



# The Burden of Pediatric Neurosurgery Contact/Interventions in Preterm Newborns with Grade III-IV Intraventricular Hemorrhage during NICU Stay

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## Abstract

**Objectives:** Significance of grade III Intraventricular Hemorrhage (IVH) versus grade IV in premature newborns in reference to neurosurgical management is not well known. We compared whether IVH grading could predict neurosurgical intervention and mortality rate.

**Study Design:** A retrospective chart study of 186 premature newborns with grade III or IV (IVH) from January 1, 2008 to December 31, 2012 was conducted to review neurosurgical contact/intervention and mortality occurrence.

**Results:** The 186 newborns were identified, 83 with grade III IVH, and 103 grade IV. Neurosurgery contact/interventions occurred in 44 patients, with significant increase in grade IV (32) than grade III patients (12) ( $p=0.008$ ). Grade IV IVH patients also required shunts more than grade III ( $p=0.049$ ), and multivariate analysis confirmed mortality rates also higher with grade IV diagnosis.

**Conclusion:** Grade IV IVH patients experienced increased neurosurgical involvement, rates of shunt insertion and revision, as well as mortality rates.

**Keywords:** Intraventricular hemorrhage; Prematurity; Neurosurgery; CSF

## Introduction

Intraventricular Hemorrhage (IVH) describes intra cerebral bleeding in and around the ventricles of a newborn infant. IVH can result from germinal matrix hemorrhages, especially within the 23<sup>rd</sup> week of gestation when the germinal matrix has reached its maximal size. Bleeding can spread in the parenchyma and into the ventricles. One of the sequelae of IVH is the potential obstruction of Cerebrospinal Fluid (CSF), resulting in hydrocephalus and increased intracranial pressure. IVH occurs among premature newborns and has been estimated to range from 30% to 90% [1,2]. The incidence of IVH in those under 32 weeks gestation is reported to be 10% to 20%, which then increases to 24% to 50% for infants weighing 1500 grams or less [3]. Premature newborns with IVH have a complex post-natal course with co-morbidities that impact neurocognitive and neurological development [1,4,5]. Premature infants are at a higher risk of cerebral palsy, often accompanied by additional neurodevelopment co-morbidities. And when later assessed at age 10, they are often associated with severe fetal growth restrictions and increased multiple cognitive and behavioral dysfunctions [6,7]. The co-morbid incidence of cerebral palsy in premature newborns with grade IV hemorrhage has been reported to be 48.7%, while the incidence of grade III was 7.4% [1,4-8]. IVH is the most powerful predictor of cerebral palsy and cognitive deficits, with higher IVH grades associated with decreased functional status [3]. In the current study, we examined a cohort population during a five-year reference period in order to investigate the significances of grade III vs. grade IV IVH, in reference to management by pediatric neurosurgery and the burden on patients and their families.

## Materials and Methods

### Patient population

A retrospective study review of 186 neonates with hospital NICU stay at UF Health Jacksonville (UFJ) or Wolfson Children's Hospital/Baptist Medical Center (BMC) was performed during the period between 1<sup>st</sup> January, 2008 and 31<sup>st</sup> December 2012, with infants having a diagnosis of

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grade III or IV IVH. The diagnostic images were reviewed by both a pediatric radiologist and pediatric neurosurgeon. Agreement by both specialized to the classification of grade III or grade IV IVH. A total of 201 records were received and reviewed from UFJ and BMC. Fifteen patients were excluded due to unconfirmed IVH grade III or IV status, resulting in a remaining 186 patients in the study. The neonatology and neurosurgery physicians are faculty of the UFJ. A uniform approach for patient management and need for neurosurgery intervention was agreed upon at the time of establishment of the UF Division of Pediatric Neurosurgery in 2003. The pediatric neurosurgery faculty established protocols for management decisions, and the type and time of surgical interventions. Infants were eligible if their records indicated having a grade III or IV IVH on their surgical charges or their NICU discharge summary. Patients diagnosed with both grade III and grade IV IVH had the higher grade assigned. Authorization for chart review and study was obtained from the Institutional Review Boards of UFJ and BMC (UF IRB-03 2013-0100, BMC IRB 13-75). Study data was collected and managed using RED Cap (Research Electronic Data Capture) software hosted at the University of Florida College of Medicine - Jacksonville.

### Data analysis

Primary variables included life status, defined for the purposes of this manuscript as alive or dead, post-discharge, neurosurgical contacts, and procedures. All procedures are listed in Table 1. Statistical tools included the chi-square contingency table and independent two-tailed Student t-test, with  $p \leq 0.05$  considered statistically significant for neurosurgical contacts and procedures. Multivariate analysis was implemented for variables association with a life status post-discharge with  $p \leq 0.05$  being included. Stepwise logistic regression was used to determine which variables were independently associated with mortality at time of NICU discharge ( $p < 0.05$ ). SPSS (version 21 IBM) and Microsoft Excel were used to conduct all statistical tests.

## Results

A total of 186 newborns with grade III or IV IVH were identified; 74 were female and 112 were male. The study comprised of 45.16% African American, 48.9% White, 1.0% Asian, 1.6% more than one race, 2.1% other, and 1.0% not specified. Eighty-three newborns experienced grade III IVH and 103 experienced grade IV IVH. Ninety-eight percent of the infants with grade III or IV IVH were categorized as extreme preterm (<28 weeks), very preterm (28 to 31 weeks), or moderate to late preterm (32 to 36 weeks). The remaining 1.7% of infants was term (37 weeks or more) (Table 2).

### Neurosurgical contacts

Documented neurosurgery contacts occurred in 44 patients (23.7%), of which 39 had a recorded pediatric neurosurgery consultation. Significantly more neurosurgical contacts/interventions occurred in grade IV patients (32) over grade III patients (12) ( $p = 0.008$ ). In five patients, documentation of consultation was not available at the time of chart review, but neurosurgical procedures were documented. Nineteen patients had pediatric neurosurgery consultation followed by a procedure, and 20 patients had a consultation without a neurosurgical procedure. Consultations were performed by one of three pediatric neurosurgeons who followed similar practice procedures and timing of interventions. Following individual patient assessment, a management protocol was instituted. This consisted of but was not limited to daily head circumference, assessment of fontanelle size and fullness, and clinical

**Table 1:** Listing of neurosurgical procedures performed on newborns.

<b>Lumbar Punctures</b>	NICU staff
	Neurosurgical staff
<b>Shunts</b>	Subgaleal shunt placement
	Ventriculoperitoneal Shunt Placement (VPS)
	VPS revisions
	Infections
<b>Ventricular Punctures</b>	<b>Cerebral reservoir</b>
	Cerebral reservoir placement
	Reservoir punctures
	Antibiotic injections
<b>External Ventricular Drain (EVD)</b>	EVD puncture and antibiotic injections
<b>Shunt Tubing</b>	Shunt tubing puncture
	Shunt tubing puncture with antibiotic injections

changes, such as pulse and respiration rate. Following the initial head ultrasound, subsequent studies were requested if there was a documented increase in head size, fontanelle fullness, or persistent changes in cardiovascular parameters. Interventions were performed based on clinical progression and/or ultrasound findings. Computed tomography was not employed to reduce infant radiation exposure. Magnetic resonance imaging was usually performed prior to discharge from the NICU, to assess ventricular size and status of the brain. The study served the purpose of pre-discharge assessment of ventricular size, as well as subsequent comparison for outpatient studies.

### Temporizing procedures

**Lumbar punctures:** Twenty-eight patients had Lumbar Punctures (LPs); 12 grade III and 16 grade IV. Of these, 21 (10 grade III, 11 grade IV) had LPs from the NICU staff, six (2 grade III, 4 grade IV) had LPs from neurosurgery staff, and two (1 grade III, 1 grade IV) had LPs from both the NICU and neurosurgery staff. Nine of the 28 patients with LPs went on to receive Ventriculoperitoneal (VP) shunts (32.1%), showing no difference between grade III and IV IVH in terms of patients with LPs needing permanent shunts.

**Ventricular puncture:** Among the 14 total patients that had ventricular punctures, four were grade III and 10 were grade IV IVH, with no significant difference between grades ( $p = 0.272$ ). Two patients (both grade IV) had one puncture, and 12 (3 grade III, and 8 grade IV) had more than one puncture.

**Subgaleal shunts and cranial reservoirs:** There were four patients with subgaleal shunts, all with grade IV IVH. All four patients had their subgaleal shunt subsequently replaced with a VP shunt. One patient underwent an initial procedure of a cranial reservoir placement. Six patients underwent placement of a cranial reservoir following temporary management with lumbar punctures and/or ventricular punctures. Of the seven patients with cranial reservoirs, three were grade III and four were grade IV IVH with no significant difference between grades ( $p = 1.000$ ). Six of the seven patients progressed to a VP shunt following temporary control of the hydrocephalus with intermittent reservoir punctures, for a total of 85.7% requiring shunting after temporization.

### Shunt insertion and revisions

Eighteen patients underwent VP shunt placement, of which 16 during their NICU admission and two patients underwent placement

**Table 2:** Patient demographics of cohort.

Variables	Number of Patients	Percent of Cohort
Total	186	
<b>Sex</b>		
Female	74	39.70%
Male	112	60.20%
<b>Race</b>		
African American	84	48%
White	91	52%
Asian	2	1%
More than one race	3	1.60%
Other	4	2.10%
Not specified	2	1%
<b>IVH Grade</b>		
Grade III	83	44.62%
Grade IV	103	55.37%
<b>Gestational Age (weeks)</b>		
Extremely preterm (<28)	137	73.65%
Very preterm (28 to 31)	34	18.27%
Moderate to late preterm (32 to 36)	12	6.45%
Term (37+)	3	1.61%

within six months of discharge. Of these 18 patients with VP shunts, four were grade III IVH and 14 were grade IV ( $p=0.049$ ). In our sample, there was a 29% increase in the odds of requiring a shunt in patients with grade IV IVH. Within one year of shunt placement, seven patients (two grade III, five grade IV) required 10 total procedures for VP shunt complications, two of which occurred during their NICU stay, and eight occurred post-discharge.

### Infection and malfunction rates

Twenty-two shunt procedures were performed on 18 patients; four patients underwent more than one shunt replacement due to infection. Based on these 22 shunt placements, the authors calculated the infection and malfunction rates at 30 days and one-year post-operation. At 30 days post-operation, there were two patients (both grade III) with infections (9.09%) and two patients (both grade IV) requiring surgery for shunt malfunction (9.09%). At one-year post-operation, four patients (two grade III, two grade IV) had shunt infections (18.2%), and six patients (one grade III, five grade IV) underwent revision for VP shunt malfunction (27.3%). Due to the small number, no statistically significant difference was found between IVH grades.

### Mortality rate

Univariate analysis demonstrated a significant association between life status and birth weight ( $p=0.0002$ ), gestational age ( $p<0.0001$ ) and IVH grade ( $p=0.0003$ ). Sex and race were not found to be associated with life status at discharge (Table 3). The significant variables from the univariate analysis (i.e., birth weight, gestational age, and IVH grade) were included in the multivariate logistic regression. The univariate statistical threshold for inclusion in the multivariate analysis was  $p \leq 0.05$ . Gestational age was independently associated with life status at discharge (OR 1.4; 95% CI 1.0-1.9;  $p=0.0488$ ), IVH grade was also independently associated (OR 2.8; 95% CI 1.4-5.8;  $p=0.0046$ ). Birth weight was not independently associated

**Table 3:** Univariate analysis of factors affecting mortality.

Variables	Alive	Deceased	p Value
No. of patients	126	60	
<b>Sex</b>			<b>0.7175</b>
Male	77 (61.1)	49 (81.7)	
Female	35 (27.8)	25 (41.7)	
<b>Race</b>			<b>0.5881</b>
White	67 (53.2)	24 (40.0)	
Black	51 (40.5)	33 (55.0)	
Asian	2 (1.6)	0 (0.0)	
More than one race	2 (1.6)	1 (1.7)	
Other	2 (1.6)	2 (3.3)	
Not specified	2 (1.6)	0 (0.0)	
<b>Birth Weight (grams)</b>			<b>0.0002</b>
Extremely low weight (<1000 g)	76 (60.3)	53 (88.3)	
Very low weight (1500 to 1000 g)	32 (25.4)	5 (8.3)	
Low weight (2500 to 1500 g)	15 (11.9)	1 (1.7)	
Normal (>2500 g)	3 (2.4)	1 (1.7)	
<b>Gestational Age (weeks)</b>			<b>&lt;0.0001</b>
Extremely preterm (<28 weeks)	83 (65.9)	54 (90.0)	
Very preterm (28 to 31 weeks)	29 (23.0)	5 (8.3)	
Moderate to late preterm (32 to 36 weeks)	11 (8.7)	1 (1.7)	
Term (37+ weeks)	3 (2.4)	0 (0.0)	
<b>IVH Grade</b>			<b>0.0003</b>
Grade III	68 (54.0)	15 (25.0)	
Grade IV	58 (46.0)	45 (75.0)	

**Table 4:** Multivariate logistic regression analysis of factors affecting mortality.

Variable	OR (95% CI)	p Value
Birth Weight (grams)	1.0 (0.9-1.0)	0.9829
Gestational Age (weeks)	1.4 (1.0-1.9)	0.0488
IVH Grade	2.8 (1.4-5.8)	0.0046

with life status at discharge ( $p=0.98$ ). There was no significance in life status for patients with neurosurgical contacts: 11 (91.6%) of grade III infants and 24 (75%) of grade IV were living at the time of hospital discharge ( $p=0.405$ ).

## Discussion

Even though incidence of severe intra cerebral hemorrhage decreased from 1983 to 2012, premature infants are nevertheless more likely to suffer from IVH, and most research is focused on improving the quality of life for these infants [9]. As described by Papile, the difference between grade III and grade IV IVH is the resultant parenchymal hemorrhage present in grade IV IVH, causing further damage of the cerebral tissue [10]. Levy et al. [11] compared preterm infants with grade III and IV IVH and concluded that grade of hemorrhage was the most important variable in determining survival. Our study paralleled these results as the differences between grade III and IV newborns showed strong statistical significance in terms of mortality, confirming that significantly more grade IV newborns died than grade III newborns ( $p=0.0046$ ). With regards to the difference between surgical management of grade III and grade IV IVH, the current authors found that a total of 18 patients (9.7%)

of the cohort received VP shunt placement, seven (3.8%) received a cranial reservoir, 28 (15.1%) received LPs, and four (2.2%) received a subgaleal shunt. Grade IV IVH shows a consistent trend of requiring more procedures compared to that of grade III newborns, highlighting the increased severity and operative management involved. Recent studies show a similar varied surgical response to infants with IVH with 49 patients having ventricular reservoirs (98%, 23 grade III and 26 grade IV), and 35 patients having VP shunts (85%, 13 grade III and 22 grade IV) [12]. This supports trends in the current study with grade IV patients receiving more procedures for both ventricular reservoirs and VP shunt placements. We also found that grade IV newborns had more VP shunt revisions due to infections and malfunctions than grade III newborns, with seven out of 10 (70%) and three out of 10 (30%), respectively. However, due to the small sample size, no statistically significant difference was found between IVH grade and VP shunt revisions. Previous studies demonstrated patients with a ventricular reservoir requiring a permanent shunt can vary from 69% to 93% [11-17]. On review of the author's data, almost all patients with cranial reservoirs (seven patients) eventually required VP shunts (six; 85.7%, two grade III and four grade IV). Only one newborn with a cranial reservoir (14.3%, one grade III) did not require permanent shunt insertion, this percentage was consistent to the five patients (10%) with temporary CSF drainage in previous studies who did not require permanent shunt insertion [13]. The numbers from this report are too small to draw accurate conclusions, which has led the authors to revisit their protocol for intervention and punctures to lower the number of infants that progress to a VP shunt.

### Shunt infections and malfunctions

During NICU stay, one patient had a shunt infection, and post-NICU discharge, there were three patients (two grade III, one grade IV) who required shunt intervention due to infection. Four out of 22 shunt insertions required VP shunt removal, resulting in an 18.2% shunt infection rate within one year. These numbers are higher compared to the approximate 8% to 10% infection rate for VP shunt placement [18-20]. These higher infection rates may be a result of this study's small sample size. The author's cohort also includes infants of low birth weight and a high incidence of ventilator support; these measures could increase the incidence of invasive procedures and the resulting infection rate. External ventricular drains were not employed to minimize hospital-acquired infections, as well as to facilitate nursing bedside management. Of note are other procedures that have been proposed to manage these children such as but not limited to ventricular lavage of the hemorrhagic materials [21]. This consists of inserting a neuroendoscope into the ventricular system and irrigating the blood products out of the CSF pathways. The authors reported a reduction in the need for insertion of CSF shunts in their patient population, thus eliminating the need for revisions due to obstruction and infections [21]. We did not include this in the protocol, awaiting further studies that document long-term results.

### Mortality rate

Univariate analysis showed that birth weight, gestational age, and IVH grade were all associated with higher rates of mortality. Multivariate analysis of significant univariate variables demonstrated that only gestational age and IVH grade were independent risk factors for mortality in this cohort. In the multivariate analysis the odds of dying were 2.8 times higher for those with grade IV IVH compared to the odds of dying for grade III when controlling for gestational age. Of the 44 newborns with neurosurgical contacts, nine expired (20.4%).

Seven of these nine newborns had a neurosurgery consultation, but no surgical intervention. This contrasts previous study in which expired patients (nine out of 91, 10%) had neurosurgical procedures, although the cause of death was reported as being unrelated to the intervention [13]. While there was a statistically significant difference in mortality between grade III and grade IV IVH newborns ( $p=0.0046$ , this difference was lost when controlled for newborns with neurosurgical contact ( $p=0.405$ ). This is likely due to a number of critical grade IV diagnoses deemed too high risk with a low probability of good outcome, resulting in the absence of neurosurgical consultations (Table 4). The timing of the neurosurgical consultation was dependent on the preference of the attending neonatologist. This varied according to each neonatologist. Based on our current findings we are proposing more defined protocols to ascertain a more cohesive approach to timing of neurosurgical consultations.

### Limitations of the study

This study has limitations due to its nature as a single-centre retrospective study. In addition, the study is limited in its total patient count of 186. Many comparisons are too limited in number to run a Student t-test or chi-square for statistical confirmation, and instead depend on comparisons of percentages and trends.

### Future directions

The authors are standardizing their treatment protocol for these infants with the aim of earlier identification and intervention to decrease or better manage hydrocephalus.

## Conclusion

Patients with grade IV IVH require more neurosurgical contacts and/or interventions than patients with grade III IVH. A higher number of VP shunt insertions was noted for the grade IV group than the grade III group ( $p=0.049$ ). Grade IV patients had a higher prevalence of need for shunt revisions within the first year following insertion, compared to that of grade III. Multivariate analysis found that IVH grade was independent risk factors for mortality in this cohort, and life status was statistically different between grade III vs. grade IV IVH, with elevated mortality in the latter. When also factoring in patients who received neurosurgical contact, this difference was lost. Physician counseling of parents with a preterm newborn with grade IV hemorrhage should include discussion of the potential burden on their child as to neurosurgical interventions and procedures. Physicians should also expect grade IV IVH newborns to need more individual interventions and shunt revisions when compared to infants with grade III. Future directions include early identification and intervention to evaluate for improved survival of patients.

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