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]

Severe forms of intraventricular hemorrhage (IVH) continue to occur in up to 15% of infants born extremely premature,[1] and more than one-half of these infants develop post-hemorrhagic ventricular dilatation (PHVD).[2] PHVD is a term that represents the progressive ventricular dilatation caused by IVH and encompasses other terms, such as post-hemorrhagic hydrocephalus. PHVD is associated with a high risk for subsequent adverse motor and cognitive neurodevelopmental outcomes. Despite many decades of investigations, there is no consensus among neonatologists, pediatric neurologists, and pediatric neurosurgeons as to the best management of PHVD. The lack of agreement relates in part to difficulty in assessing the relative contributions to adverse outcomes of (1) the primary brain injury associated with severe IVH; (2) the presence of blood products mediating brain injury; and (3) PHVD with distension causing injury that could be interrupted with cerebrospinal fluid (CSF) drainage. Over the last 5-10 years, substantial new evidence acquired from both experimental models and human clinical investigations, including randomized trials, has coalesced to inform the neonatologist, pediatric neurologist, pediatric neurosurgeon, and pediatrician caring for these patients.

Our goal is to outline the current evidence supporting the premise that PHVD contributes to the brain injury that underlies adverse neurodevelopmental outcomes and that this injury may be mitigated or prevented by targeted approaches to management. We will emphasize that the use of ventricular size, quantified

by sequential cranial ultrasound (cUS), is a critical measurement for the consideration of intervention and is the approach associated with the lowest risk for adverse neurodevelopmental outcomes.

Pathophysiology and Neuropathology of PHVD

The relation of PHVD to brain injury and dysmaturation in the human infant born premature has been supported by a variety of studies of experimental models and of human infants. These studies should be placed in the context of the rapid and complex developmental events occurring in the premature brain in the third trimester. The immature cerebral white matter, particularly the actively differentiating pre-oligodendrocyte (pre-OL), is particularly vulnerable to injury. Combined with a propensity of the immature microglia and astrocytes to proinflammatory activation, this developmental period is unique in the neuropathological consequences of PHVD.

Brain Maturation during the Premature Period

Multiple active developmental events occur in the human brain from 24-40 weeks of gestation.[3-5] The rapidity and complexity of these cellular events underlie their vulnerability to perturbation. The principal components involved include the pre-OL, cerebral white matter axons, subplate neurons, cerebral cortex (including hippocampus), thalamus, basal ganglia, and cerebellum. The principal cellular targets in PHVD appear to be the pre-OL, axon, cerebral cortex (especially hippocampus), thalamus, and cerebellum.

Microglia and astrocytes are important glial elements in the development of the white and gray matter structures just noted. They are involved in axonal development, pre-OL differentiation—myelination, vascularization, synaptogenesis, and neural circuit formation.[6,7] However, these cells, when "activated," can have multiple deleterious effects.[4] Notably,

AHW	Anterior horn width
CSF	Cerebrospinal fluid
cUS	Cranial ultrasound
DRIFT	Drainage, irrigation and fibrinolytic therapy
FOHR	Frontal and occipital horn ratio
GMH	Germinal matrix hemorrhage
HT	High threshold
IVH	Intraventricular hemorrhage
LP	Lumbar puncture
LT	Low threshold
MRI	Magnetic resonance imaging
PHVD	Post-hemorrhagic ventricular dilatation
Pre-OL	Pre-oligodendrocyte
TOD	Thalamo-occipital distance
VI	Ventricular index
VP	Ventriculoperitoneal

a large population of potentially activatable microglia are present in normal developing white matter during the premature period.[8] These "activated" cells can impair pre-OL maturation and other maturational events by release of reactive oxygen or nitrogen species or cytokines that act on pre-OLs, and likely on other cellular elements.[9] Moreover, proinflammatory microglia have been shown to induce formation of neurotoxic reactive astrocytes,[10] also important in failure of maturation of pre-OLs and likely other cellular elements.[11] The shift in microglial and astroglial phenotypes to proinflammatory phenotypes diverts the roles of these glia from the normal developmental events just noted. As noted later, abundant activated microglia and reactive astrocytes are present in cerebral white matter of neonatal IVH (non-hemorrhagic) ventriculomegaly, and PHVD.

Effects of IVH without Hydrocephalus

The vast majority of progressive ventricular dilation in premature infants occurs as a consequence of severe germinal matrix–intraventricular hemorrhage (GMH-IVH). A series of experimental studies, primarily performed in neonatal rats, demonstrated deleterious effects of intraventricular blood and blood components on the developing brain.[12-17] The injury scenario begins with hemoglobin release into the ventricular system. The ependymal injury related to the IVH likely facilitates penetration of hemoglobin and heme into brain parenchyma. Heme released from hemoglobin is taken up by microglial cells. Iron facilitates the formation of injurious reactive oxygen species, which affect both pre-OLs and axons. Heme can also be taken up by contiguous neurons, which are then injured. Such neurons could include those adjacent to blood in the ventricles (eg, hippocampus, thalamus) or in the subarachnoid space (eg, external granule cells of cerebellum). The role of free iron in the scenario leading to injury is supported by the beneficial effects of systemically administered deferoxamine in an animal model of IVH.[15] Additional blood products, especially thrombin and fibrin, are important in contributing to parenchymal injury after experimental IVH,[16] especially by promoting microglial and astroglial activation. These neuroinflammatory responses would be expected to injure vulnerable pre-OLs, axons, and contiguous neurons. The importance of the neuroinflammatory response is supported by experimental studies showing prevention of brain injury and PHVD by early systemic administration of minocycline, erythropoietin, melatonin, or mesenchymal stem cells.[18-22]

The few studies of IVH in the human premature brain postmortem and in vivo appear consistent with the experimental data. The principal findings include (1) disruption of the ventricular zone with reactive astrogliosis in areas of ependymal loss; (2) impairment of proliferation of oligodendroglial precursor cells and neuronal precursor cells in the subventricular zone of the ganglionic eminence, and in the cerebral white matter; (3) impairment of pre-OL maturation; (4) axonal injury; and (5) microglial activation.[23-25] Concerning pathophysiology, large amounts of non–protein-bound iron are present in the CSF of infants after large GMH-IVH (with PHVD),[26] and quantitative susceptibility map analysis by magnetic resonance imaging (MRI) with severe GMH-IVH shows changes consistent with accumulation of hemosiderin/ferritin iron throughout cerebral white matter.[27] The latter observations suggest that intraparenchymal diffusion of extracellular hemoglobin, and ultimately iron, is widespread after severe IVH. The mechanistic implications are clear and likely involve the free radical-mediated disturbances identified in experimental models, as described earlier.

Effects of Neonatal/Infantile Hydrocephalus without IVH

To assess the impact of neonatal PHVD on the developing brain, we must consider the effects of hydrocephalus per se, without previous IVH. Experimental studies based largely on the study of kaolin-induced hydrocephalus suggest that the principal initiating events leading to parenchymal injury are periventricular and cerebral white matter vascular impairment resulting initially in tissue hypoxia–ischemia.[28-31] A well-documented prominent inflammatory response with activated microglia and reactive astrocytes in cerebral white matter is likely involved in the elevation of free radicals and associated white matter injury.[30,32,33] The morphologic consequences involve, specifically, oligodendroglial precursors (presumably pre-OLs) and axons. In a well-characterized animal model, shunting at 1 week, but not at 4 weeks when axonal loss had occurred, allowed recovery of myelination.[34,35] Moreover, studies in rat models of PHVD also support particular value for early intervention.[22] The experimental data thus suggest that earlier rather than later intervention can prevent the pre-OL and axonal dysmaturational disturbances.

Effects of Neonatal PHVD

The previous sections concerning the effects on brain structure and pathophysiology of (1) IVH alone and (2) hydrocephalus alone set the stage for addressing the central issue of the effects of PHVD in the infant born preterm. Multiple experimental studies in developing animals have documented the occurrence of hydrocephalus after intraventricular injection of blood, hemoglobin, or iron into CSF.[18,20-22,36] Intraventricular injection of hemoglobin or iron in neonatal rats led acutely to hydrocephalus, pronounced gliosis with increased inflammatory cytokines in cerebral white matter, impaired myelination, and "cell death" in the hippocampus and "cortex." The importance of iron in the deleterious effects was shown by the lack of effect of intraventricular injection of iron-deficient protoporphyrin, the correlation of injury to hippocampus and cortex with the enhanced levels of heme oxygenase in those structures (heme oxygenase releases iron from heme), and the amelioration of hydrocephalus, inflammation, and tissue injury by the iron chelator deferoxamine.[36]

Studies of the deleterious effects of PHVD in infants born premature suggest disturbances in cerebral hemodynamics and neurophysiologic function. These disturbances and their

amelioration by CSF removal have been reviewed elsewhere.[31] Existing (although limited) studies of the morphologic consequences of PHVD in human infants at the cellular level indicate (1) ependymal disruption, (2) axonal injury, (3) microglial infiltration, and (4) impaired myelination.[23,28,37-39] Overall, the findings suggest a disturbance in development of cerebral white matter, deep nuclear structures (especially the thalamus), cerebral cortex (especially the hippocampus), and cerebellum, ie, structures contiguous to intraventricular and subarachnoid blood.

In summary, the mechanisms of the deleterious effects on the brain of the human infant with PHVD are likely multifactorial. In addition to cerebral ischemia, mechanical distortion and neuroinflammation, factors related to the presence of blood (leading ultimately to iron release and free radical formation) are pathogenic. Because the hydrocephalic state would be expected to enhance the intraparenchymal movement of blood products, the early institution of interventions that involve CSF drainage seems important. Optimal timing clearly needs further clarification.

Timing of Interventions—Relationship of Ventricular Size to Outcome

Infants born very preterm who develop a severe IVH (a grade III hemorrhage filling the lateral ventricle >50%, and resulting acutely in ventricular dilatation), or a periventricular hemorrhagic infarction (PVHI, a hemorrhagic lesion in the brain parenchyma associated with an ipsilateral grade II, or grade III hemorrhage) are prone to develop PHVD. Due to an imbalance in CSF production and reabsorption, the ventricles may dilate around 7-14 days following the onset of the IVH. PHVD can progress slowly or rapidly. In infants with slow progression, stabilization or regression occurs in 65%. In 30%-35% of infants, there is rapid progression in ventricular size over days to weeks.[2]

There is as yet no agreement when best to intervene, with some centers starting intervention based on sequential cUS measurements and others basing decisions on clinical symptoms (apneas, vomiting, full fontanel, sunsetting, splaying sutures, rapid increase in head circumference).[40,41] In the infant born preterm, there are 2 factors that reduce the sensitivity of fontanel pressure or head circumference changes for evaluating the degree of significant ventricular dilatation. The first factor is that compliance is greater in the infant born preterm and lower pressures are sufficient to cause progressive ventricular distension resulting in compression of the cortical mantle before an effect is apparent on the sutures or head circumference. The second factor relates to the larger extracerebral space in infants born very preterm requiring considerable ventricular dilatation before changes in fontanel pressure and a rapid increase in head circumference occur. Consistent with this notion, a poor correlation was found between the Evans ratio (the ratio of bifrontal horn diameter to the biparietal bone diameter) and the head circumference.[42] Therefore, sequential cUS in infants born preterm with IVH is required to diagnose and follow the progression of PHVD.

cUS Measurements

The "ventricular index" (VI), defined by Levene and Starte,[43] is the most commonly used measurement and is assessed in the coronal view. The VI is the distance between the midline (falx) and the lateral border of the lateral ventricle at the level of foramen of Monro (Figure 1, A). Another commonly used measurement is the "anterior horn width" (AHW), also measured in the coronal view just anterior to the thalamic notch.[44] (Figure 1, A) For both measurements, normal values and cut-off values for PHVD have been reported.[43-45] The "thalamo-occipital distance" (TOD) measures the occipital horn in the parasagittal plane and is of additional value because there can be a discrepancy in size between the anterior and occipital horns of the lateral ventricle (Figure 1, B). The AHW and TOD measures can indicate the "ballooning" shape of the lateral ventricles, and these measures correlate best with 3- dimensional volumetric ultrasound measurements.[46] The morphology of the ventricles can assist in the differentiation between dilatation due to PHVD or ventricular dilatation due to cerebral atrophy, because ventricular dilatation due to PHVD is typically associated with ballooning of the ventricles. In addition, assessing the extracellular space will assist in differentiating the 2 causes of dilatation. The absence of any extra-axial space supports the conclusion that the dilatation relates to CSF accumulation, whereas the presence of extra-axial space suggests cerebral atrophy.[47]

Other measures are derived mainly from axial MRI and computed tomography scans and include the Evans ratio (described previously) (F/BP; Figure 1, C) and the frontal and occipital horn ratio (FOHR), which is the average of the frontal and occipital horn dimensions divided by the biparietal diameter [(F+O)/2)/BP] (Figure 1, C) The FOHR has shown high interobserver reliability (especially when compared with the Evans ratio, only reflecting the anterior horns) and correlation with ventricular volumes.[48,49] cUS measurements of the FOHR, as well as the frontal and temporal horn ratio, were significantly correlated with the same measures derived from MRI[50] (Figure 1, C-F).

Other Measurements

Use of the Doppler ultrasound resistive index, the difference between peak systolic flow velocity and lowest diastolic flow velocity divided by the peak systolic flow velocity, provides information about cerebral hemodynamics, especially cerebrovascular resistance. With progressive PHVD, initially a rise in systolic flow is seen, followed by a decrease, absent or even inverted diastolic flow.[51] Significant changes in the resistive index following application of pressure to the anterior fontanel (a measure of cerebral compliance) have been correlated with intracranial pressure and future need for shunt placement.[52] In addition, near-infrared spectroscopy studies have shown that regional cerebral oxygen saturation is progressively impaired with increasing dilatation and
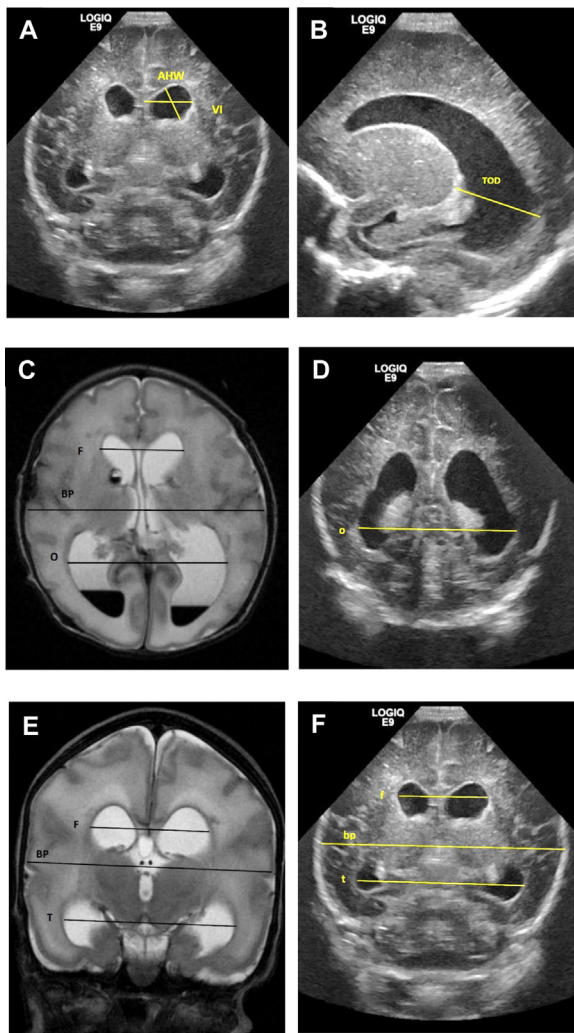
Figure 1. Demonstration of different ventricular measures and ratios. Images from cUS and brain MRI of 1-week old male infant born at 30 weeks of gestation. **A** and **F,** Coronal cUS at level of foramen of Monro; **B,** Parasagittal cUS; **C,** Axial view of T2 MRI; **D,** Coronal cUS at level of occipital horn; **E,** Coronal view of T2 MRI. MRI dimensions are in capital letters: *BP*, biparietal, *F*, bifrontal horn, *O,* biooccipital horn; *T,* bitemporal horn. cUS dimensions are in small letters: *bp*, biparietal; *f*, bifrontal horn; *o*, biooccipital horn; *t*, bitemporal horn. Evans ratio = F/BP by MRI or f/bp by US. Frontal and temporal horn ratio = (F+T/2)/BP by MRI or (f+t/2)/bp by cUS. FOHR = (F+O/2)/BP by MRI or (f+o/2)/bp by cUS.

gradually improves following CSF drainage.[53,54] As these changes occur when PHVD is severe, intervention is best started before the presence of these changes.

Intervention Studies

Intervention typically starts with temporizing lumbar punctures (LPs) to decompress the ventricle on an urgent basis while neurosurgical evaluation and surgical planning occur.

LPs also may prevent the need for further neurosurgical intervention, as was demonstrated in the ELVIS study, in which one-quarter of all cases just required 2-3 LPs and did not need any surgery.[55] Thus, the use of LPs in the immediate period after identification of significant ventricular dilatation can be helpful in temporizing or avoiding surgical intervention.

Earlier data related to the role of LPs in the management of PHVD are summarized in a Cochrane review that reported no evidence that LPs alone were effective in avoiding shunt surgery or improving neurologic development.[56] This review included 4 trials performed from 1980 to 1990 with significant variation in indication, timing, number, and effectiveness of LPs. The majority of these studies included infants with severely dilated ventricles, with LPs starting relatively late, and high variation in number of LPs (1-40) and volume drained (Table I; available at www.jpeds.com). Of note, in the largest study in this Cochrane review, >50% of the early intervention group eventually received invasive ventricular taps.[57] We hypothesize that the late, variable, and invasive approaches used in these studies explain the higher rates of ventriculoperitoneal (VP) shunt placement and worse neurodevelopmental outcomes when compared with more recent studies which focused on early effective drainage of CSF (Table II; available at www.jpeds.com).

In more recent studies, when stabilization or regression of ventricular size did not occur spontaneously, or 2-3 LPs were not successful, the insertion of a ventricular reservoir or ventricular subgaleal shunt has been used as a temporizing measure. Many centers defer such intervention until the VI has crossed the 97th percentile +4 mm line or clinical symptoms have developed. Two retrospective, observational studies showed a reduction in shunt requirement when LPs and reservoir insertion were performed before the 97th percentile +4 mm line was crossed.[58,59] In another retrospective study of 32 infants born preterm, external ventricular drainage (using bedside insertion of an intravenous catheter connected to a closed drainage plastic container) performed early (defined as ≤25 days after birth) was associated with better scores for adaptive, personal social, communication, and cognitive functions at 6 years of age compared with those with later intervention.[60] A more recent observational study has shown results favoring earlier therapeutic intervention for PHVD using cUS measures.[40] In the study by Leijser et al, neurodevelopmental outcomes at 18-24 months were compared between infants born preterm with and without intervention within cohorts undergoing either an early cUS-based approach in 2 Dutch centers or late intervention following onset of clinical signs in a Canadian center. Infants undergoing early cUS-based intervention had 2-year outcomes indistinguishable from infants not requiring CSF drainage (cognitive test score of 100 vs 95; *P* = .6; motor score of 97 vs 97; *P* = .6), even when they eventually needed insertion of a VP shunt (20%). In contrast, intervention initiated once clinical signs had occurred was associated with an increased risk of unfavorable outcome (cognitive score of 90 vs 68; *P* = .002; motor score of 90 vs 60; *P* = .03) and

intervention-related complications, with the need for a VP shunt in 92%, compared with infants not needing intervention. There were important confounders in this study, however, including a differing referral pattern between the Dutch and Canadian centers.

The most recent randomized controlled trial was the ELVIS trial (Early versus Late Ventricular Intervention Study), which enrolled 126 infants born preterm at ≤34 weeks of gestation with progressive PHVD following severe IVH. Treatment was either started at a low threshold (LT) (VI >97th percentile and AHW >6 mm and/or TOD >25 mm), or at a greater threshold (high threshold [HT]) (VI >97th percentile +4 mm and AHW >10 mm). There was no significant difference between the 2 groups for the primary outcome of death and or VP-shunt placement (30% infants in the LT group and 37% for infants in the HT group). A VP shunt was inserted in 12 of 64 (19%) infants in the LT and in 14 of 62 (23%) infants in the HT group, the lowest rates reported thus far in the literature. More neurosurgical interventions were required in the LT group.[55] In a nested substudy, brain injury was assessed by the Kidokoro score on MRI performed at term-equivalent age.[61] The total Kidokoro score was lower in the infants in the LT group (n = 44) than in the HT group (n = 44; median, 8 [IQR, 5-12] vs median 12 [IQR, 9-17], respectively; $P < .001$). Ventricular volumes could be calculated in 47 infants and were smaller in the LT group ($P = .03$). At 2 years of age, the risk of developmental impairment was low among both study groups, with 75% of all infants tested achieving a cognitive composite score of ≥85. There was no significant difference for adverse outcome (composite outcome: death/cerebral palsy/developmental test score <70) between the 2 groups.[62] However, in the post-hoc multivariable analysis, children in the LT group had a decreased risk of composite adverse outcome, after correcting for gestational age and hemorrhage severity (aOR 0.24, 95% CI 0.07-0.87, $P = .03$). Furthermore, a significant relationship was established between the maximal FOHR and cognitive and motor outcome for all infants combined. These findings support the conclusion that timely intervention with reduction of the extent of ventricular dilatation may mitigate brain injury associated with ventricular dilatation and lead to improved neurodevelopmental outcomes.

Relation of Maximal Ventricular Size to Neurodevelopmental Outcome

To justify the need for therapeutic reduction in ventricular size, an association with improved outcomes should be demonstrable. In contrast to data derived from postnatal post-inflammatory hydrocephalus in term born infants and children,[63] the association between the maximal size of ventricular measurements in PHVD in infants born preterm and neurodevelopmental outcomes has been supported by more than one study.[40,62,64] This association is additionally demonstrated in **Figure 2**, where the relationship of maximal AHW during the neonatal intensive care unit period in infants born preterm with PHVD is shown to be
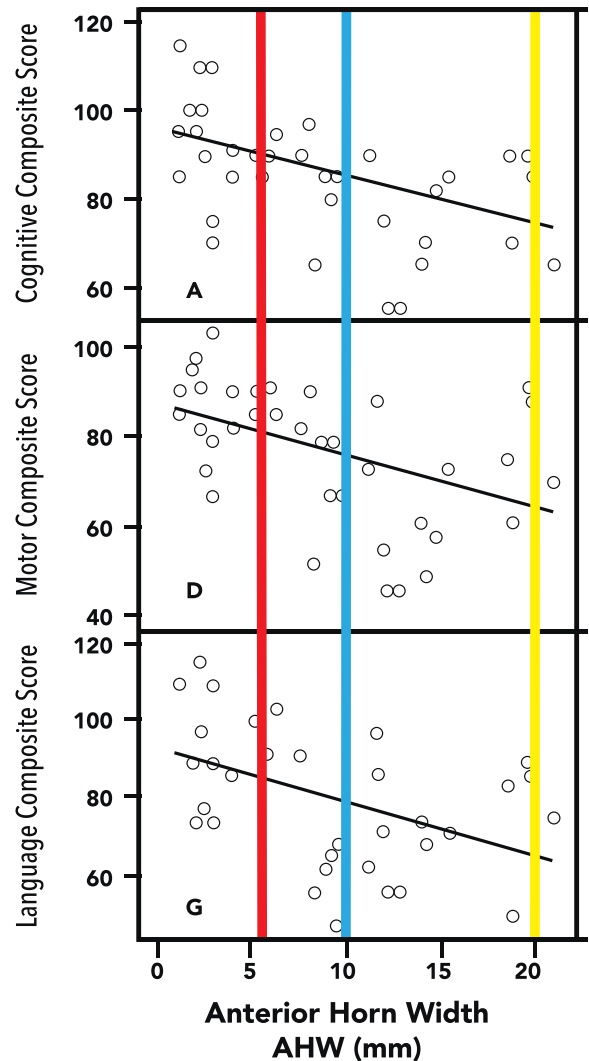
Figure 2. AHW in relation to neurodevelopmental outcomes at 18-24 months in 39 infants born preterm with PHVD. The maximal size of the AHW in the North American group of the study by Leijser et al (*yellow bar*) and the corresponding neurodevelopmental impairments with performance at 60-70 points, contrasts with the results in the ELVIS study with early (*red*) and late (*blue*), demonstrating less significant differences in outcomes. It is noteworthy that timing of the "late" intervention arm in ELVIS is much earlier than in the North American sites.

related to neurodevelopmental outcomes at 18-24 months on assessment using the Bayley Scales of Infant Development (2nd edition) assessment.[64] The bars overlaid on this graph represent the data reported from a single-center observational study of a North American population (yellow bar), with concordant mean cognitive scores of 68 and motor scores of 60.[40] These values contrast with those from the earlier intervention study (the ELVIS trial) with early (red) and late (blue) interventions both having smaller ventricular measures than the North American

cohort. The outcomes in the ELVIS study of early intervention (mean cognitive score 95) and later intervention (mean cognitive 91)[62] are consistent with the relatively small differences between study arms in the measurements used as threshold to treat. However, when the ventricular size is much larger, as is typical in the North American cohort, the associated developmental outcomes are much worse, supporting the need to avoid such large degrees of ventricular dilatation, if possible.

Alternative Intervention

Drainage, irrigation, and fibrinolytic therapy (DRIFT) was conceived due to evidence that (1) blood and its breakdown products persist for months and contribute to free radical injury and inflammation and (2) earlier reduction in ventricular enlargement may improve outcome. The intervention is intended to wash out the ventricles and reduce ventricular size. The DRIFT randomized trial recruited 77 infants with PHVD and minimum VI 97th percentile +4 mm, but there was no upper limit for ventricular size at entry. Trial recruitment was stopped early because of excess secondary hemorrhage (35%). Most of these hemorrhages were small, and drainage and irrigation continued until clearance of CSF.[65] Of the infants randomized to DRIFT, 21 of 39 (54%) died or were severely disabled vs 27 of 38 (71%) in the standard treatment group (aOR 0.25; 95% CI 0.08-0.82). Among the survivors, 11 of 35 (31%) in the DRIFT group had severe cognitive impairments (Bayley cognitive scores <55) vs 19 of 32 (59%) in the standard treatment group (aOR 0.17; 95% CI 0.05–0.57).[66] At 10 years of age, 52 children (28 from the DRIFT group and 24 with standard treatment) were assessed again.[67] The mean cognitive quotient score was 15.7 points greater (95% CI –2.9 to 34.2 points; $P = .096$) in the DRIFT group (69.3 ± 30.1 SD) compared with the standard treatment group (53.7 ± 35.7 SD). Following adjustment for sex, birth weight, and grade of IVH, significantly more children in the DRIFT group were alive without severe cognitive disability, with a difference of 23.5 points. Similarly, in another preliminary clinical study, a combination of ventricular lavage therapy using external ventricular drainage and intermittent urokinase slow intraventricular injections was associated with less VP-shunt placements and better functional outcomes at 36 weeks of age.[68]

Although the DRIFT trial provides support for the hypothesis that washing out harmful substances from the ventricles reduces overall brain injury after PHVD, DRIFT is a complicated procedure requiring highly skilled clinical monitoring and intervention over 72 hours. A simpler intervention that is easier to teach and disseminate is needed.

Considerations for Neurosurgical Interventions

Renewed interest in optimizing the neurosurgical treatment of infants with PVHD stems from (1) recognition that PHVD is the most common etiology of hydrocephalus in Europe and North America[69]; (2) increasing trends in the incidence and prevalence of PHVD[70]; (3) the severe neurologic morbidity and lifelong, complex neurosurgical care required; (4) data suggesting potential benefit to standardized intervention in PHVD; and (5) basic and translational science providing a scientific rationale for earlier intervention.[71,72] Despite this interest, however, the data concerning neurosurgical interventions for PHVD remain limited. Recent evidence-based guidelines under the auspices of the Joint American Association of Neurological Surgeons and Congress of Neurological Surgeons Pediatric Section failed to identify sufficient data to support strong recommendations in the neurosurgical treatment of PHVD.[73]

Because of the lack of strong evidence, there is great variation in practices between centers with respect to neurosurgical interventions for PHVD. This variation relates to 2 main treatment decision considerations: the timing of intervention and the type of intervention. Concerning the former, the HCRN (Hydrocephalus Clinical Research Network), a multi-institutional North American research group, identified the single most significant factor driving the timing of neurosurgical intervention of infants with PHVD to be the center at which they were treated.[41,73] As a result, the HCRN standardized the clinical assessment of these infants and developed standard definitions for reliable assessment of a bulging fontanel or split cranial sutures.[74] However, the presence of adequate inter-rater reliability did not address whether this assessment correlates well with increased ICP, in contrast to previous reports which did not show such correlation,[75] or if such "late" signs should be the target for intervention.

The HCRN also showed that the assessment and timing of intervention in these infants can be standardized with high compliance across multiple centers and developed standardized operative protocols to decrease VP-shunt infection in these high-risk infants.[76,77] The HCRN study titled "Shunting Outcomes in Post-hemorrhagic Hydrocephalus (SOPHH)" compared the impact of ventricular reservoir vs ventricular subgaleal shunt (**Figure 3**; available at www.jpeds.com) as a temporizing measure on death or requirement for shunt in a prospective, multicenter observational study.[78] In SOPHH, FOHR was used with an intervention threshold ≥0.55, which would exceed the HT group of the ELVIS trial or the threshold for the DRIFT trial. This threshold was based on previously established practice patterns and consensus agreement among the participating centers. Of note, despite agreement to intervene at FOHR ≥0.55, at the time of intervention the FOHR exceeded the intervention threshold (0.68 ± 0.07 for the ventricular subgaleal shunt group and 0.67 ± 0.06 for the ventricular reservoir group). Also notable is that the treatment threshold required a combination of a progressive increase in head circumference, full fontanel or splaying of the sagittal suture ≥2 mm in the mid-parietal region. SOPHH enrollment occurred at 6 sites over 39 months and included placement of 66 ventricular

reservoirs and 36 ventricular subgaleal shunts. Overall, 65% of infants with temporizing measures were converted to permanent shunts. Developmental follow-up in this cohort with Bayley-III cognitive, language, and motor outcomes is forthcoming.

Complications reported with temporizing measures include obstruction, infection, need for revision, and other rare complications including CSF leak, porencephalic cysts, and intracranial hemorrhage[79-81] (Table III; available at www.jpeds.com). In the SOPHH study, there was no difference between ventricular reservoir and ventricular subgaleal shunt in rates of infection, CSF leak, death, or VP shunt rate. Although the ventricular reservoir entails more frequent skin breaks than ventricular subgaleal shunt, minimizing complications from reservoir drainage can be obtained by systematic care, including strict sterile precautions, using a trained provider for removal of the CSF, removing the fluid slowly at not >1 mL/min, and carefully considering skin care over the site of the reservoir.[82]

In the absence of strong evidence about timing and types of neurosurgical interventions, neurosurgical groups have focused on standardizing the assessment and management protocols. Although helpful, such strategies have tended to result in late interventions and with an unclear benefit on neurodevelopmental outcomes.

Future Opportunities

On the horizon are potentially promising new diagnostic and therapeutic approaches that might be of further benefit to infants with PHVD. Although none are yet in clinical use, quantitative neuroimaging and analysis of CSF and blood-based analytes[72,83-86] show promise as potential diagnostic biomarkers of PHVD that could guide treatment and prediction of outcome. In addition, studies in animals have demonstrated the potential protective effect of mesenchymal stem cells by intraventricular[20] as well as intravenous[21] infusion following severe IVH. Mesenchymal stem cells attenuated the degree of PHVD as well as degree of brain injury in a severe IVH rat model, especially when given at 2 days rather than 7 days after induction of IVH.[22] The same group also published the results of a phase I trial using intraventricular transplantation of mesenchymal stem cells in 9 premature infants.[87] Other studies suggest benefit from erythropoietin/melatonin,[19] minocycline,[18] potentially via anti-inflammatory mechanisms, and deferoxamine, via iron chelation.[36] In addition, several centers now apply the principle of "washing out PHVD" by using endoscopic ventricular lavage in the operating room. Schulz et al reported on the feasibility and safety of this technique in 19 infants.[88] In addition, d'Arcangues et al reported 56 infants with PHVD treated with endoscopic ventricular lavage and concluded that the procedure may reduce the need for shunt surgery and subsequent shunt revisions.[89] Another approach, which could potentially reduce the long-term shunt-related morbidity in these infants, is endoscopic third ventriculostomy without or with choroid plexus cauterization. This intervention could serve as an alternative to CSF shunting in PHVD, although reported success rates are variable, at least early in infancy in this population.[83,90,91]

Management Approach

Combining the evidence from preclinical data, supporting the ability of early interventions to reverse brain injury, and from clinical data, indicating that the best neurodevelopmental outcomes have been reported in centers and trials using ventricular measurements as criteria for interventions (Table II), it appears prudent to adopt this evidence into clinical practice. The authors of this manuscript agree on the following approach to be considered for overall management of PHVD.

The recognition of increased intracranial pressure using clinical signs as rapid head growth, separated sutures, or bulging fontanelles is important. However, waiting for late signs can lead to late interventions and the potential for worsening brain injury. Nonetheless, the development of such signs should be concerning enough to initiate interventions even with modest increases in ventricular measurements. Doppler ultrasound and near-infrared spectroscopy may aid with the decision, given the alterations described previously.
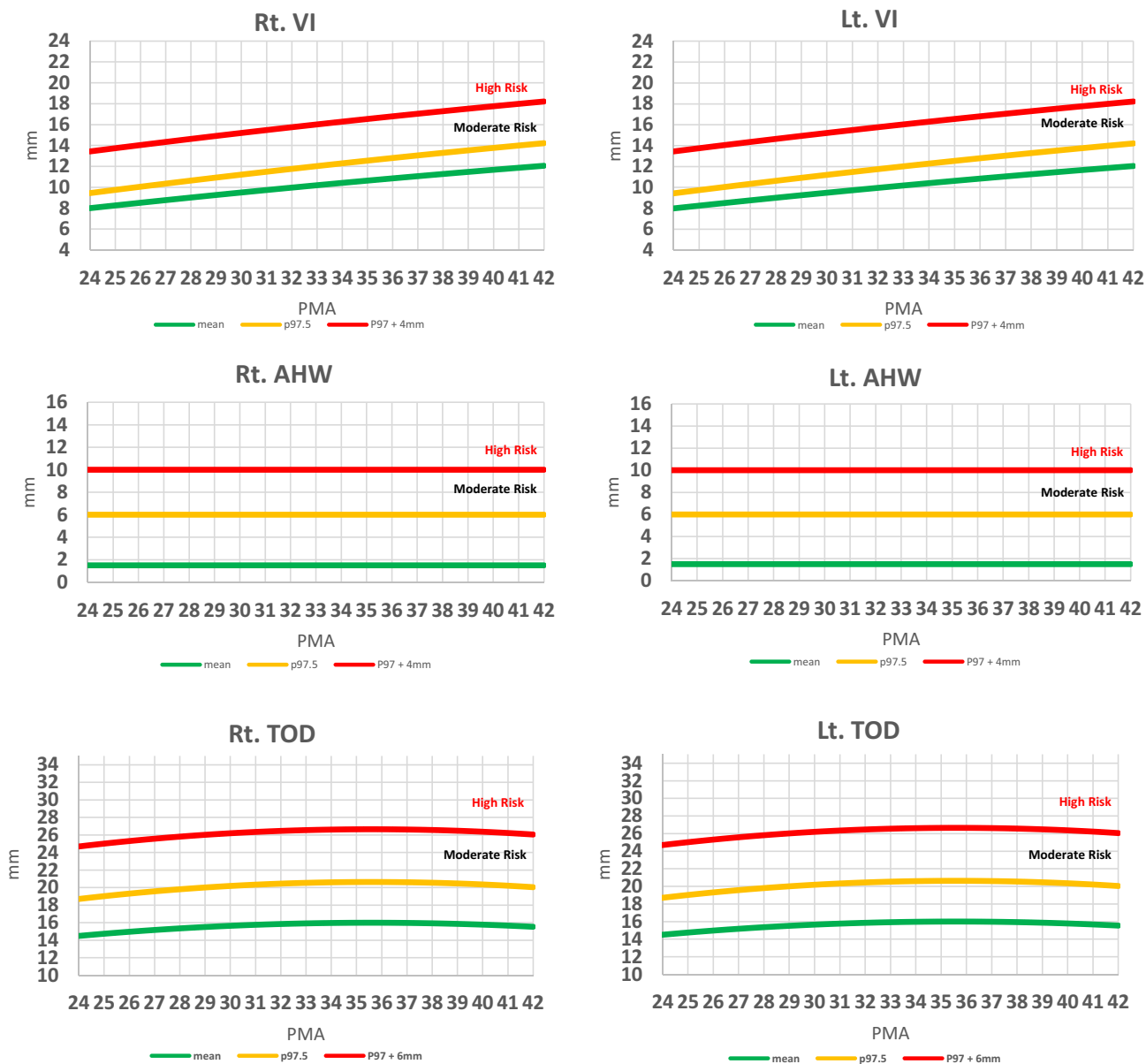
Based on these principles, we are proposing that a framework that relies on standardized ventricular measurements, clinical signs, and supplementary tests can be used to assign risk categories for infants with PHVD. Based on this risk assessment, providers can determine the frequency and types of assessments, the timing of temporizing measures, neurosurgical referral, and neurosurgical interventions. Recognition of the risk category is facilitated by the use of standardized ventricular measurements (namely VI, AHW, and TOD) in every cUS done in infants with PHVD. A simple tool was developed from data from the study by Brouwer et al to help the clinician plot ventricular measurements over time to assess risk progress (Figure 4).[45] An electronic spreadsheet is available to be downloaded, stored in secure servers, and used for individual patients in 2 formats: one is for postmenstrual age 24-42 weeks (https://tinyurl.com/PHVD-Measures-1) and another for postmenstrual age 24-29 weeks (https://tinyurl.com/PHVD-Measures-2). This spreadsheet categorizes infants with PHVD into 3 risk groups, ie, low, moderate, or high risk (Figure 5).

In our opinion, the low-risk group (green zone) should be monitored closely and evaluated by cUS at least twice weekly until the ventricles are stable for 2 weeks and then every 1-2 weeks until 34 weeks postmenstrual age. A term-equivalent MRI can be useful to delineate the degree of brain injury as well as any alterations in brain maturation.

Infants in the moderate-risk group (yellow zone) may benefit from neurosurgical consultation and 2-3 LPs, aiming for removal of 10 mL/kg of CSF. LPs can be started as soon as infants fulfill criteria for measurements of ventricular size, without any restriction on gestation or birth weight. cUS should be performed before and preferably also following

Name:
DOB:

Ventricular Measurement Risk Zones

Rt. VI

mm

24 22 20 18 16 14 12 10 8 6 4

High Risk

Moderate Risk

24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42

PMA

━━ mean ━━ p97.5 ━━ P97 + 4mm

Lt. VI

mm

24 22 20 18 16 14 12 10 8 6 4

High Risk

Moderate Risk

24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42

PMA

━━ mean ━━ p97.5 ━━ P97 + 4mm

Rt. AHW

mm

16 14 12 10 8 6 4 2 0

High Risk

Moderate Risk

24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42

PMA

━━ mean ━━ p97.5 ━━ P97 + 4mm

Lt. AHW

mm

16 14 12 10 8 6 4 2 0

High Risk

Moderate Risk

24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42

PMA

━━ mean ━━ p97.5 ━━ P97 + 4mm

Rt. TOD

mm

34 32 30 28 26 24 22 20 18 16 14 12 10

High Risk

Moderate Risk

24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42

PMA

━━ mean ━━ p97.5 ━━ P97 + 6mm

Lt. TOD

mm

34 32 30 28 26 24 22 20 18 16 14 12 10

High Risk

Moderate Risk

24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42

PMA

━━ mean ━━ p97.5 ━━ P97 + 6mm

Date	PMA	Rt. VI	Rt. AHW	Rt. TOD	Lt. VI	Lt. AHW	Lt. TOD

Figure 4. A practical clinical tool to monitor commonly used ventricular measures. Individual measures can be plotted in millimeters in the table as well as on the corresponding postmenstrual age in the graph to identify risk zone.

Green Zone	Yellow Zone	Red 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 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 >2cm 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 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

Consider alterations in NIRS (ie decrease cerebral oxygenation) or Doppler US (ie Increase in Resistive Index) as additional information that may suggest impairment in cerebral perfusion and more urgent need for intervention.

Figure 5. Proposed risk stratification and management of infants with PHVD. *HC*, head circumference; *NIRS*, near-infrared spectroscopy; *PMA*, postmenstrual age.

the LP to assess the effect, and the LP should not be performed more often than once a day. cUS should be performed at least 2-3 times per week until the ventricles are stable for 2 weeks, and then every 1-2 weeks. A term-equivalent MRI is also recommended.

Infants who reach the high-risk group (red zone) also may benefit from 2-3 LPs done acutely, while planning neurosurgical interventions. Neurosurgical interventions could include ventricular reservoir or ventricular subgaleal shunt (likely after the infant's weight is ≥700 g) based on center preference. Interventions might also include a VP shunt, based on such factors as center preferences, age, weight, clinical condition, and CSF protein and red cell count. Success rates for endoscopic third ventriculostomy without or with choroid plexus cauterization, performed following temporizing measures, are enhanced by selecting infants who are close to or preferably well beyond term equivalent age and who have no obstruction of the prepontine cistern on preoperative MRI.[92]

Conclusions

PHVD in the infant born preterm continues to be a significant problem associated with adverse neurodevelopmental outcomes. The mechanisms involved in brain injury are multifactorial and include cerebral ischemia, mechanical distortion and neuroinflammation secondary to brain exposure to blood products, especially iron. There is growing evidence that early interventions for CSF removal based on ventricular measurements can reduce brain injury and improve neurodevelopmental outcomes. Although advances are expected in this field, current evidence supports the stepwise approach described here to prevent and or attenuate the progression of injury and neurodevelopmental impairment. ∎

References

1. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA 2015;314:1039-51.
2. Murphy BP, Inder TE, Rooks V, Taylor GA, Anderson NJ, Mogridge N, et al. Posthaemorrhagic ventricular dilatation in the premature infant: natural history and predictors of outcome. Arch Dis Child Fetal Neonatal Ed 2002;87:F37-41.
3. Kinney HC, Volpe JJ. Organizational events. In: Volpe JJ, Inder TE, Darras BT, deVries LS, duPlessis AJ, Neil JJ, et al., eds. Volpe's neurology of the newborn. 6th ed. Philadelphia (PA): Elsevier; 2018. p. 145-75.
4. Volpe JJ. Dysmaturation of premature brain: Importance, cellular mechanisms and potential interventions. Pediatr Neuro 2019;95:42-66.
5. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol 2009;8:110-24.
6. Reemst K, Noctor SC, Lucassen PJ, Hol EM. The indispensable roles of microglia and astrocytes during brain development. Front Hum Neurosci 2016;10:1-28.
7. Hammond TR, Robinton D, Stevens B. Microglia and the brain: Complementary partners in development and disease. Annu Rev Cell Dev Biol 2018;34:523-44.
8. Billiards SS, Haynes RL, Folkerth RD, Trachtenberg FL, Liu LG, Volpe JJ, et al. Development of microglia in the cerebral white matter of the human fetus and infant. J Comp Neurol 2006;497:199-208.

9. Volpe JJ, Kinney HC, Jensen FE, Rosenberg PA. The developing oligo-dendrocyte: key cellular target in brain injury in the premature infant. Int J Devl Neurosci 2011;29:423-40.

10. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. Nature 2017;541:481-7.

11. Back SA. White matter injury in the preterm infant: pathology and mechanisms. Acta Neuropathol 2017;134:331-49.

12. Karimy JK, Zhang J, Kurland DB, Theriault BC, Duran D, Stokum JA, et al. Inflammation-dependent cerebrospinal fluid hypersecretion by the choroid plexus epithelium in posthemorrhagic hydrocephalus. Nat Med 2017;23:997-1003.

13. Juliet PA, Frost EE, Balasubramaniam J, Del Bigio MR. Toxic effect of blood components on perinatal rat subventricular zone cells and oligo-dendrocyte precursor cell proliferation, differentiation and migration in culture. J Neurochem 2009;109:1285-99.

14. Vinukonda G, Dohare P, Arshad A, Zia MT, Panda S, Korumilli R, et al. Hyaluronidase and hyaluronan oligosaccharides promote neurological recovery after intraventricular hemorrhage. J Neurosci 2016;36:872-89.

15. Garton TP, He Y, Garton HJ, Keep RF, Xi G, Strahle JM. Hemoglobin-induced neuronal degeneration in the hippocampus after neonatal intra-ventricular hemorrhage. Brain Res 2016;1635:86-94.

16. Garton T, Hua Y, Xiang J, Xi G, Keep RF. Challenges for intraventricular hemorrhage research and emerging therapeutic targets. Expert Opin Ther Targets 2017;21:1111-22.

17. Karimy JK, Reeves BC, Damisah E, Duy PQ, Antwi P, David W, et al. Inflammation in acquired hydrocephalus: pathogenic mechanisms and therapeutic targets. Nat Rev Neurol 2020;16:285-96.

18. Guo J, Chen Q, Tang J, Zhang J, Tao Y, Li L, et al. Minocycline-induced attenuation of iron overload and brain injury after experimental germinal matrix hemorrhage. Brain Res 2015;1594:115-24.

19. Robinson S, Conteh FS, Oppong AY, Yellowhair TR, Newville JC, Demerdash NE, et al. Extended combined neonatal treatment with erythropoietin plus melatonin prevents posthemorrhagic hydrocephalus of prematurity in rats. Front Cell Neurosci 2018;12:322.

20. Ahn SY, Chang YS, Sung DK, Sung SI, Yoo HS, Lee JH, et al. Mesen-chymal stem cells prevent hydrocephalus after severe intraventricular hemorrhage. Stroke 2013;44:497-504.

21. Ahn SY, Chang YS, Sung DK, Sung SI, Yoo HS, Im GH, et al. Optimal route for mesenchymal stem cells transplantation after severe intraven-tricular hemorrhage in newborn rats. PLoS One 2015;10:e0132919.

22. Park WS, Sung SI, Ahn SY, Sung DK, Im GH, Yoo HS, et al. Optimal timing of mesenchymal stem cell therapy for neonatal intraventricular hemorrhage. Cell Transplant 2016;25:1131-44.

23. McAllister JP, Guerra MM, Ruiz LC, Jimenez AJ, Dominguez-Pinos D, Sival D, et al. Ventricular zone disruption in human neonates with intra-ventricular hemorrhage. J Neuropathol Exp Neurol 2017;76:358-75.

24. Del Bigio MR. Cell proliferation in human ganglionic eminence and sup-pression after prematurity-associated haemorrhage. Brain 2011;134:1344-61.

25. Supramaniam V, Vontell R, Srinivasan L, Wyatt-Ashmead J, Hagberg H, Rutherford M. Microglia activation in the extremely preterm human brain. Pediatr Res 2013;73:301-9.

26. Savman K, Nilsson UA, Blennow M, Kjellmer I, Whitelaw A. Non-pro-tein-bound iron is elevated in cerebrospinal fluid from preterm infants with posthemorrhagic ventricular dilation. Pediatr Res 2001;49:208-12.

27. Tortora D, Severino M, Sedlacik J, Toselli B, Malova M, Parodi A, et al. Quantitative susceptibility map analysis in preterm neonates with germinal matrix-intraventricular hemorrhage. J Magn Reson Imaging 2018;48:1199-207.

28. Del Bigio MR. Cellular damage and prevention in childhood hydroceph-alus. Brain Pathol 2004;14:317-24.

29. Del Bigio MR, Khan OH, da Silva Lopes L, Juliet PA. Cerebral white mat-ter oxidation and nitrosylation in young rodents with kaolin-induced hydrocephalus. J Neuropathol Exp Neurol 2012;71:274-88.

30. Del Bigio MR, Di Curzio DL. Nonsurgical therapy for hydrocephalus: a comprehensive and critical review. Fluids Barriers CNS 2016;13:1-20.

31. Inder TE, Perlman JM, Volpe JJ. Preterm intraventricular hemorrhage/posthemorrhagic hydrocephalus. In: Inder TE, Volpe JJ, Darras BT, de Vries LS, du Plessis A, Neil JJ, et al., eds. Volpe's neurology of the newborn. 6th ed. Philadelphia (PA): Elsevier; 2018. p. 637-98.

32. Deren KE, Packer M, Forsyth J, Milash B, Abdullah OM, Hsu EW, et al. Reactive astrocytosis, microgliosis and inflammation in rats with neonatal hydrocephalus. Exp Neurol 2010;226:110-9.

33. Xu H, Zhang SL, Tan GW, Zhu HW, Huang CQ, Zhang FF, et al. Reac-tive gliosis and neuroinflammation in rats with communicating hydro-cephalus. Neuroscience 2012;218:317-25.

34. Del Bigio MR, Kanfer JN, Zhang YW. Myelination delay in the cerebral white matter of immature rats with kaolin-induced hydrocephalus is reversible. J Neuropathol Exp Neurol 1997;56:1053-66.

35. Del Bigio MR, Wilson MJ, Enno T. Chronic hydrocephalus in rats and humans: white matter loss and behavior changes. Ann Neurol 2003;53:337-46.

36. Strahle JM, Garton T, Bazzi AA, Kilaru H, Garton HJ, Maher CO, et al. Role of hemoglobin and iron in hydrocephalus after neonatal intraven-tricular hemorrhage. Neurosurgery 2014;75:696-705. discussion 6.

37. Weller RO, Wisniewski H, Ishii N, Shulman K, Terry RD. Brain tissue damage in hydrocephalus. Dev Med Child Neurol Suppl 1969;20:1-7.

38. Weller RO, Shulman K. Infantile hydrocephalus: clinical, histological, and ultrastructural study of brain damage. J Neurosurg 1972;36:255-65.

39. Ulfig N, Bohl J, Neudorfer F, Rezaie P. Brain macrophages and microglia in human fetal hydrocephalus. Brain Dev 2004;26:307-15.

40. Leijser LM, Miller SP, van Wezel-Meijler G, Brouwer AJ, Traubici J, van Haastert IC, et al. Posthemorrhagic ventricular dilatation in preterm in-fants: when best to intervene? Neurology 2018;90:e698-706.

41. Riva-Cambrin J, Shannon CN, Holubkov R, Whitehead WE, Kulkarni AV, Drake J, et al. Center effect and other factors influencing temporization and shunting of cerebrospinal fluid in preterm infants with intraventricular hemorrhage. J Neurosurg Pediatr 2012;9:473-81.

42. Ingram MC, Huguenard AL, Miller BA, Chern JJ. Poor correlation be-tween head circumference and cranial ultrasound findings in premature infants with intraventricular hemorrhage. J Neurosurg Pediatr 2014;14:184-9.

43. Levene MI, Starte DR. A longitudinal study of post-haemorrhagic ven-tricular dilatation in the newborn. Arch Dis Child 1981;56:905-10.

44. Davies MW, Swaminathan M, Chuang SL, Betheras FR. Reference ranges for the linear dimensions of the intracranial ventricles in preterm neo-nates. Arch Dis Child Fetal Neonatal Ed 2000;82:F218-23.

45. Brouwer MJ, De Vries LS, Groenendaal F, Koopman C, Pistorius LR, Mulder EJH, et al. New reference values for the neonatal cerebral ventri-cles. Radiology 2012;262:224-33.

46. Benavente-Fernandez I, Lubian-Gutierrez M, Jimenez-Gomez G, Le-chuga-Sancho AM, Lubian-Lopez SP, Neonatal Neurology Foundation (Fundación Nene). Ultrasound lineal measurements predict ventricular volume in posthaemorrhagic ventricular dilatation in preterm infants. Acta Paediatr 2017;106:211-7.

47. De Vries LS, van Haastert IC, Benders MJNL, Groenendaal F. Myth: ce-rebral palsy cannot be predicted by neonatal brain imaging. Semin Fetal Neonatal Med 2011;16:279-87.

48. Kulkarni AV, Drake JM, Armstrong DC, Dirks PB. Measurement of ven-tricular size: reliability of the frontal and occipital horn ratio compared to subjective assessment. Pediatr Neurosurg 1999;31:65-70.

49. O'Hayon BB, Drake JM, Ossip MG, Tuli S, Clarke M. Frontal and occi-ital horn ratio: a linear estimate of ventricular size for multiple imaging modalities in pediatric hydrocephalus. Pediatr Neurosurg 1998;29:245-9.

50. Radhakrishnan R, Brown BP, Kralik SF, Bain D, Persohn S, Territo PR, et al. Frontal occipital and frontal temporal horn ratios: comparison and validation of head ultrasound-derived indexes with mri and ventricular volumes in infantile ventriculomegaly. AJR Am J Roentgenol 2019;213:925-31.

51. van Alfen-van der Velden AA, Hopman JC, Klaessens JH, Feuth T, Sengers RC, Liem KD. Cerebral hemodynamics and oxygenation after se-rial CSF drainage in infants with PHVD. Brain Dev 2007;29:623-9.

52. Taylor GA, Madsen JR. Neonatal hydrocephalus: hemodynamic response to fontanelle compression—correlation with intracranial pressure and need for shunt placement. Radiology 1996;201:685-9.

53. Norooz F, Urlesberger B, Giordano V, Klebermasz-Schrehof K, Weninger M, Berger A, et al. Decompressing posthaemorrhagic ventricular dilatation significantly improves regional cerebral oxygen saturation in preterm infants. Acta Paediatr 2015;104:663-9.

54. Kochan M, McPadden J, Bass WT, Shah T, Brown WT, Tye GW, et al. Changes in cerebral oxygenation in preterm infants with progressive posthemorrhagic ventricular dilatation. Pediatr Neurol 2017;73:57-63.

55. de Vries LS, Groenendaal F, Liem KD, Heep A, Brouwer AJ, van 't Verlaat E, et al. Treatment thresholds for intervention in posthaemorrhagic ventricular dilation: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2019;104:F70-5.

56. Whitelaw A, Lee-Kelland R. Repeated lumbar or ventricular punctures in newborns with intraventricular haemorrhage. Cochrane Database Syst Rev 2017;4:Cd000216.

57. Group VT. Randomised trial of early tapping in neonatal posthaemorrhagic ventricular dilatation. Ventriculomegaly Trial Group. Arch Dis Child 1990;65:3-10.

58. de Vries LS, Liem KD, van Dijk K, Smit BJ, Sie L, Rademaker KJ, et al. Early versus late treatment of posthaemorrhagic ventricular dilatation: results of a retrospective study from five neonatal intensive care units in The Netherlands. Acta Paediatr 2002;91:212-7.

59. Brouwer A, Groenendaal F, van Haastert IL, Rademaker K, Hanlo P, de Vries L. Neurodevelopmental outcome of preterm infants with severe intraventricular hemorrhage and therapy for post-hemorrhagic ventricular dilatation. J Pediatr 2008;152:648-54.

60. Bassan H, Eshel R, Golan I, Kohelet D, Ben Sira L, Mandel D, et al. Timing of external ventricular drainage and neurodevelopmental outcome in preterm infants with posthemorrhagic hydrocephalus. Eur J Paediatr Neurol 2012;16:662-70.

61. Cizmeci MN, Khalili N, Claessens NHP, Groenendaal F, Liem KD, Heep A, et al. Assessment of brain injury and brain volumes after posthemorrhagic ventricular dilatation: a nested substudy of the randomized controlled ELVIS trial. J Pediatr 2019;208:191-197.e2.

62. Cizmeci MN, Groenendaal F, Liem KD, van Haastert IC, Benavente-Fernandez I, van Straaten HLM, et al. Randomized controlled Early versus Late Ventricular Intervention Study (ELVIS) in posthemorrhagic ventricular dilatation: outcome at 2 years. J Pediatr 2020. In press.

63. Kulkarni AV, Schiff SJ, Mbabazi-Kabachelor E, Mugamba J, Ssenyonga P, Donnelly R, et al. Endoscopic treatment versus shunting for infant hydrocephalus in Uganda. N Engl J Med 2017;377:2456-64.

64. Srinivasakumar P, Limbrick D, Munro R, Mercer D, Rao R, Inder T, et al. Posthemorrhagic ventricular dilatation-impact on early neurodevelopmental outcome. Am J Perinatol 2013;30:207-14.

65. Whitelaw A, Evans D, Carter M, Thoresen M, Wroblewska J, Mandera M, et al. Randomized clinical trial of prevention of hydrocephalus after intraventricular hemorrhage in preterm infants: brain-washing versus tapping fluid. Pediatrics 2007;119:e1071-8.

66. Whitelaw A, Jary S, Kmita G, Wroblewska J, Musialik-Swietlinska E, Mandera M, et al. Randomized trial of drainage, irrigation and fibrinolytic therapy for premature infants with posthemorrhagic ventricular dilatation: developmental outcome at 2 years. Pediatrics 2010;125:e852-8.

67. Luyt K, Jary SL, Lea CL, Young GJ, Odd DE, Miller HE, et al. Drainage, irrigation and fibrinolytic therapy (DRIFT) for posthaemorrhagic ventricular dilatation: 10-year follow-up of a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2020. fetalneonatal-2019-318231.

68. Park YS, Kotani Y, Kim TK, Yokota H, Sugimoto T, Nakagawa I, et al. Efficacy and safety of intraventricular fibrinolytic therapy for post-intraventricular hemorrhagic hydrocephalus in extreme low birth weight infants: a preliminary clinical study. Childs Nerv Syst 2020. In press.

69. Dewan MC, Rattani A, Mekary R, Glancz LJ, Yunusa I, Baticulon RE, et al. Global hydrocephalus epidemiology and incidence: systematic review and meta-analysis. J Neurosurg 2020. In press.

70. Christian EA, Jin DL, Attenello F, Wen T, Cen S, Mack WJ, et al. Trends in hospitalization of preterm infants with intraventricular hemorrhage and hydrocephalus in the United States, 2000-2010. J Neurosurg Pediatr 2016;17:260-9.

71. Eskandari R, Packer M, Burdett EC, McAllister JP, 2nd. Effect of delayed intermittent ventricular drainage on ventriculomegaly and neurological deficits in experimental neonatal hydrocephalus. Childs Nerv Syst 2012;28:1849-61.

72. Isaacs AM, Smyser CD, Lean RE, Alexopoulos D, Han RH, Neil JJ, et al. MR diffusion changes in the perimeter of the lateral ventricles demonstrate periventricular injury in post-hemorrhagic hydrocephalus of prematurity. NeuroImage Clin 2019;24:102031.

73. Mazzola CA, Choudhri AF, Auguste KI, Limbrick DD, Jr, Rogido M, Mitchell L, et al. Pediatric hydrocephalus: systematic literature review and evidence-based guidelines. Part 2: Management of posthemorrhagic hydrocephalus in premature infants. J Neurosurg Pediatr 2014;14(suppl 1):8-23.

74. Wellons JC, 3rd, Holubkov R, Browd SR, Riva-Cambrin J, Whitehead W, Kestle J, et al. The assessment of bulging fontanel and splitting of sutures in premature infants: an interrater reliability study by the Hydrocephalus Clinical Research Network. J Neurosurg Pediatr 2013;11:12-4.

75. Kaiser AM, Whitelaw AG. Intracranial pressure estimation by palpation of the anterior fontanelle. Arch Dis Child 1987;62:516-7.

76. Kestle JR, Riva-Cambrin J, Wellons JC, 3rd, Kulkarni AV, Whitehead WE, Walker ML, et al. A standardized protocol to reduce cerebrospinal fluid shunt infection: the Hydrocephalus Clinical Research Network Quality Improvement Initiative. J Neurosurg Pediatr 2011;8:22-9.

77. Kestle JR, Holubkov R, Douglas Cochrane D, Kulkarni AV, Limbrick DD, Jr, Luerssen TG, et al. A new Hydrocephalus Clinical Research Network protocol to reduce cerebrospinal fluid shunt infection. J Neurosurg Pediatr 2016;17:391-6.

78. Wellons JC, 3rd, Shannon CN, Holubkov R, Riva-Cambrin J, Kulkarni AV, Limbrick DD, Jr, et al. Shunting outcomes in posthemorrhagic hydrocephalus: results of a Hydrocephalus Clinical Research Network prospective cohort study. J Neurosurg Pediatr 2017;20:19-29.

79. Badhiwala JH, Hong CJ, Nassiri F, Hong BY, Riva-Cambrin J, Kulkarni AV. Treatment of posthemorrhagic ventricular dilation in preterm infants: a systematic review and meta-analysis of outcomes and complications. J Neurosurg Pediatr 2015;16:545-55.

80. Wang JY, Amin AG, Jallo GI, Ahn ES. Ventricular reservoir versus ventriculosubgaleal shunt for posthemorrhagic hydrocephalus in preterm infants: infection risks and ventriculoperitoneal shunt rate. J Neurosurg Pediatr 2014;14:447-54.

81. Tubbs RS, Banks JT, Soleau S, Smyth MD, Wellons JC, 3rd, Blount JP, et al. Complications of ventriculosubgaleal shunts in infants and children. Childs Nerv Syst 2005;21:48-51.

82. Brouwer AJ, Groenendaal F, Han KS, de Vries LS. Treatment of neonatal progressive ventricular dilatation: a single-centre experience. J Matern Fetal Neonatal Med 2015;28(suppl 1):2273-9.

83. Stone SS, Warf BC. Combined endoscopic third ventriculostomy and choroid plexus cauterization as primary treatment for infant hydrocephalus: a prospective North American series. J Neurosurg Pediatr 2014;14:439-46.

84. Kidokoro H, Anderson PJ, Doyle LW, Woodward LJ, Neil JJ, Inder TE. Brain injury and altered brain growth in preterm infants: predictors and prognosis. Pediatrics 2014;134:e444-53.

85. Dorner RA, Allen MC, Robinson S, Soares BP, Perin J, Ramos E, et al. Early neurodevelopmental outcome in preterm posthemorrhagic ventricular dilatation and hydrocephalus: Neonatal ICU Network Neurobehavioral Scale and imaging predict 3-6-month motor quotients and Capute Scales. J Neurosurg Pediatr 2019:1-11.

86. Limbrick DD, Jr, Castaneyra-Ruiz L, Han RH, Berger D, McAllister JP, Morales DM. Cerebrospinal fluid biomarkers of pediatric hydrocephalus. Pediatr Neurosurg 2017;52:426-35.

87. Ahn SY, Chang YS, Sung SI, Park WS. Mesenchymal stem cells for severe intraventricular hemorrhage in preterm infants: phase I dose-escalation clinical trial. Stem Cells Transl Med 2018;7:847-56.

88. Schulz M, Buhrer C, Pohl-Schickinger A, Haberl H, Thomale UW. Neuroendoscopic lavage for the treatment of intraventricular hemorrhage and hydrocephalus in neonates. J Neurosurg Pediatr 2014;13:626-35.

89. d'Arcangues C, Schulz M, Buhrer C, Thome U, Krause M, Thomale UW. Extended experience with neuroendoscopic lavage for posthemorrhagic hydrocephalus in neonates. World Neurosurg 2018;116:e217-24.

90. Kulkarni AV, Riva-Cambrin J, Rozzelle CJ, Naftel RP, Alvey JS, Reeder RW, et al. Endoscopic third ventriculostomy and choroid plexus cauterization in infant hydrocephalus: a prospective study by the Hydrocephalus Clinical Research Network. J Neurosurg Pediatr 2018;21:214-23.

91. Riva-Cambrin J, Kestle JRW, Rozzelle CJ, Naftel RP, Alvey JS, Reeder RW, et al. Predictors of success for combined endoscopic third ventriculostomy and choroid plexus cauterization in a North American setting: a Hydrocephalus Clinical Research Network study. J Neurosurg Pediatr 2020. In press.

92. Warf BC, Campbell JW, Riddle E. Initial experience with combined endoscopic third ventriculostomy and choroid plexus cauterization for post-hemorrhagic hydrocephalus of prematurity: the importance of pre-pontine cistern status and the predictive value of FIESTA MRI imaging. Childs Nerv Syst 2011;27:1063-71.
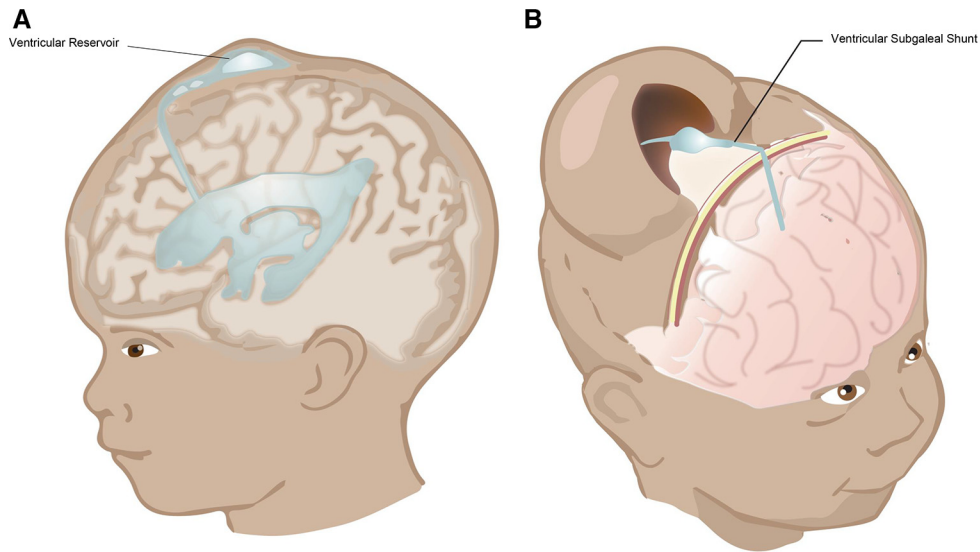
Figure 3. An illustration of the commonly used temporizing measures for PHVD: **A,** Ventricular reservoir; **B,** ventricular subgaleal shunt.

Table I. Comparisons of lumber punctures in studies included in the Cochrane Review[1]

Variables	Anwar et al[2] (n = 24)	Mantovani et al[3] (n = 19)	Dykes et al[4] (n = 22)	Ventriculomegaly group[5,6] (n = 79)
Indications	Infants with grade III-IV IVH	Infants with grade II-III IVH	Asymptomatic severe progressive posthemorrhagic hydrocephalus	VI >97th percentile + 4 mm
Time to start LPs	11 d (SD 5)			19 d (SD 11)
Number of LPs	14 (SD 10)			Median (10-90th%) 7 (1-37)
Aimed volume and end point	• Daily LP till flow stops • LPs were done every other day, or less if CSF removed at tap was <3 mL • LPs stopped if the ventricular size decreased or remained unchanged for 2 consecutive weeks	• Daily LP until the CSF was clear, colorless, and had a protein concentration <180	• Daily LP for a minimum of 1 wk and a maximum of 3 wk	• LP for max 2% of body weight • Repeat as many as possible if increase VI >2 mm above measurement before first tap • If LP <2 mL, then shift for ventricular tap
Volume, mL	Total: 67 (SD 10)			Median (10-90th%) 116 (14-678)
Volume per tap, mL	Mean 3 (SD 2)	3-5 mL	2-21 mL	
Duration	20 d (SD 16)	18 d (range 7-34)	1-3 wk	
Special description		Screening done to all infants using LP at 24 h and 72 h of life. If concerning, CT was done.		Spinal tap only (42%) Ventricular tap (9%) Spinal and ventricular tap or reservoir (42%)
Outcomes				
VPS	NA	4/19 (21%)	9/22 (41%)	41/79 (52%)
Death or disability			14/21 (67%)	61/73 (84%)

NA, not available.

Table II. Comparisons between the criteria, interventions, numbers, and outcomes reported in major studies of management of PHVD

Studies	Ventriculomegaly trial Group—early[7]	Ventriculomegaly trial Group—late[7]	Acetazolamide trial (standard arm)[8]	DRIFT—cases[9]	DRIFT—control[9]	HCRN[10]	ELVIS—early[11]	ELVIS—late[11]	Two Dutch units[12]	North America[12]
Criteria	VI >97th percentile + 4 mm		VI >97th percentile + 4 mm	(1) VI 4 mm over the 97th centile OR (2) all of the following: —AHW >4 mm —TOD >26 mm —third ventricle width >3 mm OR (3) Measurements above (1) or (2) on 1 side combined with obvious midline shift indicating a pressure effect.		FOHR >0.55 + 2 of 3 of: —Bradycardia —Split suture —Bulging fontanel	VI >97th percentile +AHW >6 mm and/or the TOD >25 mm	VI >97th percentile + 4mm +AHW >10 mm	Based on ventricular measurements VI exceeding the 97th centile and increasing toward the p97 +4 mm line and an AHW >6 mm	Based on signs of increased intracranial pressure
Intervention	Immediate CSF drainage • LP for max 2% of body weight • Repeat as many as possible if increase VI >2 mm above measurement before first tap • If LP <2 mL, then shift for ventricular tap • Shunt if tapping continued for 4 wk and head enlargement continues and other factors	Only CSF drainage if: • Increase in head circumference of twice the normal velocity for gestational age after entry to the trial or • Symptomatic raised intracranial pressure with a measured CSF pressure >12 mm Hg)	The study advised for removal of CSF to be delayed until either head growth exceeded twice the normal rate for 2 wk or the infant showed clinical symptoms or signs of raised intracranial pressure	DRIFT until fluid clears (usually 72 h)	Standard Intervention only if (1) Signs of raised intracranial pressure (irritability, apnea, reduced consciousness, bulging fontanelle, or loss of diastolic velocities on cerebral arteries) or excessive or (2) head enlargement over time (>2 mm/d) Intervention: LP × 2 or failed LP then reservoir	• Temporize till 1800-2000 g	• LPs (max 3), and followed by insertion and taps from a VR, aiming for VI <p97 over the next 7–10 d • 10 mL/kg was removed 1 or 2 taps a day, the volume adjusted according to cUS. • When taps from a VR were still needed 28 d after insertion to keep the VI well below the p97+4 mm, 1 or 2 "challenges" were performed with discontinuation of taps. Reservoir taps were resumed in case of expanding ventricles, clinical symptoms and/or excessive head growth		LPs or reservoir followed by VP shunt in the absence of stabilization	LP, reservoir or VP shunt (mostly immediate VP shunt placement)
Number	79	78	89	39	38	102 Temporize	64	62	78 (48 received intervention)	49 (24 received intervention)
Parenchymal lesions	46 (58%)	55 (71%)	40 (45%)	20 (51%)	18 (47%)	54 (53%)	24 (38%)	19 (30.6%)		
VP shunt	41 (52%)	42 (54%)	40 (45%)	16 (41%)	15 (39%)	66 (65%)	12 (19%)	14 (23%)	10 (13%)	22 (45%)
Death	14 (18%)	18 (23%)	10 (11%)	3 (8%)	5 (13%)	13 (13%)	8 (12.5%)	9 (15%)	11 (14%)	20 (41%)
Numbers at FU	59	53	79	39	38		50	45	62	27
FU age, CA Impairment	30 mo Overall Griffiths scale <70 29/59 (49%)	30 mo Overall Griffiths scale <70 25/53 (47%)	12 mo Impaired or disabled 52/79 (66%)	24 mo Severe disability 18/39 (46%)	24 mo Severe disability 22/38 (58%)	?	24 mo Combined cognitive and motor scores <70 = 6 (12%)	24 mo Combined cognitive and motor scores <70 = 11 (24%)	18-24 mo Combined cognitive and motor scores <70 = 3 (4.8%)	18-24 mo Combined cognitive and motor scores <70 = 14 (52%)

CA, Corrected Age; *FU*, Follow up.

Table III. Complications associated with ventricular reservoir vs subgaleal shunt

Complications	Ventricular reservoir	Ventricular subgaleal shunt
Common[13]		
Obstruction	7.3% (95% CI 5.0-10.4)	9.6% (95% CI 5.6-16.0)
Infection	9.5% (95% CI 7.0-12.8)	9.2% (95% CI 6.3-13.3
Revision	10.8% (95% CI 7.4-15.5)	12.2% (95% CI 8.8-16.5)
Others		
CSF leak[14-16]	6%	4.7%-6.5%
Porencephalic cysts[14]		8.7%
Intracranial hemorrhage[15]		1.1%

References

1. Whitelaw A, Lee-Kelland R. Repeated lumbar or ventricular punctures in newborns with intraventricular haemorrhage. Cochrane Database Syst Rev 2017;4:Cd000216.
2. Anwar M, Kadam S, Hiatt IM, Hegyi T. Serial lumbar punctures in prevention of post-hemorrhagic hydrocephalus in preterm infants. J Pediatr 1985;107:446-50.
3. Mantovani JF, Pasternak JF, Mathew OP, Allan WC, Mills MT, Casper J, et al. Failure of daily lumbar punctures to prevent the development of hydrocephalus following intraventricular hemorrhage. J Pediatr 1980;97:278-81.
4. Dykes FD, Dunbar B, Lazarra A, Ahmann PA. Posthemorrhagic hydrocephalus in high-risk preterm infants: natural history, management, and long-term outcome. J Pediatr 1989;114:611-8.
5. Randomised trial of early tapping in neonatal posthaemorrhagic ventricular dilatation. Ventriculomegaly Trial Group. Arch Dis Child 1990;65:3-10.
6. Randomised trial of early tapping in neonatal posthaemorrhagic ventricular dilatation: results at 30 months. Ventriculomegaly Trial Group. Arch Dis Child Fetal Neonatal Ed 1994;70:F129-36.
7. Randomised trial of early tapping in neonatal posthaemorrhagic ventricular dilatation: results at 30 months. Ventriculomegaly Trial Group. Arch Dis Child Fetal Neonatal Ed 1994;70:F129-36.
8. Kennedy CR, Ayers S, Campbell MJ, Elbourne D, Hope P, Johnson A. Randomized, controlled trial of acetazolamide and furosemide in posthemorrhagic ventricular dilation in infancy: follow-up at 1 year. Pediatrics 2001;108:597-607.
9. Whitelaw A, Jary S, Kmita G, Wroblewska J, Musialik-Swietlinska E, Mandera M, et al. Randomized trial of drainage, irrigation and fibrinolytic therapy for premature infants with posthemorrhagic ventricular dilatation: developmental outcome at 2 years. Pediatrics 2010;125:e852-8.
10. Wellons JC, 3rd, Shannon CN, Holubkov R, Riva-Cambrin J, Kulkarni AV, Limbrick DD, Jr, et al. Shunting outcomes in posthemorrhagic hydrocephalus: results of a Hydrocephalus Clinical Research Network prospective cohort study. J Neurosurg Pediatr 2017;20:19-29.
11. Cizmeci MN, Groenendaal F, Liem KD, van Haastert IC, Benavente-Fernandez I, van Straaten HLM, et al. Randomized Controlled Early versus Late Ventricular Intervention Study (ELVIS) in Posthemorrhagic Ventricular Dilatation: Outcome at 2 Years. Submitted; 2020.
12. Leijser LM, Miller SP, van Wezel-Meijler G, Brouwer AJ, Traubici J, van Haastert IC, et al. Posthemorrhagic ventricular dilatation in preterm infants: when best to intervene? Neurology 2018;90:e698-706.
13. Badhiwala JH, Hong CJ, Nassiri F, Hong BY, Riva-Cambrin J, Kulkarni AV. Treatment of posthemorrhagic ventricular dilation in preterm infants: a systematic review and meta-analysis of outcomes and complications. J Neurosurg Pediatr 2015;16:545-55.
14. Wang JY, Amin AG, Jallo GI, Ahn ES. Ventricular reservoir versus ventriculosubgaleal shunt for posthemorrhagic hydrocephalus in preterm infants: infection risks and ventriculoperitoneal shunt rate. J Neurosurg Pediatr 2014;14:447-54.
15. Tubbs RS, Banks JT, Soleau S, Smyth MD, Wellons JC 3rd, Blount JP, et al. Complications of ventriculosubgaleal shunts in infants and children. Childs Nerv Syst 2005;21:48-51.
16. Wellons JC, 3rd, Shannon CN, Holubkov R, Riva-Cambrin J, Kulkarni AV, Limbrick DD, Jr, et al. Shunting outcomes in posthemorrhagic hydrocephalus: results of a Hydrocephalus Clinical Research Network prospective cohort study. J Neurosurg Pediatr 2017;20:19-29.