk
  - Not suitable for extreme preterms
- New reference charts:
  - Brouwer et al. Radiology, 2012
  - Longitudinal data on 625 infants
  - Starts from 24 wk
- Colorful adaptation by:
  - El-Dib et al. J Pediatr, 2020

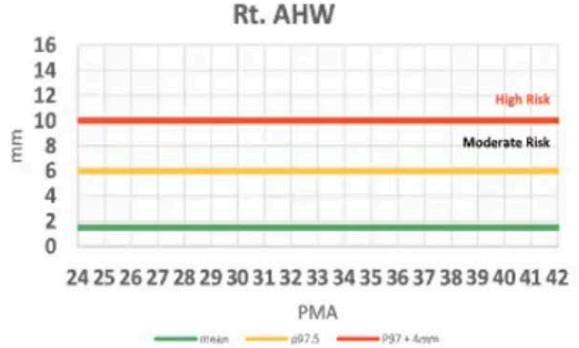


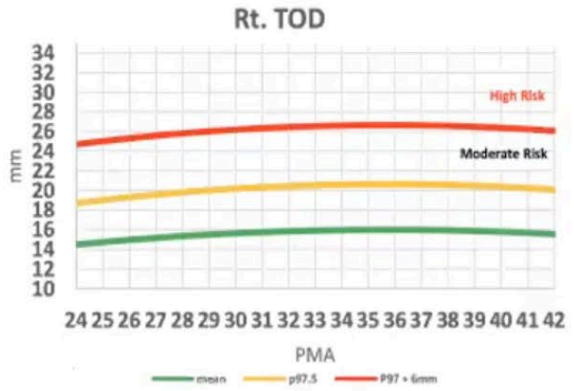
Levene MI & Starte DR. Arch Dis Child, 1981
Brouwer MJ et al. Radiology, 2012
Figure adapted from El-Dib M et al. J Pediatr, 2020

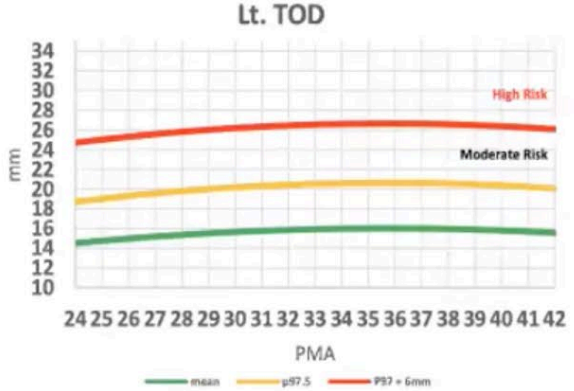
Key Points: *Ultrasonographic Follow-Up & Early Intervention*











Green Zone

Key Criteria:

Ventricular size with the following

- **VI ≤ 97th percentile**
  &
- **AHW ≤ 6 mm**

And

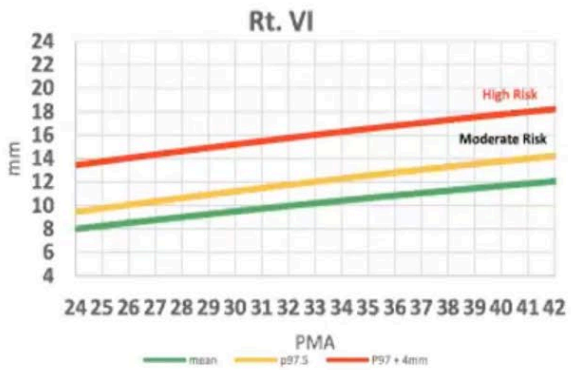
Absence of the following clinical criteria:

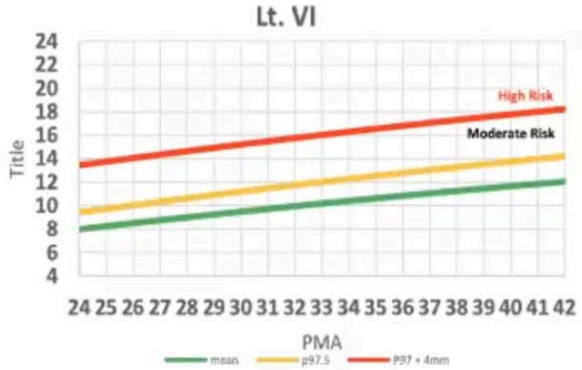
- **HC growth > 2 cm per week**
- **Separated sutures**
- **Bulging fontanelles**

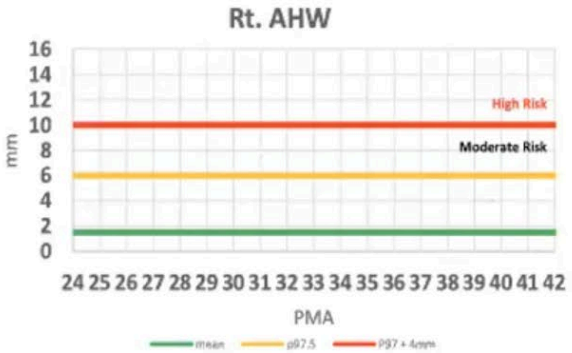
Management:

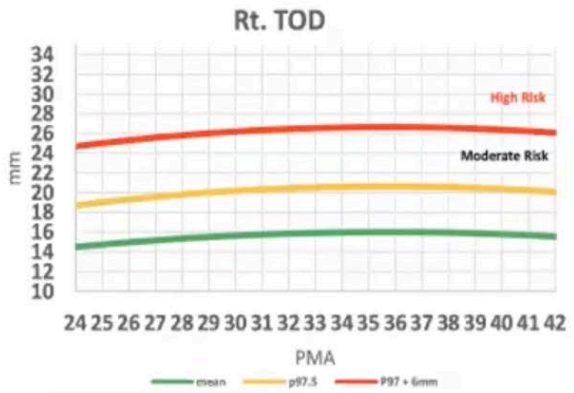
- **Observation in NICU**
- **cUS twice a week until stable for 2 weeks then every 1-2 weeks till 34 weeks PMA**
- **MRI at Term Equivalent**

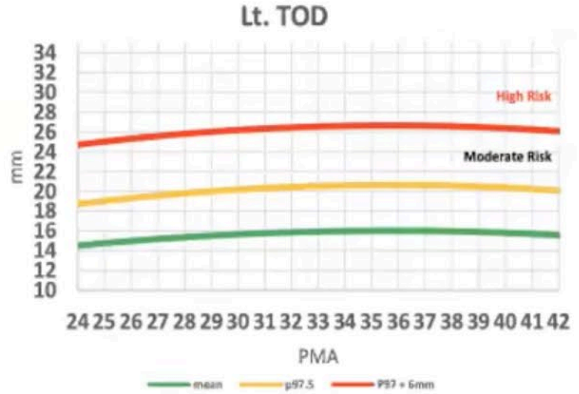
Key Points: *Ultrasonographic Follow-Up & Early Intervention*











Yellow Zone

Key Criteria:

Ventricular size with the following

- **VI > 97th percentile**

&

- **AHW > 6 mm &/or TOD > 25 mm**

And

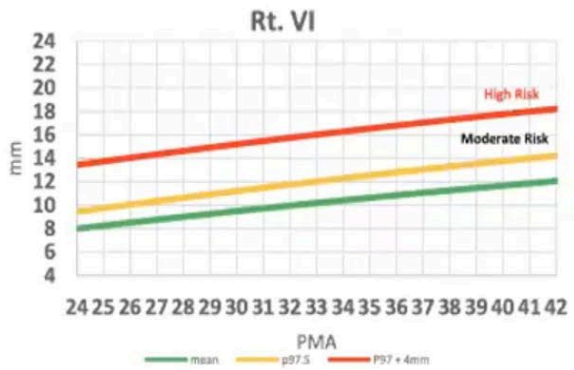
Absence of the following clinical criteria:

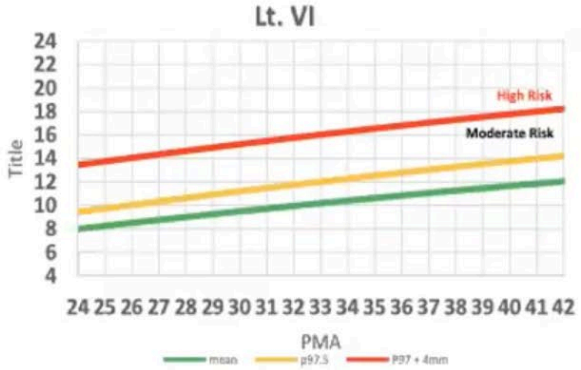
- **HC growth > 2 cm per week**
- **Separated sutures**
- **Bulging fontanelles**

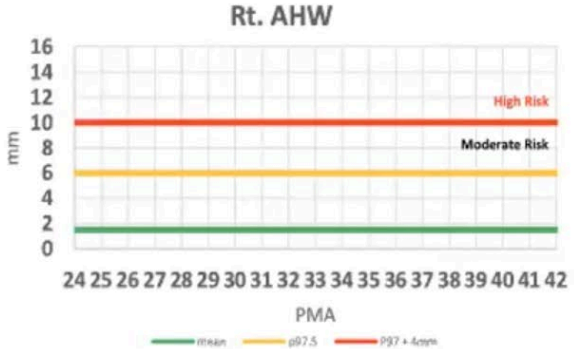
Management:

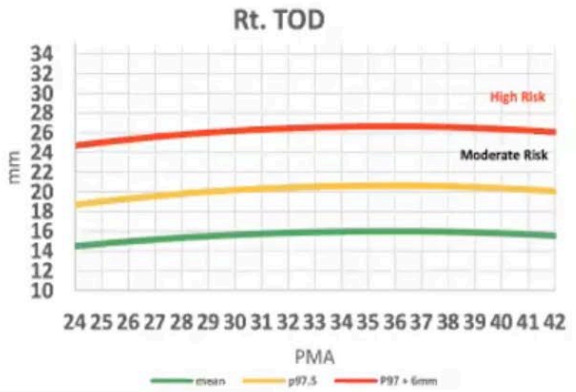
- **Referral to a regional center for neurosurgical review**
- * **Consider LP 2-3 times**
- **cUS 2-3X a week until stable for 2 weeks then every 1-2 weeks till 34 weeks PMA**
- **Neurosurgical intervention when no stabilization occurs**
- **MRI at Term Equivalent**

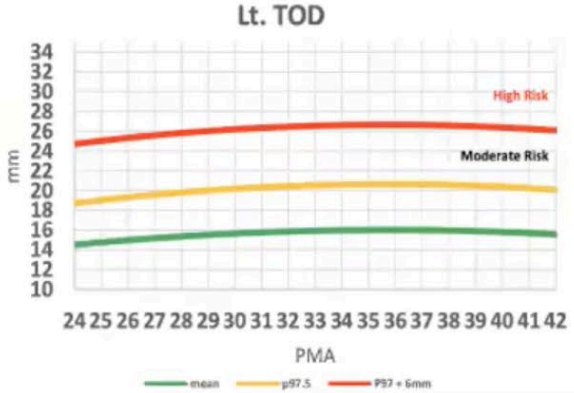
Key Points: *Ultrasonographic Follow-Up & Early Intervention*











Red Zone

Key Criteria:

Ventricular size with the following

- **VI > 97th percentile + 4mm**

&

- **AHW > 10 mm &/or TOD > 25 mm**

Or

Any of the following clinical criteria

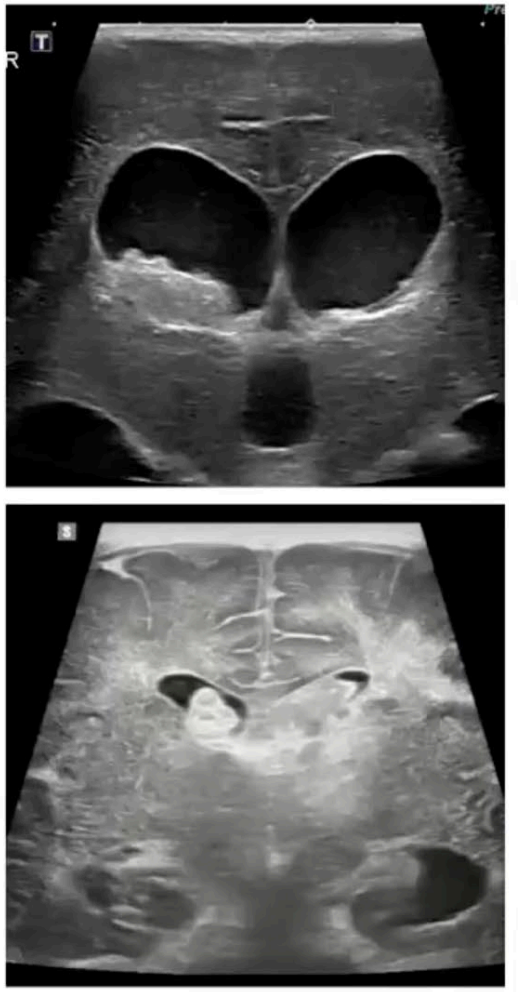
- **HC growth > 2 cm per week**
- **Separated sutures**
- **Bulging fontanelles**

Management:

- **Consider LP 2-3 times**
- **Neurosurgical intervention including either temporizing measures or VP shunt**
- **MRI at Term Equivalent**

PHVD management summary

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



Conclusions, parting words

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

Questions

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Our Mission

To advance newborn brain care through international multidisciplinary collaboration, education, and innovation.

Our Vision

A world in which all newborns have access to and receive the optimal brain care.

Join here!

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