CANADIAN CONSENSUS PRACTICE RECOMMENDATION - POST-HEMORRHAGIC VENTRICULAR DILATATION IN PRETERM INFANTS: DIAGNOSIS AND MANAGEMENT DURING THE NEONATAL PERIOD

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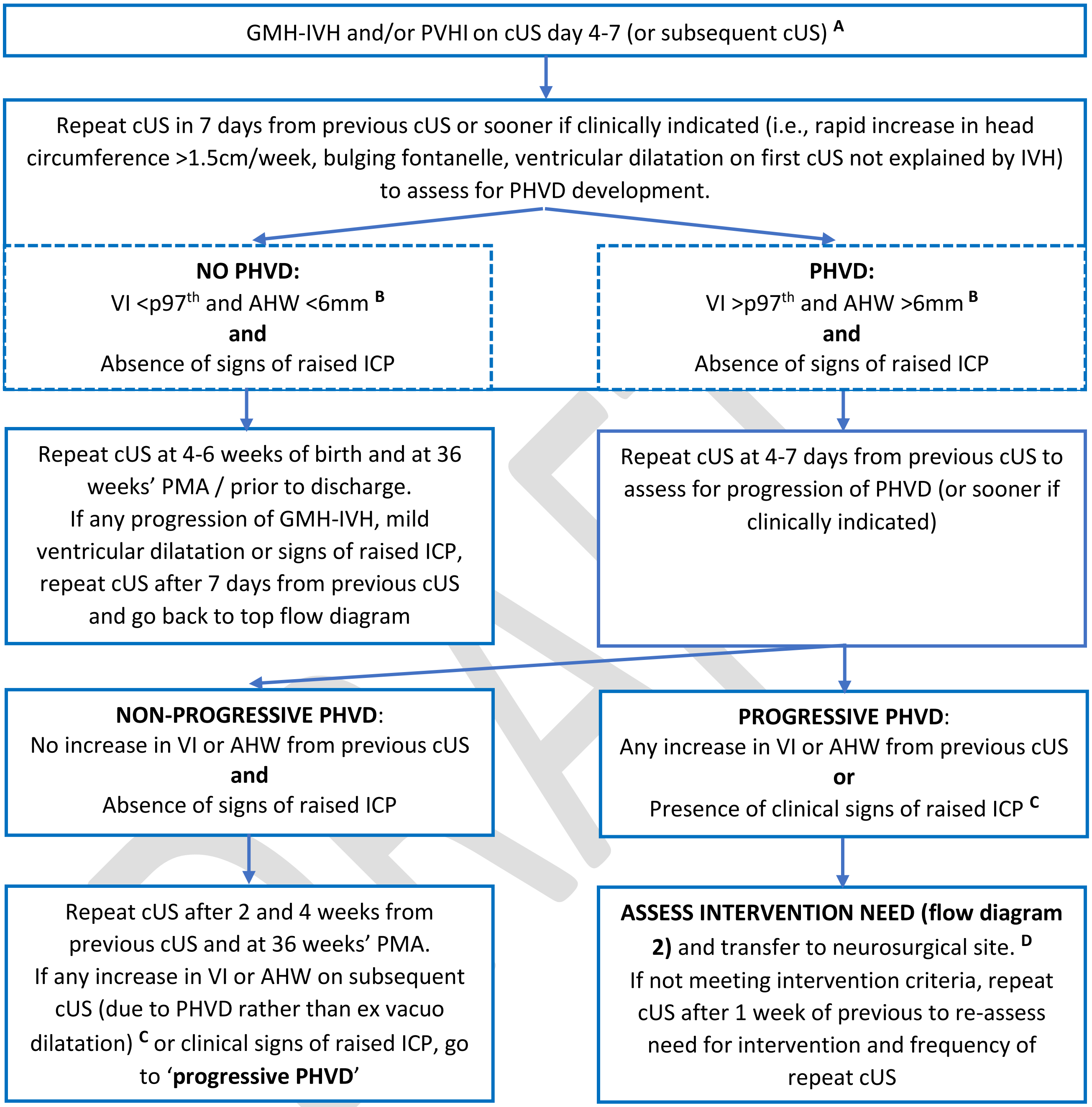
Algorithm for cranial US monitoring in preterm infants at risk for post-hemorrhagic ventricular dilatation



A - See also 'Clinical practice guidelines: Diagnoses and classification of preterm brain injury from cranial ultrasound: consensus viewpoint' for GMH-IVH grading and cUS monitoring (Mohammad et al. Front Pediatr 2021;9:618236).
B - Use the following calculators: for 24-29 weeks https://tinyurl.com/PHVD-Measures-1hyperlink; for 24-42 weeks https://tinyurl.com/PHVD-Measures-2.
C - Rule out ex vacuo dilatation as cause of ventricular dilatation prior to intervention (see pages 10-11).
D - Decisions regarding need for intervention, performance of lumbar puncture and, if needed, transfer to neurosurgical site can be made at discretion of the by neonatal team.
Of note: The timing for consultation of neurosurgical team may vary per center, from time of diagnoses of PHVD to time of need for neurosurgical intervention, as per local agreements.
Abbreviations: AHW, anterior horn width; cUS, cranial ultrasound; GMH-IVH, germinal matrix-intraventricular hemorrhage; ICP, intracranial pressure; p, percentile; PHVD, post-hemorrhagic ventricular dilatation; VI, ventricular index.

Algorithm with stepwise approach for intervention for PHVD

PHVD INTERVENTION CRITERIA:
VI >p97th + 4mm *or* AHW >10mm
or
Presence of clinical signs of raised ICP [A]

↓

OPTIONAL[B, C]: Perform therapeutic LP (10ml/kg), ideally followed by cUS with VI and AHW measurement on following day to assess need for further LP; **UNLESS:** (suspicion of) aqueduct stenosis, <1 week of birth, neurosurgical intervention readily available or preferred, LP unsuccessful, or maximum of 3 LPs reached. In the latter cases, **go to next box**.

Target of intervention: VI <p97th + 4mm **and** AHW <10mm
→ If LP successful but target not reached: Repeat LP till target or maximum of 3 LPs reached.
→ If target reached: Repeat cUS at least twice/week in the first 2 weeks, and assess need for intervention (and frequency of repeat cUS).

↓

If **VI >p97th + 4mm or AHW >10mm** despite serial LPs or LPs unsuccessful / omitted: Consider ventricular reservoir placement followed by initially daily CSF taps (optional: VSGS or EVD).[D] Each reservoir tap is ideally preceded by cUS with VI and AHW measurements to guide need and volume for tap. In case of sufficient clinical indication to tap despite unavailability of cUS, a tap can be done at discretion of medical team. [C]

Target of intervention: VI <p97th + 4mm **and** AHW <10mm
→ If target not reached: Continue reservoir taps guided by cUS till target reached.
→ If target reached: Repeat cUS at least twice/week in the first 2 weeks, and assess need for intervention (and frequency of repeat cUS).

↓

If CSF taps from reservoir ongoing when infant reaches 37-40 weeks' PMA:
Trial of ≥48-72 hours **without** reservoir tap, followed by cUS with assessment of **FOHR and/or FTHR**.

↙ ↘

If **FOHR and/or FTHR <0.55** on cUS:
Hold off on permanent CSF diversion and repeat cUS with FOHR and/or FTHR weekly until discharge.
If FOHR and/or FTHR increases on subsequent cUS (due to PHVD rather than ex vacuo dilatation) or occurrence of signs of raised ICP, re-consider reservoir tapping or permanent CSF diversion. [F]

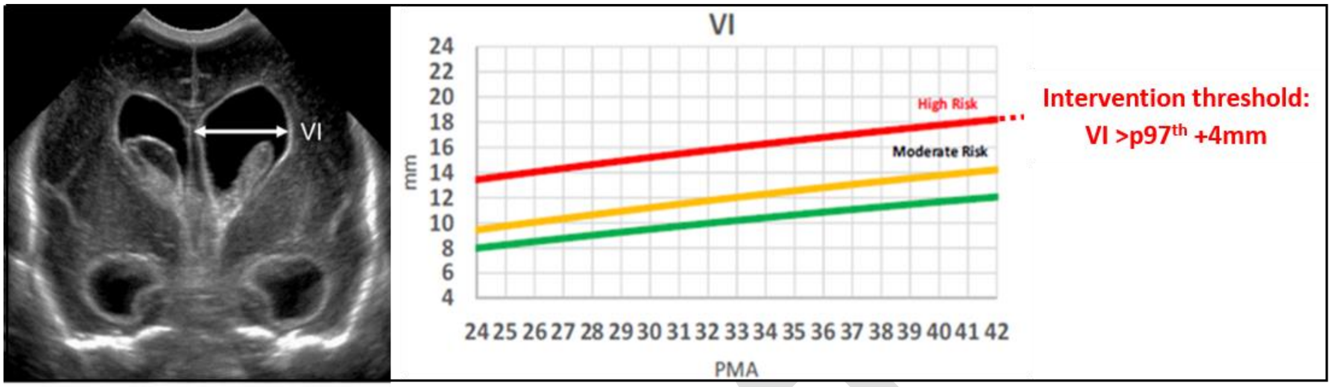
If FOHR and/or FTHR ≥0.55 on cUS:
Consider permanent CSF diversion, if meeting center-specific criteria, such as maximum CSF protein and RBC counts, minimum infant weight and age, and signs of raised ICP. [E]
Subsequent imaging with cUS and/or MRI is at the discretion of the neurosurgical team or most responsible care provider. [F]

A - No intervention should be performed when anterior fontanelle is sunken.
B - This step can be guided by the neonatal team. Consult Neurosurgery to be **considered** at this stage, based on local agreements.
C - Following each LP and reservoir tap, several mLs of CSF need to be sent to the lab for analysis of red cell and protein content and to rule out infection; See Appendix B.
D - Neurosurgery involvement is **indicated** from this step onwards

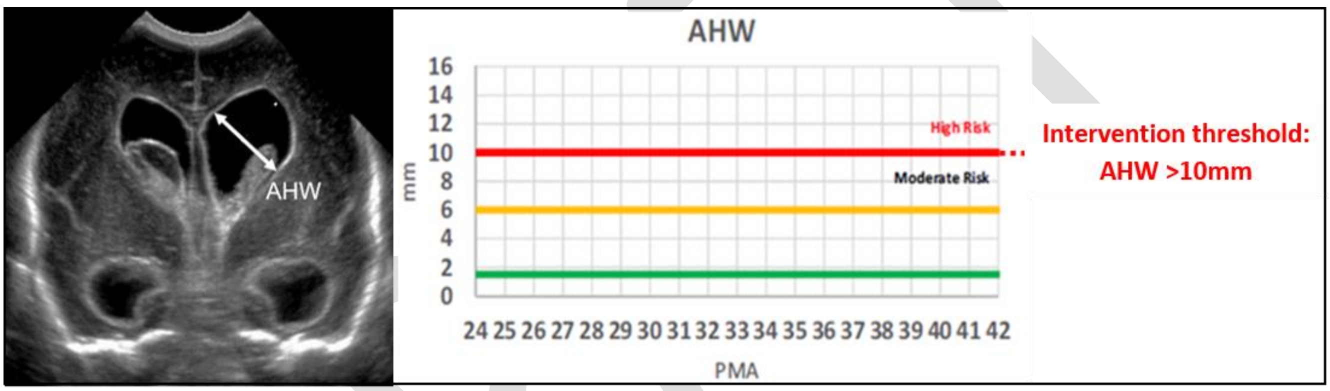
E - If these criteria are not yet reached or VP-shunt placement cannot take place within 48 hours, continue taps from ventricular reservoir in the interim; Reassessment of whether the infant meets the criteria for VP-shunt placement needs to take place on a regular (every 1-2 weeks) and case-by-case basis
F - If after VP-shunt placement infants are otherwise stable and ready to be discharged home, based on local infrastructure and expertise arrangements for outpatient follow-up by the neurosurgical team can be organized.
<u>Abbreviations</u>: AHW, anterior horn width; cUS, cranial ultrasound; ICP, intracranial pressure; FOHR, fronto-occipital horn ratio; FTHR, fronto-temporal horn ratio; LP, lumbar puncture; MRI, Magnetic Resonance Imaging; p, percentile; PHVD, post-hemorrhagic ventricular dilatation; VI, ventricular index.

<u>**Performance of ventricular measurements from cUS and intervention thresholds**</u>

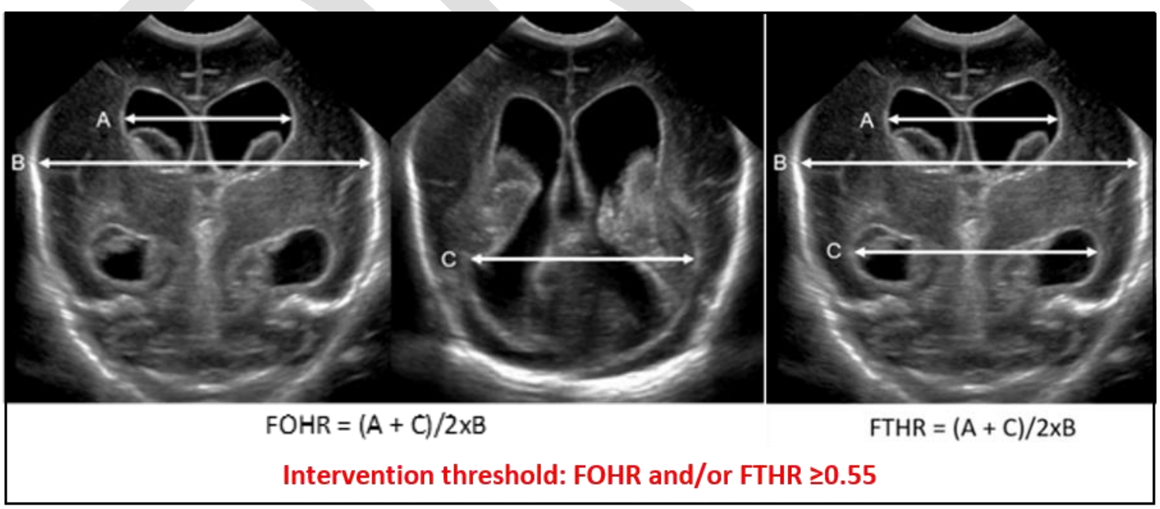
Ventricular Index (VI)



Anterior Horn Width (AHW)



Fronto-Occipital Horn Ratio (FOHR) and Fronto-Temporal Horn Ratio (FTHR)



BACKGROUND

Germinal matrix - intraventricular hemorrhage (GMH-IVH) remains common in very preterm infants (<32 weeks of gestation). The incidence increases with decreasing gestational age (GA) and is as high as 30% in infants born at a GA <29 weeks (*Leijser & de Vries 2019*). A clinically important complication of GMH-IVH is post-hemorrhagic ventricular dilatation (PHVD), which occurs in 30-50% of infants with a high-grade IVH (grade 3 with or without periventricular hemorrhagic infarction) (*Leijser & de Vries 2019*).

PHVD usually develops during the first 10-14 days after the onset of GMH-IVH. PHVD is caused by impaired drainage of cerebrospinal fluid (CSF) from the ventricular system, related to outflow obstruction of CSF due to clot formation and reduced reabsorption of CSF by arachnoid villi due to inflammation (*Leijser & de Vries 2019; El-Dib 2020; Limbrick & de Vries 2022; Holste 2022*). It is important to distinguish PHVD from distention of the lateral ventricles related to a large hemorrhage (or meningitis) in the acute phase of a GMH-IVH as the etiology and management differ (*Mohammad 2021*).

In the early stage of development, PHVD is mostly asymptomatic. This can be explained by the still compliant skull, large extracerebral spaces and high water content in the brain of preterm infants. Clinical signs of raised intracranial pressure (ICP), such as a rapid increase in head circumference (>1.5cm/week), diastasis of sutures, full fontanelle, irritability, bradycardias and apneas, often only develop several weeks after the onset of PHVD, when the ventricles may already be severely dilated (*Leijser & de Vries 2019*).

In approximately half of the infants who develop PHVD following GMH-IVH, the ventricular dilatation shows persistent progression over the course of weeks, while in the other half of the infants with PHVD, the ventricular dilatation shows initial progression followed by spontaneous arrest and even resolution over the course of days to weeks (*Murphy 2002; Inder 2024*). The progress of PHVD can be followed by serial bedside cranial ultrasound (cUS) examinations including measurements of lateral ventricular size (see below). Ventricular measurements have been shown to be superior to visual assessments of ventricular size and clinical signs of raised ICP to assess the severity and progression of PHVD, particularly in the early stage of PHVD development (*Korobkin 1975; Levene 1981; Liao 1986; Muller 1992; Ingram 2014; Obeid 2018; Lai 2022*).

Of clinical importance, severe PHVD can be associated with mortality (up to 10%) and adverse long-term neurodevelopmental outcomes, including cognitive problems (45-60%) and motor deficits such as cerebral palsy (up to 25%). PHVD has also been associated with behavioral problems, visual and hearing impairment and seizures, and can affect infant feeding skills and family quality of life and bonding (*Leijser & de Vries 2019*). The longer-term sequelae of PHVD are likely the result of injury and impaired growth and maturation of the developing preterm brain, secondary to the pressure on the brain tissue induced by ventricular dilatation (*Leijser & de Vries 2019; Obeid 2021; Nieuwets 2022*). Prolonged and/or high pressure on the periventricular white matter has been shown to directly restrict white matter perfusion, which in turn may lead to distortion, ischemia, free radical formation and inflammation of the white matter (*Leijser & de Vries 2019; El-Dib 2020*).

The timing and modality of intervention for PHVD remain controversial, as large randomized controlled trials are lacking. Available studies on short-term outcomes, such as infection rates and need for a permanent CSF diversion, do not show a consistent advantage for intervention modality (*Mazzola 2014; Badhiwala 2015; Wellons 2017*). Retrospective studies and small randomized controlled trials have shown benefits for neurodevelopmental outcomes in preterm infants with an early stepwise approach to intervention guided by a combination of ventricular measurements from serial cUS (occasionally referred to as early intervention approach) as compared to intervention guided by occurrence of clinical signs of raised ICP (occasionally referred to as late intervention approach) (*Whitelaw 2010; Srinivasakumar 2013; Leijser 2018; de Vries 2019; Luyt 2020; Cizmeci 2020; Parodi 2021; Lai 2021*). See section 'Intervention' below.

DIAGNOSIS

In most Neonatal Intensive Care Units (NICUs) in Canada, cUS is performed at least 3 times throughout the neonatal period in very preterm infants (<32 weeks' gestation), including between day 4-7 after birth, 4-6 weeks after birth and around 36 weeks' postmenstrual age (PMA). This is in accordance with the recently published Canadian Neonatal Network's 'Clinical Practice Guideline for Screening and Classification of Preterm Brain Injury Diagnosed with Cranial Ultrasound' (*Mohammad 2021*) and the position statement by the Canadian Pediatric Society 'Routine Imaging of the Preterm Neonatal Brain' (*Guillot 2020*). In case of a high-grade IVH or early signs of PHVD development on the first cUS, the frequency of cUS is intensified in order to more closely follow the onset and progress of PHVD.

An objective tool to diagnose and quantify PHVD progression and assess the effect of intervention is measurement of ventricular size. The most commonly used ventricular size indices for which normative and cut-off values for ventricular dilatation have been described are the Ventricular Index (VI), Anterior Horn Width (AHW), Fronto-Occipital Horn Ratio (FOHR) and Fronto-Temporal Horn Ratio (FTHR) (*Levene 1981; Kulkarni 1999; O'Hayon 1999; Davies 2000; Antes 2013; Radhakrishnan 2019; El-Dib 2020*). All these indices are obtained from cUS in coronal planes and measured as indicated below. The normative values can be used up to 44 weeks' PMA. See below and the online available reference charts for preterm infants 24-29 weeks' PMA (https://tinyurl.com/PHVD-Measures-1) and infants 24-42 weeks' PMA (https://tinyurl.com/PHVD-Measures-2).

Ventricular Index (VI): The distance between the midline of the brain and the most lateral border of the lateral ventricle, as measured in the coronal plane at the level of foramen of Monro (*Levene 1981; El-Dib 2020*) (*Figure 1*).

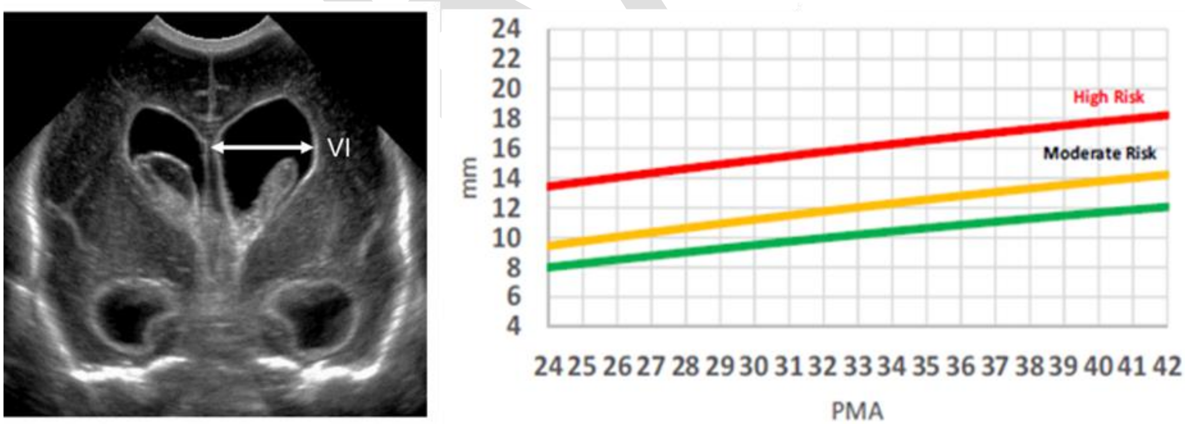


Figure 1. Coronal cUS scan (left) at the level of the foramen of Monro showing measurement of the VI (white arrow). Graph (right; *adapted from: El-Dib M, et al. J Pediatr 2020; 226: 16-27*) showing normal values and cut-off values for PHVD for the VI, with the yellow line reflecting the +2SD or 97th percentile line (moderate PHVD) and the red line reflecting the +3SD or 97th percentile +4mm line (severe PHVD). Of note: The VI cut-off for PHVD increases with increasing postmenstrual age (*Levene 1981; El-Dib 2020*).

Anterior Horn Width (AHW): The diagonal width of the anterior horn of the lateral ventricle at its widest, as measured in the coronal plane at the level of foramen of Monro (*Davies 2000; El-Dib 2020*) (*Figure 2*).

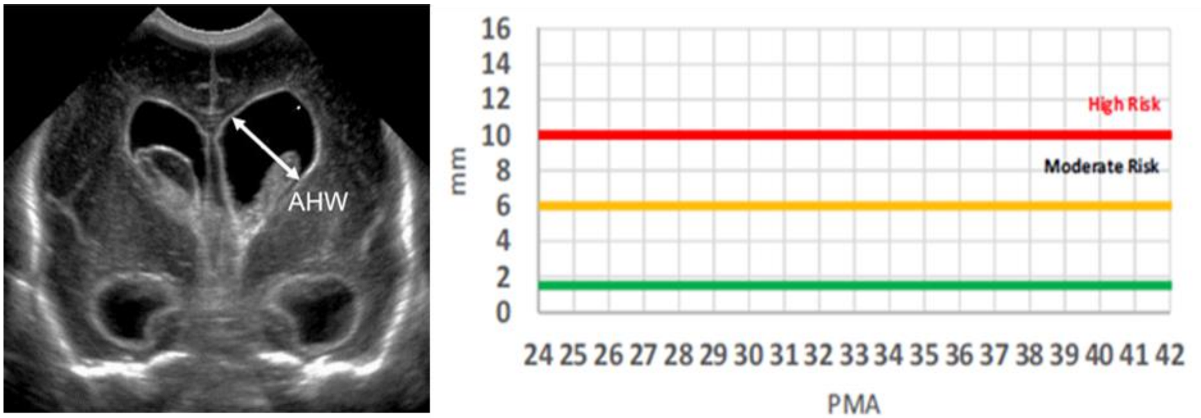
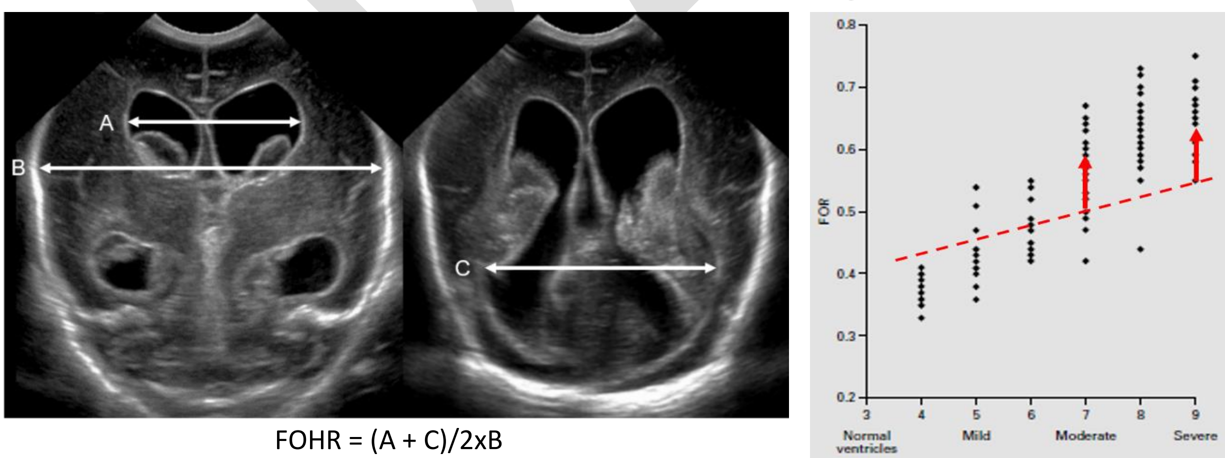


Figure 2. Coronal cUS scan (left) at the level of the foramen of Monro showing measurement of the AHW (white arrow), perpendicular to the axis of the lateral ventricle. Graph (right; *adapted from: El-Dib M, et al. J Pediatr 2020; 226: 16-27*) showing normal values and cut-off values for PHVD for the AHW, with the yellow line reflecting the +2SD or 97th percentile line (moderate PHVD) and the red line reflecting the +3SD or 97th percentile +4mm line (severe PHVD). Of note: The AHW cut-off for PHVD is 6 mm, independent of postmenstrual age (*Davies 2000; El-Dib 2020*).

Fronto-Occipital Horn Ratio (FOHR): The widest diameter of the frontal horns and the occipital horns divided by 2 times the widest bi-parietal diameter, as measured in coronal planes where the frontal and occipital horn diameter are at their widest (*Kulkarni 1999; O'Hayon 1999; Radhakrishnan 2019*) (*Figure 3*).



FOHR = (A + C)/2xB

Figure 3. Coronal cUS scans (left) showing the measurement of the three indices comprising the FOHR at their widest dimension, including bi-frontal horn distance (A), bi-parietal distance (B) and bi-occipital horn distance (C). Graph (right) showing normal values and cut-off values for PHVD (red dashed line) for the FOHR. The FOHR cut-off for PHVD is 0.5, independent of postmenstrual age up to 44 weeks (*Kulkarni 1999*).

Fronto-Temporal Horn Ratio (FTHR): The widest diameter of the frontal horns and the temporal horns divided by 2 times the widest bi-parietal diameter, as measured in the coronal plane where the frontal and temporal horns are at their widest (*Antes 2013; Radhakrishnan 2019*) (*Figure 4*).

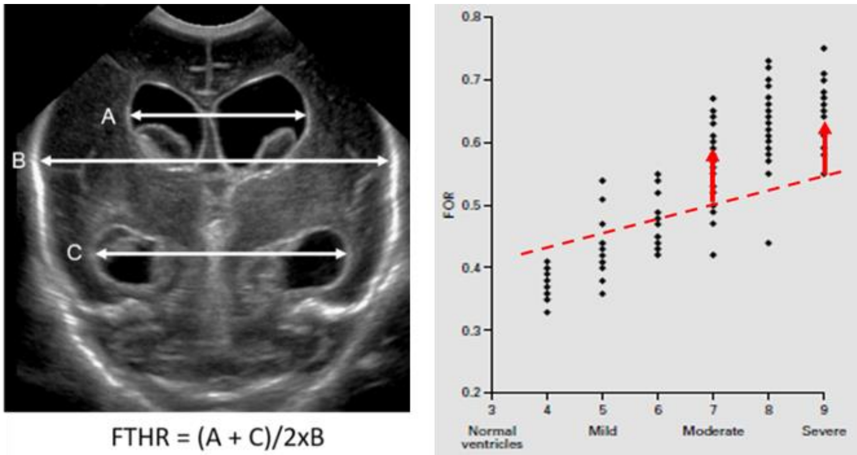


Figure 4. Coronal cUS scan (left) showing the measurement of the three indices comprising the FTHR at their widest dimension, including bi-frontal horn distance (A), bi-parietal distance (B) and bi-temporal horn distance (C). Graph (right) showing normal values and cut-off values for PHVD (red dashed line) for the FTHR. The FTHR cut-off for PHVD is 0.5, independent of postmenstrual age up to 44 weeks (*Antes 2013*).

There is a strong linear correlation between the FOHR and the FTHR. Thus, both ratios can be used interchangeably, using the same cut-off value for PHVD (*Radhakrishnan 2019*) (*Figure 5*).

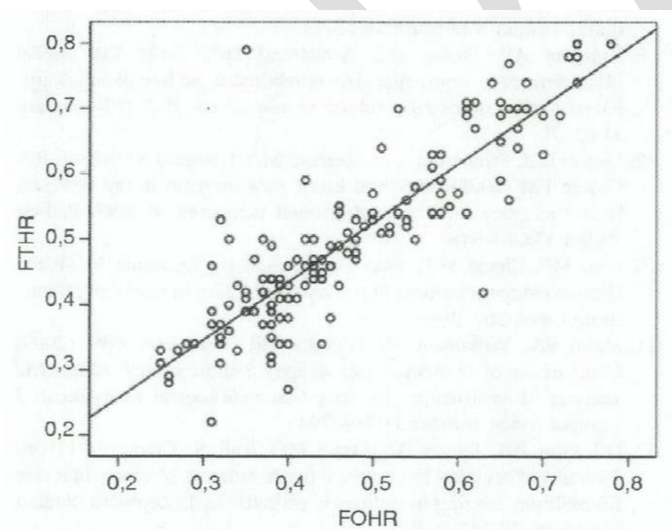


Figure 5. Graph showing a strong linear correlation between measurements of the FTHR and FOHR in preterm and term infants with ventricular dilatation during the neonatal period. *Adapted from: Radhakrishnan, AJR Am J Roentgenol 2019.*

DEFINITION

The above lateral ventricular size measurements are used variably in clinical practice, depending on center and clinician preference. No consensus exists in the literature as to which measurement (VI, AHW, FOHR and/or FTHR) has the best inter- and intra-observer reliability or best predictive value for PHVD severity and neurodevelopmental outcomes. The AHW has however been suggested to be the best indicator of early ventricular dilatation as it reflects rounding of the anterior horn of the lateral ventricles related to raised ICP (also called ballooning) and often precedes changes in the VI (*Govaert 1997*). The FOHR and FTHR show a high reliability when the lateral ventricles are severely dilated and in older infants and children (*Kulkarni 1999; O'Hayon 1999; Antes 2013; Radhakrishnan 2019; El-Dib 2020; Leijser 2020; Obeid 2021*).

Given their ease of measurement (i.e., single linear measurement in one coronal plane), proven robustness to assess PHVD and AHW showing ventricular dilatation in an early stage, the AHW and VI are most often used in the NICU for defining PHVD and decision-making on initial steps of intervention. The FOHR and FTHR are used as alternatives, particularly by Neurosurgeons and in the more severe stages of PHVD. Studies have however consistently shown an inverse relationship between ventricular size (indexed by AHW, FOHR or FTHR) and neurodevelopmental outcomes including motor, cognitive and language development (*Leijser 2018; Cizmeci 2020; El-Dib 2020; Obeid 2021*). So, ensuring consistency in the use and application of one or two ventricular size measurements with which experience and proficiency has been gained is most important.

> PHVD is defined based on the most severely dilated side as:
>
> - **Moderate**: VI >97^{th} percentile *and* AHW >6mm
> - **Severe**: VI >97^{th} percentile + 4mm *and* AHW >10mm
>
> Optional:
>
> - **Moderate PHVD**: FTHR *and/or* FOHR 0.50-0.54
> - **Severe PHVD**: FTHR *and/or* FOHR ≥0.55

There are several **pitfalls** to consider when measuring ventricular size and diagnosing PHVD (*El-Dib 2020*):

1) Unilateral or asymmetric ventricular dilatation with or without midline shift: In case of unilateral or asymmetric ventricular dilatation, ventricular size measurements from the most severely dilated side need to be taken and used to assess presence of PHVD. In case of a midline shift, the VI needs to be taken from the shifted midline to the most lateral wall of both ventricles. However, in case of unilaterality and asymmetry, the existence of ex vacuo dilatation and/or porencephalic cyst (see item 2 and 3 below) as a cause needs to be considered.

2) Ex vacuo ventricular dilatation: Ventricular dilatation with irregularly shaped ventricular walls and/or signs of brain tissue volume loss (e.g., increased extra-axial CSF spaces), reflecting low pressure or passive ventricular dilatation, needs to be distinguished from the high pressure PHVD as the underlying etiology of these conditions is different. In case of PHVD, the ventricular walls generally are smoothly rounded, being most prominent at the occipital horns.

3) Porencephalic cyst: A porencephalic cyst can develop in the location of periventricular hemorrhagic infarction (previously referred to as grade IV IVH) due to necrosis of the infarcted brain tissue. It develops within several weeks of the onset of the infarction and generally communicates with the ipsilateral ventricle. This is another form of ex vacuo ventricular dilatation and needs to be distinguished from PHVD. When performing the ventricular measurements, attempts need to be made to exclude the cyst from the measurement by using the (imaginary) continuation of the ventricular wall as a reference point for the measurement (*Mohammad 2021*).

MONITORING

Cranial ultrasound

Cranial ultrasound (cUS) continues to be the preferred, bedside technique to monitor PHVD in preterm infants. When an GMH-IVH is diagnosed on the first cUS performed between day 4-7 after birth, cUS needs to be repeated in 7 days or earlier when clinically indicated (e.g., PHVD already present on first cUS, rapid increase in head circumference, bulging fontanelle). Depending on the progression of PHVD on subsequent cUS, repeat screening should occur at an interval of 1-2 times per week. The frequency of the serial cUS can be adjusted depending on the findings and/or need for intervention. All cUS examinations need to include measurements of ventricular size, including VI, AHW and/or FTHR or FOHR. Flow diagram 1 shows the recommendation for cUS monitoring in very preterm infants (<32 weeks' gestation) with GMH-IVH and/or periventricular hemorrhagic infarction.

In case intervention is required to divert CSF from the ventricular system to reduce pressure on the brain, either a temporary or more permanent approach can be chosen (see below). In case of temporary approaches (e.g., lumbar puncture and ventricular access device such as Ommaya reservoir), cUS prior to and directly following the intervention can play a role in assessing the need and effect of the CSF diversion.

Clinical signs of raised intracranial pressure

Findings on serial cUS need to be combined with clinical signs of raised ICP related to PHVD. The clinical signs can include: rapid increase in head circumference (>1.5 cm/week), full fontanelle, vomiting, irritability, bradycardias, apneas and eventually sunset appearance. However, due to the still compliant skull, large extracerebral spaces and high brain water content, the majority of preterm infants with PHVD are asymptomatic during the first weeks, even when the ventricular dilatation is rapidly progressive. The signs of raised ICP generally only develop after several weeks of persistently progressive PHVD, at a stage when the ventricles may already be severely dilated (*Leijser & de Vries 2019*).

Optional

<u>MRI</u>

Brain MRI is generally not required to assess the presence and severity of PHVD and is an impractical tool to follow the progress of PHVD. However, an MRI around term equivalent age is advisable in preterm infants with PHVD to assess the presence, type and severity of associated / secondary brain lesions. The attending neurosurgeon may request a brain MRI earlier, prior to surgery, to explore the most optimal modality and route of intervention. An earlier brain MRI can also be of value in case of suspicion of aqueduct obstruction and/or doubt about the underlying etiology of the ventricular dilatation. In most cases, a limited MRI will be sufficient for this purpose.

Doppler ultrasound
Doppler ultrasound can be added to the serial cUS scans to provide information about cerebral hemodynamics, especially cerebrovascular resistance. The increased pressure on the periventricular white matter, and on the arteries supplying the white matter, can impair cerebral perfusion. Measurement of the Resistance Index (RI), the difference between peak systolic flow velocity and end diastolic flow velocity divided by the peak systolic flow velocity, from the anterior cerebral artery can be used to assess the presence of impaired cerebral perfusion. Previous studies in very preterm infants (GA <32 weeks) without brain injury have described a mean RI of 0.71 (range 0.56-0.86) after the first 7 days of birth (*Zamore 2014*). In case of progression of PHVD, an initial rise in systolic flow velocity is seen followed by a decrease, absence or even inverted diastolic flow velocity (*van Alfen - van der Velden 2007*). This results in a rise in RI up to 1. The sensitivity of the RI can be improved by applying pressure to the anterior fontanelle during the Doppler flow measurements. While the RI remains almost stable when applying pressure to the anterior fontanel in a 'healthy' brain, significant changes in RI when applying pressure (a measure of cerebral compliance) have been correlated with height of ICP and need for shunt placement (*Taylor 1996; Zamore 2014*). In case of intervention (aimed at reducing the amount of CSF in the ventricular system), measuring the RI before and after the intervention can play a role in assessing the effect of intervention. However, Doppler ultrasound is a technique that requires additional training and is not routinely used in all NICUs. It is important to be aware that the RI can also be increased due to other causes than PHVD, e.g., a patent ductus arteriosus with ductal steal (resulting in low diastolic velocity), cerebral edema, shunt placement or ECMO.

Near infrared spectroscopy (NIRS):
NIRS is able to detect changes in the cerebral blood flow and the potential impact of raised ICP on cerebral oxygen delivery. Some tertiary NICUs in Canada are currently routinely using NIRS for assessment for infants with or at risk for PHVD. Compromised cerebral blood flow is considered if cerebral oxygen saturation is less than 55% in absence of other factors that might affect CBF, which may inform need for intervention. In addition, assessment of the trends in NIRS values after intervention can be helpful to reflect the impact of the intervention on cerebral blood flow (*Lang 2019*). Application of NIRS in this setting, however, requires a standardized guideline and training of all NICU staff.

Other
Several studies have shown that other neuro-monitoring tools, including 3D ultrasound, evoked potentials (EP) and amplitude-integrated EEG (aEEG), can be used in infants with PHVD to monitor cerebral perfusion and brain (background) activity and the effect of intervention. These tools are, however, not readily available in all centers and require specialized training. Therefore, they are not part of this recommendation but can be added to the diagnostic tool set when local expertise and infrastructure is available.

Neonatal Neuro-Critical Care (NNCC) program
Some Canadian NICUs have a team specialized in Neonatal Neurology, which can provide advice on multi-modality neuro-monitoring (cUS, Doppler, aEEG and NIRS) in neonates and on management strategies for neurological conditions. For infants with PHVD such team can advise on cUS monitoring and decision-making regarding start of intervention and ensure close and timely communication with the neurosurgical team.

INTERVENTION

The overall goal of intervention for PHVD is to prevent direct and indirect injury of the preterm brain by reducing pressure on the brain tissue surrounding the ventricular system through CSF diversion.

Timing and Modality

The optimal timing and modality of intervention for PHVD remains a debate, with some centers intervening 'early' based on ventricular size measurements from serial cUS, while other centers intervene 'late' based on a combination of ventricular size and clinical signs of raised ICP (e.g., rapid increase in head circumference, apneas, bradycardia, vomiting, full fontanel, splaying sutures, sunsetting sign). The lack of consensus on optimal approach is related to a paucity of evidence from large randomized controlled trials and cohort size. Also, available studies on short-term outcomes, such as infection rates and need for permanent shunt, do not show a consistent immediate advantage for one specific approach to intervention (i.e., timing and modality) (*Mazzola 2014; Badhiwala 2015; Wellons 2017*). Growing literature, however, suggests benefits for long-term neurodevelopmental outcomes of preterm infants with PHVD with a stepwise intervention approach, initiated 'early' in the development of PHVD based on cUS derived ventricular measurements, over a later intervention approach primarily guided by clinical signs (*de Vries 2002; Whitelaw 2010; Srinivasakumar 2013; Leijser 2018; de Vries 2019; Luyt 2020; Cizmeci 2020; El-Dib 2020; Parodi 2021; Lai 2021*). The optimal timing for initiating 'early' intervention has not been established. The ELVIS trial, comparing an early intervention approach at a low (i.e., VI >p97 and AHW >6 mm) versus a high cUS-based threshold (i.e., VI >p97 + 4 mm and AHW >10 mm) in preterm infants with progressive PHVD did not show significant differences between groups for composite adverse outcomes (i.e., death, any grade of cerebral palsy or severe neurodevelopmental disability) at 2 years. Post-hoc analysis showed that initiation of intervention at low threshold was associated with lower odds of composite adverse outcomes (*Cizmeci 2020*). Of note, both thresholds in the ELVIS trial, guided by cUS measurements of lateral ventricular size, are relatively early in the trajectory of PHVD development, at a time when infants are mostly asymptomatic, as compared to a more traditional approach guided by clinical signs of raised ICP. The lack of significant differences in neurodevelopmental outcomes between the ELVIS groups in the primary analysis may be explained by both intervention thresholds being relatively early.

Based on the available literature and balancing the benefits and risks of intervention, the PHVD management working group members have reached consensus on an earlier intervention approach based on a combination of lateral ventricular size measurements from serial cUS and clinical signs of raised ICP, aligning with the recent recommendation on management of PHVD by El-Dib et al. (*El-Dib 2020*). Flow diagram 2 outlines a stepwise approach to intervention for PHVD including timing and intervention modality. The early intervention approach requires close monitoring and expertise in ventricular size measurement performance and interpretation. A dedicated team of clinicians can contribute to the management of infants with PHVD and had been shown to reduce the risk of infection from ventricular reservoir tapping (*Brouwer 2007*).

Flow diagram 1. Algorithm for cUS monitoring in preterm infants at risk for PHVD

GMH-IVH and/or PVHI on cUS day 4-7 (or subsequent cUS) [A]

↓

Repeat cUS in 7 days from previous cUS or sooner if clinically indicated (i.e., rapid increase in head circumference >1.5cm/week, bulging fontanelle, ventricular dilatation on first cUS not explained by IVH) to assess for PHVD development.

↓

NO PHVD:
VI <p97th and AHW <6mm [B]
and
Absence of signs of raised ICP

→ Repeat cUS at 4-6 weeks of birth and at 36 weeks' PMA / prior to discharge.
If any progression of GMH-IVH, mild ventricular dilatation or signs of raised ICP, repeat cUS after 7 days from previous cUS and go back to top flow diagram

PHVD:
VI >p97th and AHW >6mm [B]
and
Absence of signs of raised ICP

→ Repeat cUS at 4-7 days from previous cUS to assess for progression of PHVD (or sooner if clinically indicated)

↓

NON-PROGRESSIVE PHVD:
No increase in VI or AHW from previous cUS
and
Absence of signs of raised ICP

→ Repeat cUS after 2 and 4 weeks from previous cUS and at 36 weeks' PMA.
If any increase in VI or AHW on subsequent cUS (due to PHVD rather than ex vacuo dilatation) [C] or clinical signs of raised ICP, go to '**progressive PHVD**'

PROGRESSIVE PHVD:
Any increase in VI or AHW from previous cUS
or
Presence of clinical signs of raised ICP [C]

→ **ASSESS INTERVENTION NEED (flow diagram 2)** and transfer to neurosurgical site. [D]
If not meeting intervention criteria, repeat cUS after 1 week of previous to re-assess need for intervention and frequency of repeat cUS

A - See also 'Clinical practice guidelines: Diagnoses and classification of preterm brain injury from cranial ultrasound: consensus viewpoint' for GMH-IVH grading and cUS monitoring (Mohammad et al. Front Pediatr 2021;9:618236).
B - Use the following calculators: for 24-29 weeks https://tinyurl.com/PHVD-Measures-1hyperlink; for 24-42 weeks https://tinyurl.com/PHVD-Measures-2.
C - Rule out ex vacuo dilatation as cause of ventricular dilatation prior to intervention (see pages 10-11).
D - Decisions regarding need for intervention, performance of lumbar puncture and, if needed, transfer to neurosurgical site can be made at discretion of the by neonatal team.
Of note: The timing for consultation of neurosurgical team may vary per center, from time of diagnoses of PHVD to time of need for neurosurgical intervention, as per local agreements.
Abbreviations: AHW, anterior horn width; cUS, cranial ultrasound; GMH-IVH, germinal matrix-intraventricular hemorrhage; ICP, intracranial pressure; p, percentile; PHVD, post-hemorrhagic ventricular dilatation; VI, ventricular index.

Over the past decades, multiple intervention strategies aimed at lowering the intraventricular pressure, either by limiting the production of CSF or by increasing the CSF outflow and/or reabsorption (e.g., choroid plexus coagulation, 3rd ventriculostomy, fibrinolytic agents, diuretics), have been explored for PHVD. Also, multi-center studies, such as by the Hydrocephalus Clinical Research Network and the Children's Hospitals Neonatal Consortium Neurosurgery Focus Group, are ongoing to test novel intervention approaches to re-establish the balance between CSF production and drainage / reabsorption.

So far, CSF diversion using temporary or more permanent approaches has shown to be effective in lowering intraventricular pressure and improving brain development and neurodevelopmental outcomes (*de Vries 2002; Leijser 2018; de Vries 2019; Cizmeci 2020*). A variety of (neurosurgical) intervention modalities, such as lumbar punctures [LP], ventricular reservoir, ventriculosubgaleal shunt (VSGS), external ventricular drain (EVD), and ventriculoperitoneal [VP]-shunt, are available to either temporarily or more permanently divert CSF from the ventricular system. In most Canadian centers, ventricular reservoirs and VP-shunts are preferred and therefore these modalities are outlined in flow diagram 2. The choice for type of intervention modality is made by the local neurosurgical and neonatal teams based on the infant's weight, postnatal age, CSF criteriaand skin condition, as well as previous experience, training and comfort of the operating neurosurgeon and supports available for post-intervention care. Given the associated risks, direct ventricular taps are only recommended in exceptional circumstances and at the discretion of the neonatal and neurosurgical teams.

Of note, the minimum postnatal age or PMA and weight of the infant for (neurosurgical) intervention may vary by center and the locally preferred intervention modality. No absolute minimum weight exists for performing a neurosurgical intervention for PHVD. The decision for intervention at a low infant weight is made on a case-by-case basis, balancing factors such as anticipated risk for skin breakdown (depending on skin integrity and thickness), postnatal age and illness severity of the infant, and the locally preferred neurosurgical procedure. In addition, while the minimum postnatal age may vary by center, under no circumstances should an intervention for PHVD take place within the first 7 days of birth.

Temporary CSF Diversion

<u>Lumbar punctures (LPs)</u>:
LPs may be performed as an <u>optional</u> first intervention in a stepwise approach to PHVD, with the purpose to instantly reduce intraventricular pressure, and in some occasions alleviate the need for neurosurgical intervention. The literature on the benefits of LPs for PHVD progression and their effectiveness is inconclusive. Also, LPs may not be successful and the experience with LPs varies between neonatal centers. When successful, CSF diversion through LPs has the <u>benefits</u> of fast reduction of pressure (and potential clinical signs of raised ICP), removal of some excessive proteins and blood from CSF, and allowing time for neurosurgical consultation to be initiated. LP should **NOT** be performed within the first week of birth given the risk of a rebleed. Suspicion of aqueduct obstruction showing as enlarged 3rd ventricle and small 4th ventricle is a relative contraindication for a LP. Other relative contraindications are 4th ventricular outlet obstruction or posterior fossa outlet obstruction. Large volume LP could also increase the risk of herniation due to a pressure differential created between the intracranial and spinal compartments in case of inadequate communication. LPs <u>can be omitted</u> as first intervention in case of (suspected) aqueduct stenosis, imminent option for neurosurgical intervention, need for transfer to neurosurgical center and/or center preference. In some centres, (fast) MRI is performed to rule out aqueduct stenosis prior to LP and/or LPs are guided by spinal ultrasound to assess adequate CSF volume before the procedure. For details on LP procedure, target and precautions, see Appendix C.

Ventricular reservoir:

A ventricular reservoir (e.g., Ommaya reservoir) or subcutaneous ventricular access device is used to divert CSF from the ventricular system through repeated taps from the reservoir (*Figure 6*). Important benefits of a ventricular reservoir are that the device can be inserted in preterm infants who are too small and/or unstable to have a permanent shunt placed, and it may delay or abrogate the need for a permanent shunt when a relatively aggressive approach to CSF diversion (e.g., once or twice *daily* CSF taps of 7.5-10mL/kg/tap based on VI and AHW; see below and flow diagram 2) is applied following placement. In addition, it allows for clearance of CSF of proteins and blood (products); this reduces the risk for shunt blockage if subsequent shunt insertion is required (*Willis 2009; Wellons 2009; Limbrick 2010; Leijser 2018; de Vries 2019*). While the reservoir is inserted under intravenous antibiotics prophylaxis and the procedure of reservoir tapping is relatively straightforward, there is always a risk of introducing infection, cautioning strict peri- and post-procedure hygiene care. Also, CSF needs to be drawn slowly at a maximum rate of 1mL/minute to avoid fast changes in ICP and rebleeds. The minimum infant weight and age cut-offs for reservoir insertion are not absolute and differ between centers; they are mostly over 800-1,000 grams. The decision for insertion in view of minimum weight per center is based on the anticipated risk for skin breakdown, postnatal age and illness severity of the infant and the neurosurgical team's training and prior experience. For details on ventricular reservoir tapping, target and precautions, see Appendix C.

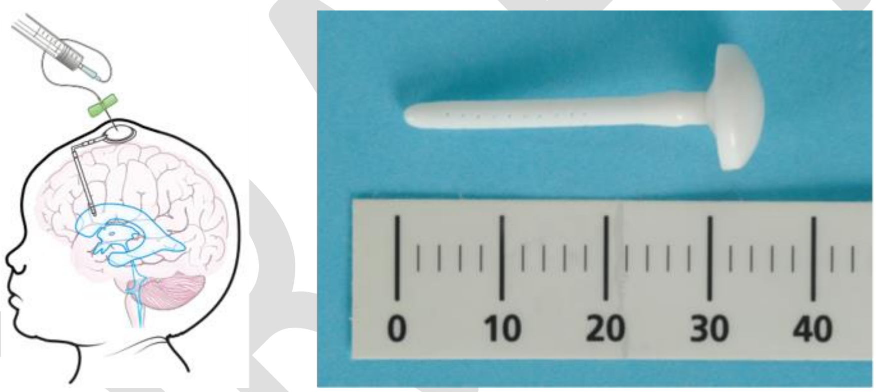


Figure 6. Schematic drawing of a ventricular reservoir placement and tapping from the reservoir (left) and image of a ventricular reservoir (right). *Adapted from: Leijser & de Vries – Tapping of a ventricular reservoir, 2019.*

Ventriculosubgaleal shunt (VSGS):

A VSGS is used in some Canadian centers as a temporary intervention for PHVD, as an alternative to the ventricular reservoir. The operative procedure consists of inserting a ventricular catheter into the lateral ventricle's frontal horn. The proximal end of the catheter is closed at the end and has slits to offer some mechanical resistance and provide unidirectional movement of CSF and debris. A large subgaleal pouch is formed through blunt dissection to create a space for CSF absorption (*Falsaperla* 2023).

Like a ventricular reservoir, a VSGS can bridge the time until a more permanent intervention is possible and may negate the need for a permanent shunt altogether. As opposed to the ventricular reservoir, the VSGS is a closed system for continuous CSF drainage from the ventricular system (*Figure 7*), which may reduce the risks associated with repeated CSF tapping and better maintain fluid and electrolyte level.

VSGSs often have a lifespan of 4-6 weeks and are limited by the eventual scarring down or healing of the subgaleal pocket, at which point a permanent shunt may need to be placed (*Eid 2018*). The initial creation of a large subgaleal space may improve the absorptive capacity of the subgaleal space and thus the functional longevity of the shunt. Once the production of CSF exceeds the absorptive capacity of the subgaleal space, the ventricles may re-enlarge (*Drapkin 1980*). When the VSGS exceeds its functional lifespan, the subgaleal pocket of CSF accumulation can be tapped or the subgaleal space re-dissected if a permanent shunt cannot yet be inserted. In American cohorts, the rate of conversion to VP-shunt and the rate of infection were similar between VSGS and ventricular reservoir (*Wang 2014; Wellons 2017*). In one Canadian cohort, the rate of conversion from VSGS to VP-shunt was 90% (*Groulx-Boivin 2023*).

A VSGS may also have an access point or reservoir as part of the construct, which allows for tapping and removal of additional CSF. Some VSGSs have a valve, while others allow free unidirectional flow between the ventricular and subgaleal spaces.

The minimum infant weight and age for VSGS placement are not absolute and differ between centers. The rates of infection and conversion to a VP-shunt are similar for a VSGS and ventricular reservoir (*Wellons 2017*). The decision on which type of device to place is institution and neurosurgeon dependent, and may account for some disparity in outcome and complications between devices.

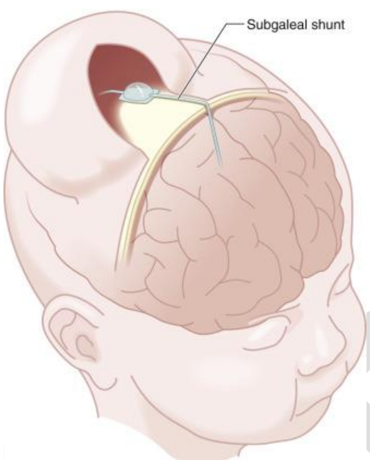


Figure 7. Schematic drawing of a ventriculosubgaleal shunt placement with drainage of CSF from the ventricular system into the subcutaneous CSF pocket. *Adapted from: El-Dib M, et al. J Pediatr 2020; 226: 16-27*

External ventricular drain (EVD):

EVD placement is the preferred initial, temporary intervention for PHVD in few centres as for the ease of placement and use of the device (*Bassan 2012; de Angelis 2021*). One end of a catheter is placed in the lateral ventricle and the other end is connected to an external CSF catchment system (*Figure 8*). Unique to other temporary interventions, an EVD allows for direct visualization of CSF output, CSF sampling, and adjustment of CSF outflow by increasing or decreasing outflow resistance based on the degree of ventricular dilatation and other relevant parameters. As opposed to reservoirs, an EVD allows for continuous CSF drainage similar to a ventriculosubgaleal shunt (VSGS).

In Canada, EVDs are placed considerably less frequent than other temporary drainage devices due to concerns specifically around potential major complications and complexity of post-insertion care. An EVD is associated with a relatively high risk of meningitis (and potential colonization), ranging from 5-50%, given the potential communication of the CSF spaces with the outside world (*Badhiwala 2015, Falsaperla 2023*). The rate of infection may be lower in centers where EVDs are often routinely replaced as a precautionary measure (*Mazzola 2014*), as compared to in Canada where experience with EVDs is limited. CSF leakage and wound breakdown are other important considerations when placing an EVD. In addition, an EVD can cause over drainage of CSF and requires frequent assessments and cUS monitoring to evaluate CSF dynamics. Finally, the presence of an additional catheter may increase the complexity of nursing care and risk of inadvertent dislodgement (*Cornips 1997; Collins 2014; Zaben 2016; Kumar 2017; de Angelis 2021; Cheng 2022*).

No universally accepted guidelines currently exist for minimum infant weight or age for EVD placement, and its use is center and neurosurgeon specific. Decisions on whether to place an EVD as opposed to other forms of CSF diversion involves weighing the potential ease of placement versus the risk of complications associated with ongoing use. EVDs are usually offered only as a temporary measure at the discretion of the surgical team. While variation exists with respect to the type of EVD that may be placed, increasing evidence suggests that antibiotic impregnated catheters (over non-antibiotic impregnated) mitigate, but do not eliminate, the risk of perioperative infection (*Jaeger 2017; Malucci 2020; Mallucci 2020; Sedano 2023*).

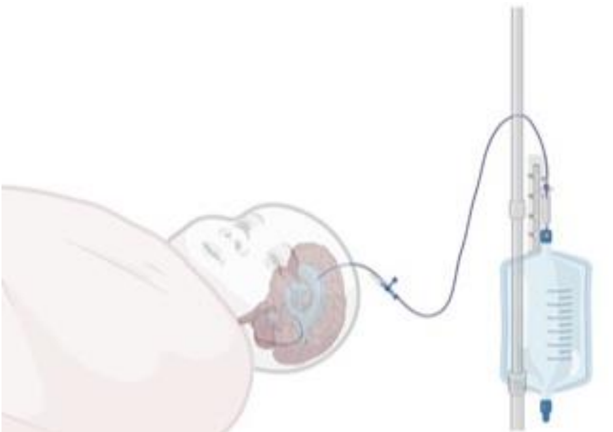


Figure 8. Schematic drawing of an external ventricular device placement and continuous drainage from ventricular system to CSF catchment system. *Adapted from: Falsaperla R, et al. Neurosurgery 2023; 93: 622-627*

Permanent CSF Diversion

<u>Ventriculoperitoneal (VP) shunt</u>:

A VP-shunt is a modality for permanent CSF diversion through continuous drainage of CSF into the peritoneal cavity (*Figure 9*). CSF drainage occurs when the intraventricular pressure exceeds the pressure threshold of the pressure valve. Although all components of the shunt are in situ, one should always be aware of the risk of infection and/or shunt blockage. VP-shunt insertion is mostly only done in case of persistently progressive or severe PHVD, despite prolonged CSF diversion from a temporary device or malfunction or obstruction of such device. Long term follow-up studies have found shunt revision rates approaching 25% in the first year after placement, and 40-80% over the course of the child's lifespan. A single shunt revision significantly increases the risk for further shunt infection or revisions. These risks need to be balanced against the benefit of placement of a VP-shunt versus an alternative intervention (*Kestle 2000; Stone 2013; Al-Tamimi 2014; Paff 2018; Harada 2023*).

The criteria for VP-shunt placement vary per center based on the local neurosurgical team's preference and may include infant weight (range of 1,200-2,000 grams minimum), CSF protein count (often <1.5g/L), CSF red blood cell count (often <100/mm^3), postnatal age or PMA of infant (often over 37 weeks' PMA), and signs of raised ICP; See flow diagram 2. Given the strong correlation between FOHR (and FTHR) and lateral ventricular size, in particular at the PMA the need for VP-shunt placement in an infant is evaluated (often from 37 weeks' onwards), assessment of ventricular size using the ratios for decisions on VP-shunt placement is often preferred over the VI and AHW (*Kulkarni 1999*). VP-shunt placement is followed by monitoring of PHVD trajectory, and potential VP-shunt malfunction, based on clinical signs of raised ICP and repeated cUS including measurement of FOHR and FTHR. One should be aware of the risk of VP-shunt infection although the utility of CSF parameters in neonates with VP-shunts is limited due to poor sensitivity and specificity (*Lenfestey 2007*).

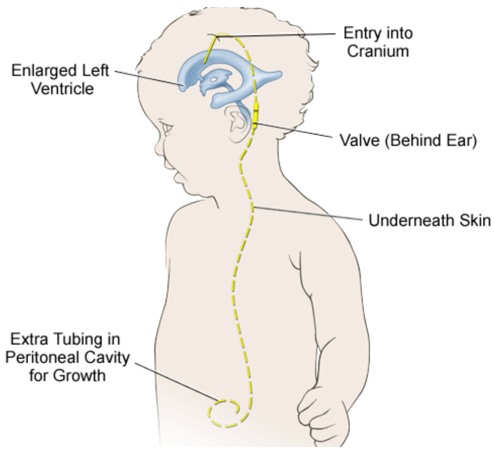


Figure 9. Drawing of a VP-shunt placement with diversion of CSF from the ventricular system into the peritoneal cavity. *From: https://www.stanfordchildrens.org/en/topic/default?id=hydrocephalus-90-P02367*

Flow diagram 2. Algorithm with stepwise approach for intervention for PHVD

All intervention steps are guided by ventricular size measurements from cUS and criteria for intervention. As ventricular reservoirs, if necessary, followed by VP-shunt placement, are the neurosurgical modalities used in most EPIQ centers, these are outlined in flow diagram 2. Other modalities (such as VSGS and EVD) can be used as per center preference. Decisions on intervention are shared between neonatal and neurosurgical teams.

PHVD INTERVENTION CRITERIA:
VI >p97th + 4mm *or* AHW >10mm
or
Presence of clinical signs of raised ICP [A]

↓

OPTIONAL[B, C]: Perform therapeutic LP (10ml/kg), ideally followed by cUS with VI and AHW measurement on following day to assess need for further LP; **UNLESS:**
(suspicion of) aqueduct stenosis, <1 week of birth, neurosurgical intervention readily available or preferred, LP unsuccessful, or maximum of 3 LPs reached. In the latter cases, **go to next box**.

Target of intervention: VI <p97th + 4mm **and** AHW <10mm
→ If LP successful but target not reached: Repeat LP till target or maximum of 3 LPs reached.
→ If target reached: Repeat cUS at least twice/week in the first 2 weeks, and assess need for intervention (and frequency of repeat cUS).

↓

If **VI >p97th + 4mm or AHW >10mm** despite serial LPs or LPs unsuccessful / omitted:
Consider ventricular reservoir placement followed by initially daily CSF taps (optional: VSGS or EVD).[D]
Each reservoir tap is ideally preceded by cUS with VI and AHW measurements to guide need and volume for tap. In case of sufficient clinical indication to tap despite unavailability of cUS, a tap can be done at discretion of medical team. [C]

Target of intervention: VI <p97th + 4mm **and** AHW <10mm
→ If target not reached: Continue reservoir taps guided by cUS till target reached.
→ If target reached: Repeat cUS at least twice/week in the first 2 weeks, and assess need for intervention (and frequency of repeat cUS).

↓

If CSF taps from reservoir ongoing when infant reaches 37-40 weeks' PMA:
Trial of ≥48-72 hours **without** reservoir tap, followed by cUS with assessment of **FOHR and/or FTHR**.

↙ ↘

If **FOHR and/or FTHR <0.55** on cUS:
Hold off on permanent CSF diversion and repeat cUS with FOHR and/or FTHR weekly until discharge.
If FOHR and/or FTHR increases on subsequent cUS (due to PHVD rather than ex-vacuo dilatation) or occurrence of signs of raised ICP, re-consider reservoir tapping or permanent CSF diversion. [F]

If FOHR and/or FTHR ≥0.55 on cUS:
Consider permanent CSF diversion, if meeting center-specific criteria, such as maximum CSF protein and RBC counts, minimum infant weight and age, and signs of raised ICP. [E]
Subsequent imaging with cUS and/or MRI is at the discretion of the neurosurgical team or most responsible care provider. [F]

A - No intervention should be performed when anterior fontanelle is sunken.
B - This step can be guided by the neonatal team. Consult Neurosurgery to be **considered** at this stage, based on local agreements.
C - Following each LP and reservoir tap, several mLs of CSF need to be sent to the lab for analysis of red cell and protein content and to rule out infection; See Appendix B.
D - Neurosurgery involvement is **indicated** from this step onwards
E - If these criteria are not yet reached or VP-shunt placement cannot take place within 48 hours, continue taps from ventricular reservoir in the interim; Reassessment of whether the infant meets the criteria for VP-shunt placement needs to take place on a regular (every 1-2 weeks) and case-by-case basis
F - If after VP-shunt placement infants are otherwise stable and ready to be discharged home, based on local infrastructure and expertise arrangements for outpatient follow-up by the neurosurgical team can be organized.
Abbreviations: AHW, anterior horn width; cUS, cranial ultrasound; ICP, intracranial pressure; FOHR, fronto-occipital horn ratio; FTHR, fronto-temporal horn ratio; LP, lumbar puncture; MRI, Magnetic Resonance Imaging; p, percentile; PHVD, post-hemorrhagic ventricular dilatation; VI, ventricular index.

Potential Future Neurosurgical Modalities

(Endoscopic) Third ventriculostomy (ETV / TV)

Recent studies have evaluated the role of ETV in the management of hydrocephalus in infants and children. The procedure involves endoscopic fenestration of the floor of the 3rd ventricle for communication of the ventricular system with the premedullary cistern. In theory, ETV results in flow of CSF from the ventricles into the subarachnoid space, where it may eventually be reabsorbed at the level of the arachnoid granulations.

Evidence suggests that the procedure is most effective for treating hydrocephalus when the hydrocephalus is caused by obstruction below the level of the 3rd ventricle (such as the cerebral aqueduct) and the normal absorptive pathways have remained intact (*Verhey 2024*). However, there is an increasing body of literature to suggest that in some preterm infants with PHVD, ETV may result in arrest of the ventricular dilation or stabilization of their clinical status. The underlying mechanism of this is unclear and the success rate of ETV in this population is well below 50% (*Warf 2011; Chamiraju 2014; Weil 2016; Kulkarni 2018; Usami 2021*).

ETV goes along with a significantly increased risk for injury to major arterial vessels, such as the basilar artery, and mortality from acute hemorrhage. In addition, injury to the hypothalamus or connections to the pituitary stalk have been reported, manifesting as immediate perioperative diabetes insipidus which can be transient or require long term supplementation (*Albalkhi 2023; Pasqualotto 2023; Konar 2024; Minta 2024*). Unlike other interventions for CSF drainage where ventricular size decreases correspondingly to volume of CSF removed, infants and children undergoing ETV may not have a significant change in ventricular size despite a good response in other clinical criteria (such as flat, soft fontanelle, arrest of head growth). The significance of a persistently dilated ventricular system despite clinical response is unknown.

A clear understanding of which infants and children (such as minimum age and weight) benefit (most) from ETV is pending and, at present, ETV for PHVD should only be considered for a subgroup of preterm infants at the discretion of the neurosurgical team. Inflammatory blood products in PHVD can lead to septal formation within the lateral ventricles and CSF circulatory pathways. The formation of these septations and cysts may result in loculated pockets within the ventricular system with accumulation of CSF (*Sandberg 2005; Behrens 2020; Frassanito 2021; Dvalishvili 2022; El-Ghandour 2023*). In such cases, endoscopic fenestration in combination with other interventions to facilitate CSF drainage may be considered. The optimal approach to ETV (such as timing and use as an isolated or combined intervention modality) remains an area of ongoing research.

ABBREVIATIONS

AHW	Anterior horn width
CSF	Cerebrospinal fluid
cUS	Cranial ultrasound
FOHR	Fronto-Occipital Horn Ratio
FTHR	Fronto-Temporal Horn Ratio
GA	Gestational age
GMH	Germinal matrix hemorrhage
HC	Head circumference
ICP	Intracranial pressure
IVH	Intraventricular hemorrhage
LP	Lumbar puncture
P	Percentile
PHVD	Post-hemorrhagic ventricular dilatation
PMA	Postmenstrual age
RI	Resistance Index
TEA	Term equivalent age
VI	Ventricular index
VP	Ventriculoperitoneal
WBC	White blood cell

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APPENDIX A: CSF DRAINAGE REPORTING SHEETS (VI and AHW or FOHR and FTHR)

Name:

ID:

DATE	PMA (wks)	WEIGHT (kg)	MODALITY (LP / reservoir / VSGS)	VOLUME CSF DRAINED (mL)	VENTRICULAR SIZE (mm) AND RI									
					PRE-DRAINAGE					POST-DRAINAGE				
					RIGHT		LEFT		RI	RIGHT		LEFT		RI
					VI	AHW	VI	AHW		VI	AHW	VI	AHW	

Name:

ID:

DATE	PMA (wks)	WEIGHT (kg)	MODALITY (LP / reservoir / VSGS)	VOLUME CSF DRAINED (mL)	VENTRICULAR SIZE (mm) AND RI					
					PRE-DRAINAGE			POST-DRAINAGE		
					FOHR	FTHR	RI	FOHR	FTHR	RI

APPENDIX B

Lumbar Puncture

- *Procedure*: The procedure and pain control measures are similar to when performing a LP as part of a full septic work-up, as per center's local practices (*https://nncceducation.thinkific.com/courses/PHVD-dagnosis-and-management*). The LP is a **sterile procedure**, including surgical scrubbing, full gowning and sterile gloves, as for the risk of introducing infection (*Whitelaw 2017*).
- *Target*: Evident reduction in lateral ventricular size to VI < 97th percentile + 4mm and AHW < 10mm over the course of days, with a maximum of 3 LPs.
- *CSF volume*: To be determined on an individual basis and, if applicable, with the NNCC team depending on the size of the lateral ventricles (can be quickly assessed with one plane cUS) and the effect of a prior LP. Often a volume of 7-10mL of CSF per kg per day (7-10mL/kg/day) on 2-3 occasions is required to achieve the above aim. Maximum volume: 10mL/kg/day on 2-3 consecutive days with a maximum of 5 LPs over 1-2 weeks.
- *CSF analysis*: Several mL of each CSF sample (with maximum of 1 sample per day) need to be sent for analysis of white blood cell (WBC) count, glucose and protein and bacterial culture to rule out meningitis. See below for interpretation and treatment.
- *Who*: Physician, nurse practitioner
- *Contraindications*: The first week of birth as for risk of re-bleed. (Suspected) aqueduct obstruction (i.e., enlargement of 3rd ventricle with small 4th ventricle) is a relative contraindication. An aqueduct obstruction can be suspected from cUS (in particular when including imaging through mastoid window and/or using Doppler) and diagnosed or ruled out with (fast) MRI. If in doubt, consider omitting the LP step.

Ventricular Reservoir Tapping

- *Procedure*: See https://vimeo.com/484200574; and *https://nncceducation.thinkific.com/courses/PHVD-dagnosis-and-management* for instructions on ventricular reservoir tapping, including hygiene precautions, speed of CSF draws and CSF analysis. The reservoir tap is a **sterile procedure**, including surgical scrubbing, full gowning, and double sterile gloves, as for the risk of infection.
- *Target*: Reduction in lateral ventricular size to VI < 97th percentile + 4mm and AHW < 10mm within 1 week of ventricular reservoir placement.
- *CSF volume to tap*: To be determined on an individual basis and, if applicable, with the NNCC team depending on size of the lateral ventricles (can be quickly assessed with one plane cUS) and the effect of a prior reservoir tap. In the first days after reservoir placement often *daily* CSF taps of 10mL/kg/tap are required to achieve the above aim. The frequency and volume of CSF taps can be gradually reduced (and discontinued) upon stabilization and/or regression of PHVD. Of note, the volume of the first tap after reservoir placement is mostly guided by the Neurosurgical team based on volume tapped in the OR and CSF pressure. A maximum of 1mL/minute may be drawn from the reservoir. Maximum volume:

If over 10mL/kg/day is required to achieve the anticipated ventricular size, the volume needs to be divided over 2 taps, up to a maximum of 15-20mL/kg/day.

- *CSF analysis*: Several mLs of CSF sample (with maximum of 1 sample per day) need to be sent for analysis of WBC count, glucose and protein and bacterial culture twice per week or on indication. See below for interpretation and treatment.
- *Other precautions:* Check serum / urine Na and K levels twice per week and supplement Na if required to maintain urine Na >20 mmol/L. In some centers, CSF diversion volume is supplemented by increasing the total fluid intake (TFI) in case of frequent taps.
- *Who*: Physician, nurse practitioner, nurse clinician (preferably from dedicated, trained team to reduce risk of infection) (*Brouwer 2007*).
- *Contraindication*: Reservoir blockage

Cerebrospinal Fluid Analysis

As for the risk of infection with invasive procedures despite using aseptic techniques, CSF samples need to be sent to the laboratory for analysis to rule out meningitis and device infections. In case of LPs a CSF sample need to be sent with each LP, while for ventricular reservoir tapping a CSF sample can be sent twice per week (if applicable). CSF samples should preferably also be sent directly prior to ventricular reservoir or VP-shunt insertion. Analysis should include WBC count, glucose and protein analysis and bacterial culture.

WBC count and glucose and protein levels in CSF in presence of PHVD should however be interpreted with caution and differently from those in CSF in absence of PHVD. Studies have shown that WBC count and glucose and protein levels are abnormal in presence of PHVD, prior to intervention and without signs of meningitis. Also, no differences have been found in WBC count and only marginal differences in glucose and protein levels in CSF between neonates with PHVD with and without ventricular reservoirs or VP-shunts (*Smith 1986; Lenfestey 2007*). The sensitivity and specificity of a cut-off value of 20 WBCs/mm^3 for diagnosing meningitis in neonates with positive cultures and ventricular drainage devices were only 67% and 62%, respectively (*Smith 1986; Lenfestey 2007*). The changes in CSF values are likely caused by the inflammation related to the GMH-IVH and ventricular dilatation as such.

Antibiotics treatment for meningitis is therefore not recommended in case of an isolated elevation of WBC in CSF, unless there is **a positive CSF culture and/or clinical signs of meningitis** (other than those attributable to raised ICP). However, local preferences and guidelines may differ. In case of positive CSF culture or clinical signs of meningitis, antibiotics treatment should be chosen according to the local protocol.