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REVIEW ARTICLE

Intraventricular hemorrhage and posthemorrhagic hydrocephalus in preterm infants: diagnosis, classification, and treatment options

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Abstract

Purpose Intraventricular hemorrhage is the most important adverse neurologic event for preterm and very low weight birth infants in the neonatal period. This pathology can lead to various delays in motor, language, and cognition development. The aim of this article is to give an overview of the knowledge in diagnosis, classification, and treatment options of this pathology.

Method A systematic review has been made.

Results The cranial ultrasound can be used to identify the hemorrhage and grade it according to the modified Papile grading system. There is no standardized protocol of intervention as there are controversial results on which of the temporizing neurosurgical procedures is best and about the appropriate parameters to consider a conversion to ventriculoperitoneal shunt. However, it has been established that the most important prognosis factor is the involvement and damage of the white matter.

Conclusion More evidence is required to create a standardized protocol that can ensure the best possible outcome for these patients.

Keywords Intraventricular hemorrhage · Posthemorrhagic hydrocephalus · Ventricular access device · Ventriculosubgaleal shunt · Ventriculoperitoneal shunt

Abbreviations

CBF	Cerebral blood flow
CP	Cerebral palsy
CSF	Cerebrospinal fluid
DRIFT	Drainage, irrigation, and fibrinolytic therapy
EVD	External ventricular drainage
GM	Germinal matrix
GMH	Germinal matrix hemorrhage
IVH	Intraventricular hemorrhage
LP	Lumbar puncture
PHH	Posthemorrhagic hydrocephalus
PVHI	Periventricular hemorrhagic infarction
RT-US	Real-time ultrasound
TNPs	Temporizing neurosurgical procedures
VAD	Ventricular access device
VLBW	Very low birth weight
VP	Ventriculoperitoneal
VSG	Ventriculosubgaleal

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Introduction

Germinal matrix hemorrhage (GMH) represents the most important adverse neurologic event for preterm and very low birth weight (VLBW) newborns during neonatal period [1, 2]. Pathogenesis is mainly attributed to germinal matrix (GM) inherent vascular fragility and fluctuations in cerebral blood flow (CBF) [3]. Among GMH, intraventricular

hemorrhage (IVH), defined as blood leakage into the ventricular space, is the main form of presentation [1] with subsequent development of posthemorrhagic hydrocephalus (PHH) in 35% of cases. Approximately 20% of preterm and VLBW newborns develop IVH. Higher-grade hemorrhages are more common as age and weight decrease [4]. More than 50% of hemorrhages will develop on the first 24 h postpartum, and 90% of them within the first week after partum [5]. Diagnosis is made by cranial ultrasound performed at bedside using the Papile grading system severity scale [6]. Grade I IVH minimally involves the ventricle (< 10%) or is restricted to subependymal parenchyma, grade II IVH extends into the ventricle but does not expand or occupy more than 50% of it, and grade III involves more than 50% of the ventricle and distends it [7]. Periventricular hemorrhagic infarction (PVHI), previously classified as grade IV IVH, refers to an extensive IVH with parenchymal involvement, likely due to terminal venous occlusion with venous infarction and subsequent secondary hemorrhage (Table 1) [8].

Risk factors

Incidence of IVH in preterm and VLWB infants had a relevant decline from the 1980s to the late 1990s, mainly associated with routine implementation of antenatal steroids [10, 11]. Unfortunately, occurrence in the past two decades has remained stationary [12, 13]. Several environmental and medical risk factors have been implicated in IVH pathogenesis and progression, most of them associated with alterations in cerebral blood flow and central nervous system blood pressure [13]. In this article, we present the verified risk factors and discard those that remain controversial or lack data to sustain them (Table 2) [1, 10, 12–14].

Pathogenesis of GMH-IVH

Two major factors are thought to contribute to IVH in the preterm infant: the inherent fragility of the GM vasculature and disturbances of the cerebral blood flow (CBF) [13].

Table 2 Classification of risk factors [1, 10, 12–14]; *GM*, germinal matrix; *IL*, interleukin; *TNF*, tumor necrosis factor

Antenatal/inherent risk factors
- Gestational age (preterm infants)
- Very low weight birth (< 1500 kg)*
- Genetics (factor V Leiden, prothrombin G20210A, IL-1β, IL-6, and TNFα)
- Lack of antenatal steroid therapy
- Autonomic dysregulation of GM vasculature
Factors associated to disturbance of cerebral blood flow
- Hypoxia and low APGAR scores
- Hypercarbia
- Hypotension and catecholamine treatment
- Cardiopulmonary anatomic disturbances/malformations
- Asynchrony between newborn and ventilator breathe
Factors predisposing hemostatic disturbances
- Low platelet count
- Altered coagulation factors
- Sepsis and acidosis
Factors associated with direct or indirect damage to GM vasculature
- Indirect damage
Prolonged labor delivery or cesarean delivery with previous active phase
Vertex presentation
Intra- and inter-hospital transport
- Direct damage
Inflammatory response to placental pathology

*Taken from Engle's age terminology during the perinatal period [15]

The high risk of hemorrhage of the GM vasculature has been attributed to a high vascularity and a fragility of the vessels caused by alterations in the components and stability of the blood-brain barrier (BBB). Because of its high metabolic activity and high oxygen demand, this area is in a relative hypoxic state [13]. Hypoxia upregulates the production of vascular endothelial growth factor (VEFG), which, together with angiopoietin-2 (ANGPT-2), is responsible for the rapid angiogenesis in the GM. High vascularity enhances the probability of hemorrhage [16–19]. Additionally, differences in the composition of the vasculature of the GM increase its

Table 1 Comparison of grading systems; *GM*, germinal matrix; *PVHI*, periventricular hemorrhagic infarction [6, 8]

Papile's grading system	Volpe's grading system
CT scan findings	Echosonographic findings
Grade I: subependymal hemorrhage	Grade I: hemorrhage confined to the subependymal GM
Grade II: intraventricular hemorrhage without dilation	Grade II: hemorrhage within the lateral ventricle without ventricular dilation and/or hemorrhage occupying less than 50% of the ventricle
Grade III: intraventricular hemorrhage with ventricular dilation*	Grade III: hemorrhage with distention resulting in ventricular dilation and/or hemorrhage occupying more than 50% of the ventricle*
Grade IV: intraventricular hemorrhage with parenchymal hemorrhage	PVHI: ventricular hemorrhage that extends into the surrounding parenchyma

*Ventricular dilation taking as reference Levene's index values above 97 percentile [9]

predisposition to bleed. A reduction of the glial fibrillary acidic protein (GFAP) in the astrocyte end feet affects the mechanical strength of the vessels [18]; a decrease of the fibronectin expression in the basal lamina alters its structural stability [20]; and a reduced signaling of TGF-β1 decreases the density of pericytes in the GM vessels [17]. It has been observed that antenatal glucocorticoids help prevent GMH by increasing GFAP and fibronectin [18, 20].

Disturbances of CBF due to the immaturity of the cardiovascular system, together with an impaired cerebrovascular reactivity, increase the risk of GMH [1, 21]. Cerebral autoregulation is a physiological mechanism that maintains constant blood flow to the brain despite variations in cerebral perfusion pressure [22]. In preterm infants, cerebral autoregulation may be impaired, so their CBF becomes BP-passive [23]; this means that their CBF will change in concordance with BP changes. It is speculated that cerebral pressure-passivity is a risk factor for cerebrovascular injury [21, 24]. Hypercapnia might play a role in the impairment of cerebral autoregulation by producing vasodilation of the cerebral resistance arterioles. In the setting of an increased BP and hypercapnia, hypercapnic hyperemia will overcome the autoregulatory mechanism resulting in an increased CBF [22].

It was observed that infants who required mechanical ventilation experienced more fluctuations in BP and CBF velocity secondary to asynchrony with the respiratory effort and the ventilator. The use of pancuronium in the first 24 h removed infant's contribution to the ventilation, thereby reducing CBF velocity fluctuating pattern along with the incidence and severity of IVH [25]. Nonetheless, this drug was found to have multiple cardiovascular side effects and to cause an increase in the need for higher ventilator pressures to maintain adequate oxygenation [26]. Some ventilator modalities, such as synchronized intermittent mandatory ventilation and assist control, can reduce this asynchrony between the patient and the machine [13, 26].

Hypotension is the most common BP alteration found among preterm infants [27]. Numerous studies have found a direct association between hypotension and an increased risk of IVH [21, 23, 28]. Hypotension produces vasodilation of the brain vasculature [21], thereby increasing the risk of vessel rupture and hemorrhage. Others have found an association between GMH and a hypoperfusion-reperfusion pattern [3, 28, 29].

Pathogenesis of posthemorrhagic hydrocephalus

The mechanism by which hydrocephalus develops after GMH-IVH is still uncertain. A most common held view is that initially blood clots obstruct the cerebrospinal fluid (CSF) flow by blocking the cerebral aqueduct or the fourth ventricle outlets, thus producing an obstructive hydrocephalus [30]. Later on, a delayed communicating hydrocephalus develops, and it is speculated that it is due to an impairment of CSF resorption caused by an increased production of extracellular matrix (ECM) proteins throughout the cerebroventricular system [1, 31]. Increased TGF-β1 in CSF might play a role in the pathogenesis PHH by upregulating the genes encoding ECM proteins, such as fibronectin and collagen [1, 32, 33]. Others have proposed that thrombin may play a role as well [34, 35]. Some evidence supports the role of iron in the pathogenesis of PHH. By generating hydroxyl radicals and inducing oxidative damage, iron may cause ventricular dilation and neuronal death [2, 9]. The use of iron chelators was found to attenuate ventricular dilation by reducing iron overload after GMH and iron-induced brain injury [2, 36]. Ventricle dilation can lead to hypoxia, ischemia, decreased cerebral perfusion, increased free radicals, and ultimately white matter destruction [30].

Diagnosis

The clinical presentation of IVH typically follows three patterns: (a) catastrophic deterioration which occurs over minutes or hours and mimics the rapid neurological deterioration of an older patient with large intracranial hemorrhages (associated with a very poor prognosis); (b) the saltatory course which evolves over hours to days and includes decreased alertness and activity, hypotonia, abnormality tight popliteal angle, abnormal eye movements, and respiratory difficulties; (c) and a clinically silent course, which supports the use of surveillance cranial ultrasonography [37].

An excessive head enlargement is defined as a persistent increase of 2 mm per day. When measuring the head circumference, it is not easy to detect a difference day to day but rather with the cumulative head growth from several days, or when there is additional evidence of raised intracranial pressure like increased splaying of the cranial sutures, a full tense fontanel and worsening of the apnea and bradycardia episodes, lethargy, and feeding intolerance [7]. These clinical findings have a limited reliability. However, the most reliable clinical indication of increased pressure is progressive splaying of the sagittal suture [1].

Visualization of the cerebral ventricles is essential in investigation of the child with suspected hydrocephalus. Real-time ultrasound (RT-US) has been widely accepted as a reliable method to diagnose intraventricular hemorrhage and hydrocephalus in infants, the latter defined as a ventricular enlargement with index > 97th percentile. The limitation was that there was no data on the size of the ventricular system in preterm infants; for this reason, Levene performed a study where he produced reference ranges for ventricular index according to the gestational age (from week 26 to week 42), using RT-US [38, 39]. The ventricular index is measured from the falx to the lateral wall of the body of the lateral ventricle. An index of 4 mm over the 97th centile

(p97+4) has been widely accepted as the "action line" to start the interventions (Fig. 1) [7].

Sometimes, ventricles do not expand laterally but become rounded or expand occipitally. Therefore, different reference ranges for anterior horn width and third ventricular width, measured in coronal plane, as well as the thalamo-occipital dimension, measured in the sagittal plane are now used as an alternative definition of posthemorrhagic ventricular dilation (PHVD): anterior horn width > 4 mm (1 mm over 97th centile), thalamo-occipital dimension > 26 mm (1 mm over the 97th centile), and third ventricular width > 3 mm (> 1 mm over 97th centile) [7].

While MRI is more sensitive in identifying subtle white matter damage associated with prematurity [40], rapid ultrasound provides a method for measuring ventricular size and allows diagnosis of dilated ventricles given gestational age, and regular assessment of size permits early detection of deviation in ventricular growth [38]; it is also a better choice for preterm and unstable infants during the first week of life [40].

The diagnostic method of choice is still RT-US because of its sensitivity and specificity in the diagnosis of this pathology, and because of the benefit of being a bedside study. A disadvantage of this method is the fact that it is operator dependent and that it does not confer continuous monitoring. New methods have been proposed for the diagnosis and monitoring of PVHD, such as Doppler ultrasound, which provides additional information about intracranial pressure and parenchymal perfusion [7, 41]; flash visual evoked potentials and amplitude-integrated electroencephalography that can aid in the monitoring of increased intracranial pressure even before clinical manifestations appear [42], and 3D ultrasound which can give us a more accurate characterization of ventricle dilation measures [43].

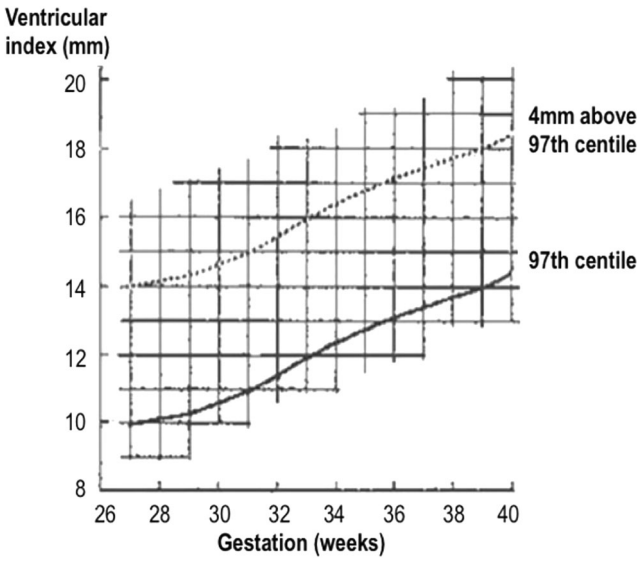

Fig. 1 Reference values of ventricular width. Taken from Whitelaw A. and Aquilina K. [7]

Treatment

Currently, the only intervention that seems to be effective in the prevention of IVH is the use of antenatal steroid therapy. Many medical interventions, such as postnatal phenobarbital and prophylactic indomethacin, have been proposed for the control and management of IVH but have not proven to be effective. For the moment, the optimal management of IVH is based on the early diagnosis with serial RT-US, control of ventricular dilation by different invasive procedures to drain the excessive CSF out of the ventricular system, and prevention of future complications which are directly related to the degree of ventricular dilation and subsequent parenchymal damage. Definitive treatment of progressive PHH is made with the placement of a VP (ventriculoperitoneal) shunt; however, this procedure is rarely used as a first intervention for several reasons: the risk of skin ulceration in VLBW infants, the high incidence of shunt malfunction, and frequent need of revision, among others. In many cases, the ventricular dilation will be controlled with the use of temporizing neurosurgical procedures (TNPs): lumbar punctures (LP), external ventricular drainage (EVD), insertion of a ventricular access device (VAD), or a ventriculosubgaleal (VSG) shunt. In cases where PHH is not controlled with these procedures, the placement of a VP shunt is indicated [1, 7]. The lack of conclusive recommendations for the treatment of this pathology makes it very difficult to have a standardized protocol; most centers use institutional guidelines, medical expertise, and available resources to guide their treatment (Table 3).

Pharmacological treatment

Postnatal phenobarbital

Considering the role CBF fluctuations play in the pathogenesis of GMH, it was hypothesized that the administration of phenobarbital would reduce the incidence of IVH by stabilizing the blood pressure. However, Cochrane review meta-analysis failed to demonstrate a reduction in the risk of IVH and showed an increase on the need for mechanical ventilation [44].

Prophylactic indomethacin

Indomethacin has shown to reduce the risk of severe IVH; however, its effectiveness is limited to short-term outcome as it has not shown to reduce mortality or to improve neurodevelopmental outcomes [45].

Diuretic therapy

Acetazolamide and furosemide decrease the production of CSF, and the use of these drugs was hoped to decrease the

Table 3 Summary of the treatments of IVH; *LP*, lumbar puncture; *VSG*, ventriculosubgaleal; *EVD*, external ventricular drainage; *VAD*, ventricular access device; *VP*, ventriculoperitoneal; *DRIFT*, drainage, irrigation, and fibrinolytic therapy; *PHH*, posthemorrhagic hydrocephalus [43–55]

Procedure	Infection rate	OR/NICU	Need of a neurosurgeon	Ventricular dilation control/VP shunt conversion rate	Continuous sampling of CSF	Recommendation/ strength of recommendation	Comments
Diuretic therapy	–	NICU	No	51%	–	Not recommended to decrease the risk of shunt placement or control progression of PHH Level I	Increased risk of morbidity and poor neurodevelopmental outcome Nephrocalcinosis reported in 24%
Intraventricular fibrinolytic agents	16%	NICU	Yes	60%	–	Not recommended to decrease the risk of shunt placement or control progression of PHH Level I	Risk of secondary hemorrhage (16%)
DRIFT	10%	OR	Yes	28–72%	Yes	Not recommended to decrease the risk of shunt placement or control progression of PHH Level I	Risk of a secondary hemorrhage
Ventricular lavage	4.3%	OR	Yes	58–60%	No	Not enough evidence to recommend	
LP	9%	NICU	No	62%	Yes	Not recommended to decrease the risk of shunt placement or control progression of PHH Level I	No more than three LP for control of increased intracranial pressure
Ventricular puncture	9%	NICU	Yes	62%	Yes	Not recommended to decrease the risk of shunt placement or control progression of PHH	60% porencephalic cyst. Procedure is reserved in cases where VP shunt placement is contraindicated for urgency, OR is inaccessibility, CSF infection
Third ventriculostomy	–	OR	Yes	–	No	Insufficient evidence Level III	
EVD	5.4–40%	NICU/OR	Yes	64–78%	Yes	Treatment option in the management of PHH Level II	Infection rates are lower due to better protocols
VSG shunt	8–16%	NICU/OR	Yes	60–86%	No	Treatment option in the management of PHH Level II	Highly cost effective in hospitals lacking resources in developing countries
VAD	15–22%	OR	Yes	69–88%	Yes	Treatment option in the management of PHH Level II	CSF removal and sampling as needed; direct administration of antibiotics
VP shunt	5–33%	OR	Yes	100%	No	Only definite treatment	There is insufficient evidence to recommend a specific optimal timing of VP shunt conversion (weight and CSF protein concentration)

need of surgery and to increase disability-free survival [56, 57]. A trial conducted by the International PHVD Drug Trial Group included 177 infants that underwent treatment with acetazolamide (100 mg/kg/day) and furosemide (1 mg/kg/day) once their ventricular width was 4 mm above 97th percentile. The results of this trial were disappointing with an increased risk of death, neurological morbidity, and shunt placement in comparison to the control group [57]. The use

of acetazolamide and furosemide in posthemorrhagic hydrocephalus is not recommended [58].

Intraventricular fibrinolytic agents

It was hypothesized that the early use of a fibrinolytic agent could prevent the progression of permanent hydrocephalus, thus reducing the need of a permanent shunt [59]. Studies have been conducted using various intraventricular agents, recombinant tissue plasminogen activator (rTPA), streptokinase, and urokinase, and results have failed to prove effectiveness [58]. Additionally, studies with streptokinase were found to increase the risk of meningitis and secondary IVH [59]. The use of intraventricular fibrinolytic therapy is not recommended [58].

Temporizing neurosurgical procedures for CSF removal

Lumbar and ventricular punctures

It was hypothesized that the repeated CSF tapping would reduce intracranial pressure and remove proteins and blood, thereby allowing the flow and absorption of CSF. Controlled trials have failed to demonstrate any benefit in the reduction for VP shunt placement [46, 58]. Some of the advantages that this procedure confers are an immediate CSF drainage with the possibility of sampling [58], without the need of moving the patient to an operating room, with no need of a neurosurgeon to perform the procedure. However, every tap can only evacuate 10 ml/kg of CSF per tap, which might not be enough to decrease the ventricular dilation [47]. Recent recommendations suggest performing a maximum of 3 LPs, and if ventricular dilation progresses, another intervention should be considered [48]. Repeated taps are associated with an increased risk of CSF infection (meningitis or ventriculitis) and increased risk of shunt infection [46, 56]. Although repeated LPs are not recommended as a definitive treatment, they may be useful for drawing of CSF as an immediate treatment of increased intracranial pressure (ICP) [58]. An exception can be made when the ventricles are not connected with the lumbar subarachnoid space [7], like in the case of aqueductal stenosis.

Ventricular punctures are not a procedure recommended in the control of ventricular dilation because of the high risk of porencephalic cyst development and higher CSF infection rates [46]. This procedure should only be considered in cases of extreme urgency, when the patient's life is at risk and there is no other method available [47].

External ventricular drains

EVDs consist in the insertion of a catheter in the dilated anterior horn of the right lateral ventricle that externally connects to an adjustable draining system. The main advantage offered by this technique is its effectiveness in evacuating sufficient CSF volume in a continuous manner to reduce intracranial pressure. Several authors have reported different rates of infection, ranging from very low rates to unacceptable levels (5.4 to 40%) [49, 56, 60]. Controversy exists regarding the relationship between the duration of catheterization and risk of infection, and most studies consider extended catheter duration, usually exceeding 5 days, to be an important risk factor for subsequent infection [50, 51]. Other problems, such as over drainage and development of subdural hygromas, have also been reported [49, 56, 60].

Ventriculosubgaleal shunt

VSG shunt procedure consists on the insertion of a ventricular catheter into the dilated lateral ventricle. The catheter is then fixed to the dura and placed in a subgaleal pouch that is made by the surgeon during the procedure (Fig. 2) [49]. This low pressure and continuous and more physiological drainage of CSF helps to decrease the intracranial pressure and potentially decrease shunt dependence by continuously draining hemorrhagic debris, thus reducing further progression of hydrocephalus [56, 61]. Some of the benefits that this procedure confers over VADs are the decrease in need of daily taping, maintenance of a closed system in which no fluids and electrolytes are lost, and a potential earlier discharge [52, 61]. An additional advantage seen in this

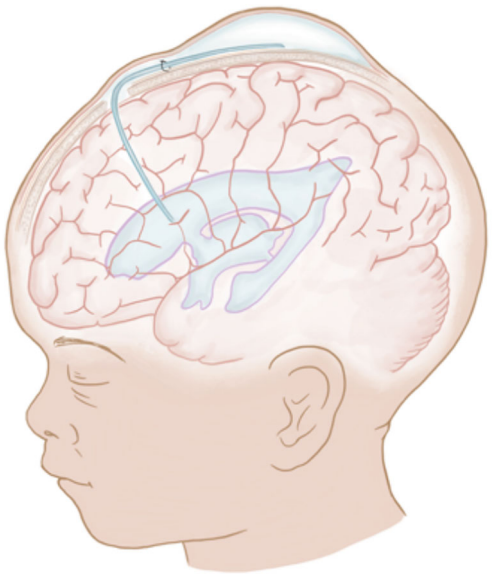

Fig. 2 Ventriculosubgaleal shunt

procedure is its low cost. Reported complications of VSG shunt are CSF leakage from the incision site, meningitis, malfunction, migration of the catheter from the ventricle or slippage into the ventricle, and intraparenchymal hemorrhage. The rate of leakage varies from 4.7 up to 32%, infectious complications occur in approximately 8% of the cases, while the other complications are rarely seen. Permanent VP shunt is necessary in 60–85% of cases [49].

Ventricular access devices/reservoirs

The use of ventricular reservoirs allows controlled, intermittent transcutaneous CSF withdrawal to be performed on as-needed basis [52, 62]. Intermittent CSF removal from the reservoir might promote the return of normal CSF absorption, thereby reducing shunt dependence (Fig. 3) [52]. However, the conversion rates to VP shunt reported in the literature range from 75 to 88% [63]. Potential benefits include the facility to obtain CSF to examine it and the possibility to simultaneously infuse medication and avoid the BBB [62]. Some complications reported from this procedure include increased risk of CSF infection, which occurs in approximately 9.5% of the cases and might be due to continuous tapping that exposes the intraventricular environment to the exterior [49, 62, 64], CSF leakage, skin necrosis, and loss of electrolytes and fluids. The appearance of hyponatremia after repeated CSF tapping has been reported [65] and in cases of repeated LPs and ventricular taps [66]. It is essential to identify the electrolyte alteration and replace sodium loss promptly in cases of frequent CSF tapping [65, 66]. Despite possible complications, evidence has demonstrated that the use of VAD decreases morbidity and mortality compared with EVDs [58].

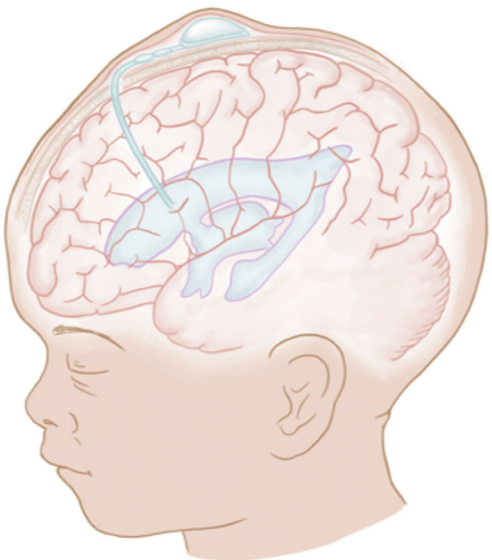

Fig. 3 Ventricular access device

DRIFT

The DRIFT (drainage, irrigation, and fibrinolytic therapy) randomized trial involved 77 infants with PHH, in which irrigation and drainage were performed through the placement of two catheters, one in the right frontal and the other in the left occipital, and fibrinolysis was carried out with rTPA. The rationale behind this protocol was to eliminate the blood clots obstructing the absorption pathways of CSF and to decompress the distended ventricles by draining the CSF containing proinflammatory cytokines, iron, and free radicals, thus decreasing secondary injury to the brain. The aim was to decrease the mortality and the severe cognitive, motor, and sensory disabilities [67]. The trial was suspended because of the increased risk of secondary bleeding. However, developmental outcome at 2 years showed a reduction of death and severe cognitive disability in survivors in comparison to the control group [68]. DRIFT is not recommended for the treatment of PHH [56].

Endoscopic ventricular lavage

Endoscopic ventricular lavage has been proposed as treatment of PHH. The hypothesis of Schulz et al. was based on the 2-year outcome results of DRIFT trial, and the removal of the hematoma would eliminate the proinflammatory cytokines, iron, and free radicals and reduce the risk of progression of the hydrocephalous. Several studies have shown a decreased conversion to VP shunt in those who undergo an early endoscopic ventricular lavage; however, these studies have potential limitations, including the design of the studies and the small patient sample. This procedure is technically feasible but there is insufficient evidence to recommend its use [69, 70] .

Endoscopic third ventriculostomy

A third ventriculostomy is generally indicated for obstructive hydrocephalus, as seen in the initial phase of PHH. However, controversy exists with the use of this procedure in children under age of 2 years; failure rates are higher among infants under age of 6 months [71]. There is insufficient evidence to recommend the use of this procedure as a treatment for PHH [58].

Ventriculoperitoneal shunt

Despite the fact that VP shunt is the best definite treatment for progressive PHH [56], many complications of the procedure may be seen when used as the primary therapy in VLWB infants [7]. There is a high risk of shunt obstruction due to the high concentrations of proteins and blood in the CSF, which leads to a higher rate of shunt revisions. Because of

the fragile and thin skin of the VLWB infants, there is a high incidence of ulceration of the skin above the valve [56]. There are no standardized criteria to define when to convert to a permanent shunt [58]. Nonetheless, the following must be present for a VP shunt to work: a mature immune system, an adequate absorption capacity of the abdomen, the effective elimination of blood products from CSF flow, and the sufficient thickness of subcutaneous tissue [58]. The most important parameter that can be monitored and used as guidance to decide when conversion is feasible is the body weight. Some authors recommend waiting until the baby reaches 2.5 kg [7], others suggest the surgery once the infant weighs 2 kg [72, 73], and there are reports of good outcomes if surgery is performed in patients weighing over 1.5 kg [53, 56, 74, 75]. Because of the high incidence of shunt obstruction, it has been proposed that protein concentration should be low to avoid these malfunctions. There are different recommendations as to what is the ideal CSF protein content. A retrospective study of Fulkerson et al. showed no statistical significance with an increased risk of shunt failure and the CSF content of protein [76]. Some studies report better results when waiting for protein concentration to decrease, some recommend to wait until proteins are below 1.5 g/l [7], others suggest to wait until they are less than 1000 mg/dl [49], while others prefer to wait until protein concentration is below 200 mg/dl due to a decrease risk of shunt malfunction and the need of short interval revisions [56, 74, 77]. The authors of this article use as parameters of conversion a weight above 1.5 kg and proteins below 200 mg/dl in a study, with results pending publishing, and we suggest for future studies to register these parameters to make comparisons. Additionally, it should not be considered as a first-line treatment since not all patients will require a VP shunt conversion as the TNP will suffice to control the hydrocephalus; a correlation can be made with the grade of IVH at the time of the diagnosis and the need for VP shunt. Different studies have reported that only 1% of their patients with IVH grades 1 and 2 required shunt placement, while grade 3 and grade 4 ranged between 18 and 29% [78, 79].

Ventriculoatrial shunts can be considered as an alternative method if a contraindication for VP shunt exists; however, a higher rate of shunt failure has been reported [56, 73].

At the moment, an optimal standardized protocol to ensure a better neurodevelopmental outcome remains to be determined. There are controversial results on which of the TNP is best, taking into account the risk of infection, known to be an independent factor for poor neurodevelopmental outcome [8], and the need for VP shunt conversion. Some studies support that VP shunt placement is directly associated with poor neurodevelopmental outcome, while others relate the adverse outcome to the extent parenchymal involvement [15], with the VP shunt being an indirect factor of poor prognosis associated to the need of its placement due to progressive ventricular dilation and subsequent parenchymal damage. Either way, the conversion to VP shunt is a way to evaluate the effectiveness of TNPs. The most commonly used TNPs are VSG and VAD, and many factors have been analyzed to determine which is superior. Badhiwala et al. compared the risk of infection, obstruction, and surgical revision between these two methods and reported a slightly lower incidence in infection with VSG (9.2% vs. 9.5%), but a lower obstruction rate (7.3% vs. 9.6%) and need of surgical revision (10.8% vs. 12.2%) when using VAD. However, these results lacked statistical significance [64]. No conclusion can be made with these results since there are many variables that may influence the need of permanent shunt, such as the time of intervention and the decision to convert to a permanent shunt [52, 54].

There is still no consensus on when best to intervene once the hydrocephalus has developed. In practice, the decision is made based on the head circumference growth, the fontanel bulging, and the presence of neurological signs of increased ICP. Levene's ventricular index is also used to make the decision, and usually treatment is started once the ventricles are > p97+4 [56]. Recent trials propose that early treatment (> 97p to 97p+4) could have an impact in the neurodevelopmental outcome and shunt-free survival rate, and early treatment is defined as an intervention done after the ventricular dilation has reached the 97th centile but before crossing the > 4 mm above 97th centile threshold [15, 55, 78]. Between 1992 and 1996, de Vries et al. made a study involving 95 infants, 22 underwent no treatment because ventricular dilation stopped above the 97th centile, 31 were treated early, and the rest started treatment once they crossed > 4 mm above 97th centile (late intervention). Results of this study showed that more infants of the late intervention group required VP shunt placement and had worst neurodevelopmental outcomes at the 24 months of follow-up [55]. An observational study conducted by Brouwer et al. reported similar results, infants in whom treatment was started before crossing > p97+4 had a better developmental quotient at 2 years of follow-up [78].

Developmental outcomes

As mentioned before, IVH increases the risk of cerebral palsy (CP), motor and mental disabilities, and death. However, neurodevelopmental outcome among preterm infants who suffered IVH differs widely. Many trials have been conducted to identify which factors determine the outcome.

A few authors stablished that a poorer outcome was related to the severity grade of IVH, being worse in those with grade IV IVH [80]. Others have stated that the use of VP shunt is an indicator of poor prognosis and that its insertion represents an additional risk factor [79, 81]. More recently, it was identified that the injury of white matter was a determinant for prognosis [82], and based on this assumption, different studies have proposed an early intervention to control ventricular dilation

and reduce the risk of white matter injury, having better results in those who were intervened early [39, 55, 78].

With the results of different studies, the authors of this article infer that the developmental outcome is most influenced by the involvement and damage of white matter lesions, and that IVH severity, shunt insertion, and increasing ventricular size are factors that contribute to this damage rather than being determinants for later developmental problems.

Conclusion

IVH is a rare pathology with a complex evolution and usually with a poor outcome. More evidence is required, regarding new technology and results of ongoing clinical trials, to create a standardized protocol that can ensure the best possible outcome for these patients. Special attention must be taken if risk factors are identified and treatment should be decided in interdisciplinary context.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

References

1. Robinson S (2012) Neonatal posthemorrhagic hydrocephalus from prematurity: pathophysiology and current treatment concepts. J Neurosurg Pediatr 9:1–23. https://doi.org/10.1088/1367-2630/15/1/015008.Fluid
2. Guo J, Chen Q, Tang J, Zhang J, Tao Y, Li L, Zhu G, Feng H, Chen Z (2015) Minocycline-induced attenuation of iron overload and brain injury after experimental germinal matrix hemorrhage. Brain Res 1594:115–124. https://doi.org/10.1016/j.brainres.2014.10.046
3. Ballabh P (2014) Pathogenesis and prevention of intraventricular hemorrhage. Clin Perinatol 41:47–67. https://doi.org/10.1016/j.clp.2013.09.007
4. Kazan S, Güra A, Uçar T, Korkmaz E, Ongun H, Akyuz M (2005) Hydrocephalus after intraventricular hemorrhage in preterm and low-birth weight infants: analysis of associated risk factors for ventriculoperitoneal shunting. Surg Neurol 64:77–81. https://doi.org/10.1016/j.surneu.2005.07.035
5. Ment LR, Oh W, Philip AGS, Ehrenkranz RA, Duncan CC, Allan W, Taylor KJW, Schneider K, Katz KH, Makuch RW (1992) Risk factors for early intraventricular hemorrhage in low birth weight infants. J Pediatr 121:776–783. https://doi.org/10.1016/S0022-3476(05)81915-8
6. Papile LA, Burstein J, Burstein R, Koffler H (1978) Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 92:529–534. https://doi.org/10.1016/S0022-3476(78)80282-0
7. Whitelaw A, Aquilina K (2012) Management of posthaemorrhagic ventricular dilatation. Arch Dis Child Fetal Neonatal Ed 97:229–234. https://doi.org/10.1136/adc.2010.190173
8. Inder TE, Perlman JM, Volpe JJ (2018) Preterm IVH/posthemorrhagic hydrocephalus. In: Volpe's neurology of the newborn, 6th edn. Elsevier, pp 637–698
9. Savman K, Nilsson UA, Blennow M, Kjellmer I, Whitelaw A (2001) Non-protein-bound iron is elevated in cerebrospinal fluid from preterm infants with posthaemorrhagic ventricular dilatation. Pediatr Res 49:208–212
10. Poryo M, Boeckh JC, Gortner L, Zemlin M, Duppré P, Ebrahimi-Fakhari D, Wagenpfeil S, Heckmann M, Mildenberger E, Hilgendorff A, Flemmer AW, Frey G, Meyer S, PROGRESS study consortium and NGFN - Nationales Genomforschungsnetz Deutschland (2018) Ante-, peri- and postnatal factors associated with intraventricular hemorrhage in very premature infants. Early Hum Dev 116:1–8. https://doi.org/10.1016/j.earlhumdev.2017.08.010
11. Waitz M, Nusser S, Schmid MB, Dreyhaupt J, Reister F, Hummler H (2016) Risk factors associated with intraventricular hemorrhage in preterm infants with ≤28 weeks gestational age. Klin Padiatr 228:245–250. https://doi.org/10.1055/s-0042-111689
12. McCrea HJ, Ment LR (2008) The diagnosis, management, and postnatal prevention of intraventricular hemorrhage in the preterm neonate. Clin Perinatol 35:777–792. https://doi.org/10.1016/j.clp.2008.07.014
13. Ballabh P (2010) Intraventricular hemorrhage in premature infants: mechanism of disease. Semin Perinatol 67:42–53
14. Szpecht D, Szymankiewicz M, Nowak I, Gadzinowski J (2016) Intraventricular hemorrhage in neonates born before 32 weeks of gestation—retrospective analysis of risk factors. Childs Nerv Syst 32:1399–1404. https://doi.org/10.1007/s00381-016-3127-x
15. Bassan H, Eshel R, Golan I, Kohelet D, Ben Sira L, Mandel D, Levi L, Constantini S, Beni-Adani L, External Ventricular Drainage Study Investigators (2012) Timing of external ventricular drainage and neurodevelopmental outcome in preterm infants with posthemorrhagic hydrocephalus. Eur J Paediatr Neurol 16:662–670. https://doi.org/10.1016/j.ejpn.2012.04.002
16. Ballabh P, Xu H, Hu F, Braun A, Smith K, Rivera A, Lou N, Ungvari Z, Goldman SA, Csiszar A, Nedergaard M (2007) Angiogenic inhibition reduces germinal matrix hemorrhage. Nat Med 13:477–485. https://doi.org/10.1038/nm1558
17. Braun A, Xu H, Hu F, Kocherlakota P, Siegel D, Chander P, Ungvari Z, Csiszar A, Nedergaard M, Ballabh P (2007) Paucity of pericytes in germinal matrix vasculature of premature infants. J Neurosci 27:12012–12024. https://doi.org/10.1523/JNEUROSCI.3281-07.2007
18. El-Khoury N, Braun A, Hu F et al (2006) Astrocyte end-feet in germinal matrix, cerebral cortex, and white matter in developing infants. Pediatr Res 59:673–679. https://doi.org/10.1203/01.pdr.0000214975.85311.9c
19. Semenza GL (2002) Signal transduction to hypoxia-inducible factor 1. Biochem Pharmacol 64:993–998. https://doi.org/10.1016/s0006-2952(02)01168-1
20. Xu H, Hu F, Sado Y, Ninomiya Y, Borza DB, Ungvari Z, LaGamma EF, Csiszar A, Nedergaard M, Ballabh P (2008) Maturational changes in laminin, fibronectin, collagen IV, and perlecan in germinal matrix, cortex, and white matter and effect of betamethasone. J Neurosci Res 86:1482–1500. https://doi.org/10.1002/jnr.21618
21. du Plessis AJ (2008) Cerebrovascular injury in premature infants: current understanding and challenges for future prevention. Clin Perinatol 35:609–641. https://doi.org/10.1016/j.clp.2008.07.010
22. Kaiser JR, Gauss CH, Williams DK (2005) The effects of hypercapnia on cerebral autoregulation in ventilated very low birth weight infants. Pediatr Res 58:931–935. https://doi.org/10.1203/01.pdr.0000182180.80645.0c
23. Bada HS, Korones SB, Perry EH, Arheart KL, Ray JD, Pourcyrous M, Magill HL, Runyan W III, Somes GW, Clark FC, Tullis KV (1990) Mean arterial blood pressure changes in premature infants and those at risk for intraventricular hemorrhage. J Pediatr 117:607–614

24. Soul JS, Hammer PE, Tsuji M, Saul JP, Bassan H, Limperopoulos C, Disalvo DN, Moore M, Akins P, Ringer S, Volpe JJ, Trachtenberg F, du Plessis AJ (2007) Fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants. Pediatr Res 61:467–473. https://doi.org/10.1203/pdr.0b013e31803237f6
25. Perlman JM, Goodman S, Kreusser KL, Volpe JJ (1985) Reduction in intraventricular hemorrhage by elimination of fluctuating cerebral blood-flow velocity in preterm infants with respiratory distress syndrome. N Engl J Med 312:1353–1357
26. Rennie JM, South M, Morley CJ (1987) Cerebral blood flow velocity variability in infants receiving assisted ventilation. Arch Dis Child 62:1247–1251. https://doi.org/10.1136/adc.62.12.1247
27. Fanaroff JM, Fanaroff AA (2012) Blood pressure disorders in the neonate: hypotension and hypertension. Neonatol A Pract Approach to Neonatal Dis:585–592. https://doi.org/10.1007/978-88-470-1405-3_78
28. Miall-Allen VM, de Vries LS, Whitelaw AG (1987) Mean arterial blood pressure and neonatal cerebral lesions. Arch Dis Child 62:1068–1069. https://doi.org/10.1542/neo.8-1-e32
29. Perlman JM, McMenamin JB, Volpe JJ (1983) Fluctuating cerebral blood-flow velocity in respiratory-distress syndrome. Relation to the development of intraventricular hemorrhage. N Engl J Med 309:204–207
30. Strahle J, Garton HJL, Maher CO, Muraszko KM, Keep RF, Xi G (2012) Mechanisms of hydrocephalus after neonatal and adult intraventricular hemorrhage. Transl Stroke Res 3:25–38. https://doi.org/10.1007/s12975-012-0182-9
31. Oi S, Di Rocco C (2006) Proposal of "evolution theory in cerebrospinal fluid dynamics" and minor pathway hydrocephalus in developing immature brain. Childs Nerv Syst 22:662–669. https://doi.org/10.1007/s00381-005-0020-4
32. Whitelaw A, Christie S, Pople I (1999) Transforming growth factor-β1: a possible signal molecule for posthemorrhagic hydrocephalus? Pediatr Res 46:576–580
33. Manaenko A, Lekic T, Barnhart M, Hartman R, Zhang JH (2014) Inhibition of transforming growth factor-p attenuates brain injury and neurological deficits in a rat model of germinal matrix hemorrhage, Departments of Basic Science. Stroke 45:828–834. https://doi.org/10.1161/STROKEAHA.113.003754
34. Lekic T, Klebe D, McBride DW et al (2015) Protease-activated receptor 1 and 4 signal inhibition reduces preterm neonatal hemorrhagic brain injury. Stroke 46:1710–1713. https://doi.org/10.1161/STROKEAHA.114.007889
35. Lekic T, Krafft PR, Klebe D et al (2016) PAR-1, −4, and the mTOR pathway following germinal matrix hemorrhage. Acta Neurochir Suppl 121:3–6. https://doi.org/10.1007/978-3-319-18497-5
36. Strahle JM, Garton T, Bazzi AA, Kilaru H, Garton HJL, Maher CO, Muraszko KM, Keep RF, Xi G (2014) Role of hemoglobin and Iron in hydrocephalus after neonatal intraventricular hemorrhage. Neurosurgery 75:696–705. https://doi.org/10.1227/NEU.0000000000000524
37. Robinson S (2012) Neonatal posthemorrhagic hydrocephalus from prematurity: pathophysiology and current treatment concepts. J Neurosurg Pediatr 9:242–258. https://doi.org/10.3171/2011.12.PEDS11136
38. Levene MI (1981) Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. Arch Dis Child 56:900–904. https://doi.org/10.1136/adc.56.12.900
39. Srinivasakumar P, Limbrick D, Munro R, Mercer D, Rao R, Inder T, Mathur A (2013) Posthemorrhagic ventricular dilatation-impact on early neurodevelopmental outcome. Am J Perinatol 30:207–214. https://doi.org/10.1055/s-0032-1323581
40. Jary S, Kmita G, Wroblewska J, Whitelaw A (2012) Quantitative cranial ultrasound prediction of severity of disability in premature infants with post-haemorrhagic ventricular dilatation. Arch Dis Child 97:955–959. https://doi.org/10.1136/archdischild-2012-301778
41. Taylor GA, Madsen JR (1996) Neonatal hydrocephalus : hemodynamic response to fontanelle compression correlation with intracranial pressure and need for shunt placement' pediatric radiology. Radiology 201:685–689. https://doi.org/10.1177/875647939701300125
42. Klebermass-Schrehof K, Rona Z, Waldhör T, Czaba C, Beke A, Weninger M, Olischar M (2013) Can neurophysiological assessment improve timing of intervention in posthaemorrhagic ventricular dilatation? Arch Dis Child Fetal Neonatal Ed 98:291–298. https://doi.org/10.1136/archdischild-2012-302323
43. Kishimoto J, De Ribaupierre S, Lee DSC et al (2013) 3D ultrasound system to investigate intraventricular hemorrhage in preterm neonates. Phys Med Biol 58:7513–7526. https://doi.org/10.1088/0031-9155/58/21/7513
44. Whitelaw A (2001) Postnatal phenobarbitone for the prevention of intraventricular hemorrhage in preterm infants. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD001691
45. Fowlie PW, Davis PG (2010) Cochrane review: prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Evid Based Child Heal A Cochrane Rev J 5:416–471. https://doi.org/10.1002/ebch.526
46. Whitelaw A, Lee-Kelland R (2017) Repeated lumbar or ventricular punctures in newborns with intraventricular haemorrhage. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD000216.pub2
47. Garton HJL, Piatt JJH (2004) Hydrocephalus. Pediatr Clin N Am 51:305–325. https://doi.org/10.1016/j.pcl.2003.12.002
48. de Vries LS, Leijser LM (2018) Germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH) in the newborn: prevention, management, and complication. In: Post TW (ed) UpToDate. UpToDate Inc., Waltham. https://www.uptodate.com. Accessed March 2019
49. Köksal V, Öktem S (2010) Ventriculosubgaleal shunt procedure and its long-term outcomes in premature infants with post-hemorrhagic hydrocephalus. Childs Nerv Syst 26:1505–1515. https://doi.org/10.1007/s00381-010-1118-x
50. Lozier AP, Sciacca RR, Romagnoli MF, Connolly ES (2002) Ventriculostomy-related infections> a critical review of the literature. Neurosurgery 51:170–182. https://doi.org/10.1227/01.NEU.0000017465.78245.6C
51. Byers K, Kaplan SL, Tunkel AR et al (2016) 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis*. Clin Infect Dis 64:e34–e65. https://doi.org/10.1093/cid/ciw861
52. Wellons JC, Shannon CN, Kulkarni AV, Simon TD, Riva-Cambrin J, Whitehead WE, Oakes WJ, Drake JM, Luerssen TG, Walker ML, Kestle JRW (2009) A multicenter retrospective comparison of conversion from temporary to permanent cerebrospinal fluid diversion in very low birth weight infants with posthemorrhagic hydrocephalus. J Neurosurg Pediatr 4:50–55. https://doi.org/10.3171/2009.2.PEDS08400
53. Benzel EC, Reeves JP, Nguyen PK, Hadden TA (1993) The treatment of hydrocephalus in preterm infants with intraventricular haemorrhage. Acta Neurochir 122:200–203
54. Limbrick DD, Mathur A, Johnston JM, Munro R, Sagar J, Inder T, Park TS, Leonard JL, Smyth MD (2010) Neurosurgical treatment of progressive posthemorrhagic ventricular dilation in preterm infants: a 10-year single-institution study. J Neurosurg Pediatr 6:224–230. https://doi.org/10.3171/2010.5.PEDS1010
55. de Vries LS, Liem KD, van Dijk K et al (2002) Early versus late treatment of posthaemorrhagic ventricular dilatation: results of a retrospective study from five neonatal intensive care units in The Netherlands. Acta Paediatr 91:212–217. https://doi.org/10.3171/2011.12.PEDS11136

56. Shooman D, Portess H, Sparrow O (2009) A review of the current treatment methods for posthaemorrhagic hydrocephalus of infants. Cerebrospinal Fluid Res 6:1–15. https://doi.org/10.1186/1743-8454-6-1
57. Kennedy CR, Kennedy C, Campbell M et al (1998) International randomised controlled trial of acetazolamide and furosemide in posthaemorrhagic ventricular dilatation in infancy. Lancet 352: 433–440. https://doi.org/10.1016/S0140-6736(97)12390-X
58. Mazzola CA, Choudhri AF, Auguste KI, Limbrick DD, Rogido M, Mitchell L, Flannery AM (2014) Pediatric hydrocephalus: systematic literature review and evidence-based guidelines. Part 2: management of posthemorrhagic hydrocephalus in premature infants. J Neurosurg Pediatr 14:8–23. https://doi.org/10.3171/2014.7.PEDS14322
59. Whitelay A, Odd D, Brion LP, Kennedy CR (2007) Intraventricular streptokinas after intraventricular hemorrhage in newborn infants. Cochrane Database Syst Rev 4:CD000498. https://doi.org/10.1002/14651858.CD000498.pub2
60. Brown EM (2000) The management of neurosurgical patients with postoperative bacterial or aseptic meningitis or external ventricular drain-associated ventriculitis. Br J Neurosurg 14:7–12
61. Lam HP, Heilman CB (2009) Ventricular access device versus ventriculosubgaleal shunt in post hemorrhagic hydrocephalus associated with prematurity. J Matern Neonatal Med 22:1097–1101. https://doi.org/10.3109/14767050903029576
62. Jian L, Hang-Song S, Zheng-Lang L et al (2012) Implantation of Ommaya reservoir in extremely low weight premature infants with posthemorrhagic hydrocephalus: a cautious option. Childs Nerv Syst 28:1687–1691. https://doi.org/10.1007/s00381-012-1847-0
63. Rizvi SAA, Wood M (2011) Ventriculosubgaleal shunting for posthaemorrhagic hydrocephalus in premature neonates. Pediatr Neurosurg 46:335–339. https://doi.org/10.1159/000320135
64. Badhiwala JH, Hong CJ, Nassiri F, Hong BY, Riva-Cambrin J, Kulkarni AV (2015) Treatment of posthemorrhagic ventricular dilation in preterm infants: a systematic review and meta-analysis of outcomes and complications. J Neurosurg Pediatr 16:545–555
65. Tenbrock K, Kribs A, Roth B (2003) Hyponatraemia as a consequence of serial liquor punctures in preterm infants with a ventricular access device after posthaemorrhagic hydrocephalus. Arch Dis Child Fetal Neonatal Ed 88:F359. https://doi.org/10.1136/fn.88.4.F349
66. Macmahon P, Cooke RWI (1983) Hyponatraemia caused by repeated cerebrospinal fluid drainage in post haemorrhagic hydrocephalus. Arch Dis Child 58:385–386. https://doi.org/10.1136/adc.58.5.385
67. Whitelaw A, Pople I, Cherian S, Evans D (2003) Phase 1 trial of prevention of hydrocephalus after intraventricular hemorrhage in newborn infants by drainage, irrigation, and fibrinolytic therapy. Pediatrics 111:759–766
68. Whitelaw A, Jary S, Kmita G, Wroblewska J, Musialik-Swietlinska E, Mandera M, Hunt L, Carter M, Pople I (2010) Randomized trial of drainage, irrigation and fibrinolytic therapy for premature infants with posthemorrhagic ventricular dilatation: developmental outcome at 2 years. Pediatrics 125:e852–e858. https://doi.org/10.1542/peds.2009-1960
69. Etus V, Kahilogullari G, Karabagli H, Unlu A (2018) Early endoscopic ventricular irrigation for the treatment of neonatal posthemorrhagic hydrocephalus: a feasible treatment option or not? A multicenter study. Turk Neurosurg 28:137–141. https://doi.org/10.5137/1019-5149.JTN.18677-16.0
70. Schulz M, Bührer C, Pohl-Schickinger A, Haberl H, Thomale UW (2014) Neuroendoscopic lavage for the treatment of intraventricular hemorrhage and hydrocephalus in neonates. J Neurosurg Pediatr 13:626–635. https://doi.org/10.3171/2014.2.PEDS13397
71. Fani L, De Jong THR, Dammers R, Van Veelen MLC (2013) Endoscopic third ventriculocisternostomy in hydrocephalic children under 2 years of age: appropriate or not? A single-center retrospective cohort study. Childs Nerv Syst 29:419–423. https://doi.org/10.1007/s00381-012-1961-z
72. Horinek D, Cihar M, Tichy M (2003) Current methods in the treatment of posthemorrhagic hydrocephalus in infants. Bratisl Lek List 104(11):347–351
73. Reinprecht A, Dietrich W, Berger A, Bavinzski G, Weninger M, Czech T (2001) Posthemorrhagic hydrocephalus in preterm infants: long-term follow-up and shunt-related complications. Childs Nerv Syst 17:663–669. https://doi.org/10.1007/s00381-001-0519-2
74. Pulido-Rivas P, Martínez-Sarriés F, Ochoa M, Soía R (2007) Treatment of hydrocephalus secondary to intraventricular haemorrhage in preterm infants. A review of the literature. Rev Neurol 44: 616–624
75. Leonard JR, Limbrick DD (2014) Intraventricular hemorrhage and posthemorrhagic hydrocephalus. In: Principles and practice of pediatric neurosurgery, 3rd edn. Thieme Medical Publishers, New York, pp 137–145
76. Fulkerson DH, Vachhrajani S, Bohnstedt BN, Patel NB, Patel AJ, Fox BD, Jea A, Boaz JC (2011) Analysis of the risk of shunt failure or infection related to cerebrospinal fluid cell count, protein level, and glucose levels in low-birth-weight premature infants with posthemorrhagic hydrocephalus. J Neurosurg Pediatr 7:147–151. https://doi.org/10.3171/2010.11.PEDS10244
77. Heep A, Engelskirchen R, Holschneider A, Groneck P (2001) Primary intervention for posthemorrhagic hydrocephalus in very low birthweight infants by ventriculostomy. Childs Nerv Syst 17: 47–51. https://doi.org/10.1007/s003810000363
78. Brouwer A, Groenendaal F, van Haastert I-L, Rademaker K, Hanlo P, de Vries L (2008) Neurodevelopmental outcome of preterm infants with severe intraventricular hemorrhage and therapy for posthemorrhagic ventricular dilatation. J Pediatr 152:648–654. https://doi.org/10.1016/j.jpeds.2007.10.005
79. Adams-Chapman I, Hansen NI, Stoll BJ, Higgins R (2008) Neurodevelopmental outcome of extremely low birth weight infants with posthemorrhagic hydrocephalus requiring shunt insertion. Pediatrics 121:e1167–e1177. https://doi.org/10.1542/peds.2007-0423
80. Radic JAE, Vincer M, McNeely PD (2015) Outcomes of intraventricular hemorrhage and posthemorrhagic hydrocephalus in a population-based cohort of very preterm infants born to residents of Nova Scotia from 1993 to 2010. J Neurosurg Pediatr 15:580–588. https://doi.org/10.3171/2014.11.PEDS14364
81. Sasidharan P, Marquez E, Dizon E, Sridhar CV (1986) Developmental outcome of infants with severe intracranial-intraventricular hemorrhage and hydrocephalus with and without ventriculoperitoneal shunt. Childs Nerv Syst 2:149–152. https://doi.org/10.1007/BF00270845
82. O'Shea TM, Allred EN, Kuban KCK et al (2012) Intraventricular hemorrhage and developmental outcomes at 24 months of age in extremely preterm infants. J Child Neurol 27:22–29. https://doi.org/10.1177/0883073811424462