Myelomeningocele-associated hydrocephalus: nationwide analysis and systematic review

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OBJECTIVE Myelomeningocele (MMC), the most severe form of spina bifida, is characterized by protrusion of the meninges and spinal cord through a defect in the vertebral arches. The management and prevention of MMC-associated hydrocephalus has evolved since its initial introduction with regard to treatment of MMC defect, MMC-associated hydrocephalus treatment modality, and timing of hydrocephalus treatment.

METHODS The Nationwide Inpatient Sample (NIS) database from the years 1998–2014 was reviewed and neonates with spina bifida and hydrocephalus status were identified. Timing of hydrocephalus treatment, delayed treatment (DT) versus simultaneous MMC repair with hydrocephalus treatment (ST), and treatment modality (ETV vs ventriculoperitoneal shunt [VPS]) were analyzed. Yearly trends were assessed with univariable logarithmic regression. Multivariable logistic regression identified correlates of inpatient shunt failure. A PRISMA systematic literature review was conducted that analyzed data from studies that investigated 1) MMC closure technique and hydrocephalus rate, 2) hydrocephalus treatment modality, and 3) timing of hydrocephalus treatment.

RESULTS A weighted total of 10,627 inpatient MMC repairs were documented in the NIS, 8233 (77.5%) of which had documented hydrocephalus: 5876 (71.4%) were treated with VPS, 331 (4.0%) were treated with ETV, and 2026 (24.6%) remained untreated on initial inpatient stay. Treatment modality rates were stable over time; however, hydrocephalic patients in later years were less likely to receive hydrocephalus treatment during initial inpatient stay (odds ratio [OR] 0.974, $p = 0.0331$). The inpatient hydrocephalus treatment failure rate was higher for patients who received ETV treatment (17.5% ETV failure rate vs 7.9% VPS failure rate; $p = 0.0028$). Delayed hydrocephalus treatment was more prevalent in the later time period (77.9% vs 69.5%, $p = 0.0287$). Predictors of inpatient shunt failure included length of stay, shunt infection, jaundice, and delayed treatment. A longer time between operations increased the likelihood of inpatient shunt failure (OR 1.10, $p < 0.0001$). However, a meta-analysis of hydrocephalus timing studies revealed no difference between ST and DT with respect to shunt failure or infection rates.

CONCLUSIONS From 1998 to 2014, hydrocephalus treatment has become more delayed and the number of hydrocephalic MMC patients not treated on initial inpatient stay has increased. Meta-analysis demonstrated that shunt malfunction and infection rates do not differ between delayed and simultaneous hydrocephalus treatment.

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KEYWORDS myelomeningocele; spina bifida; hydrocephalus; cerebrospinal fluid shunting

MYELOMENINGOCELE (MMC) is the most severe form of spina bifida, characterized by protrusion of the meninges and spinal cord through a defect in the vertebral arches. The incidence of MMC ranges between 0.2 and 2 per 1000 live births, resulting in a spectrum of devastating clinical manifestations, including Chiari II malformation, genitourinary dysfunction, sensory and motor defects, and hydrocephalus.^{23,52} While all patients with MMC have ventriculomegaly, not all require

treatment for hydrocephalus. The reported incidence of MMC-related hydrocephalus following postnatal closure of the MMC defect ranges from 57% to 86%.^{6,8,14,19,26,37,48,59,63,65} The management of MMC-associated hydrocephalus has evolved since its initial introduction in the early 1950s. While a CSF shunt was initially the only treatment, some patients are now treated with endoscopic third ventriculostomy (ETV) or a combination of ETV and choroid plexus cauterization (ETV/CPC). Additionally, some patients are

ABBREVIATIONS CPC = choroid plexus cauterization; DT = delayed treatment; ETV = endoscopic third ventriculostomy; MMC = myelomeningocele; MOMS = Management of MMC Study; NIS = Nationwide Inpatient Sample; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ST = simultaneous treatment; VPS = ventriculoperitoneal shunt.

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treated for hydrocephalus at the same time as initial closure, while others are followed after closure to determine whether they will require intervention for hydrocephalus.

The pathophysiology of MMC-associated hydrocephalus is not fully elucidated; however, one theory is that inappropriate in-utero CSF outflow through the MMC defect leads to underdevelopment of normal CSF drainage pathways.³² These theories laid the scientific foundation for the initial animal studies and pilot human studies that evaluated prenatal MMC closure, with the hope that earlier closure of the defect would result in milder neurological deficits and less postnatal hydrocephalus.^{16,17,33,34,56}

Ultimately, these studies were the foundation for the Management of MMC Study (MOMS). Published in 2011, MOMS compared prenatal intrauterine MMC closure to traditional postnatal repair and demonstrated that hydrocephalus rates in prenatal MMC repair were favorable to those of postnatal closure.¹ A critique of this MOMS trial conclusion was that CSF diversion practices may have evolved over the trial period and since, with the thought that the threshold for treating hydrocephalus has increased and more patients are treated with ETV with or without CPC.

We hoped to elucidate shifts in MMC hydrocephalus management with a nationwide database. We review the Nationwide Inpatient Sample (NIS) from 1998 to 2014 for MMC patients, reporting the incidence and postnatal management of MMC-associated hydrocephalus. Additionally, we conduct a systematic review of the literature identifying studies that investigate MMC closure technique and hydrocephalus rate, MMC hydrocephalus treatment modality, and timing of hydrocephalus treatment.

Methods

NIS Review

The NIS from the years 1998–2014 was reviewed. Details regarding the NIS can be found on <http://hcupnet.ahrq.gov>. Patients less than 28 days old with spina bifida (ICD-9 code 741.xx) and repair of spinal meningocele procedure (ICD-9 codes 035.1, 035.9) were identified. Patients were separated by hydrocephalus status (ICD-9 codes 741.9x, 741.0x). Patients with ICD-9 codes of spina bifida without hydrocephalus and concomitant codes of hydrocephalus (ICD-9 331.3, 331.4) or hydrocephalus treatment (ventriculoperitoneal shunt [VPS] ICD-9 02.3x; ETV ICD-9 0.22, 0.222) were considered to have hydrocephalus. Shunt infection was defined as ICD-9 codes 996.63 or 996.60. Additional ICD-9 coding was utilized to identify common neonatal disease processes such as respiratory distress syndrome, wound infection, hematological disorders, necrotizing enterocolitis, bradycardia, tachycardia, jaundice, and electrolyte abnormalities.

NIS Statistics

For the years 1998–2011 and 2012–2014 the adjusted NIS weights “TRENDWT” and “DISCWT” were utilized, respectively, to adjust for temporal database changes. Categorical variables were presented as estimated weighted frequency and either row or column percentiles. Statistical analyses of categorical variables were performed using

chi-square and Fisher’s exact tests, as appropriate. The normality of continuous variables was assessed graphically and statistically, with nonparametric distributions represented as medians and interquartile ranges (IQRs), whereas normal distributions were represented as weighted mean estimates. Comparisons of means of parametric variables were performed using least-squared means analysis, while nonparametric distributions were compared using the Wilcoxon rank-sum test adjusting for clustering and stratification.³⁸

Time trend series plots were created for treatment modality and time of treatment for hydrocephalus. Patient records with procedure date available for both MMC repair and hydrocephalus treatment procedures were analyzed to assess timing of hydrocephalus treatment and MMC repair with simultaneous hydrocephalus treatment (ST) versus delayed hydrocephalus treatment (DT), defined as hydrocephalus treatment on a different day than initial closure. To assess for significant shifts in MMC hydrocephalus management, the earlier period was defined as the years 1998–2006 and the later period as 2007–2014. Yearly trends were assessed with univariable logarithmic regression with year treated as a continuous variable. Furthermore, records with time of treatment available were assessed with a univariable and multivariable logistic regression to identify correlates of inpatient shunt failure, defined as documented return to the operating room. Correlates with a significance level of $p < 0.2$ were included in the multivariable regression. A backward elimination multivariable model was utilized and only covariates with p values < 0.1 remained in the final model. A p value ≤ 0.05 was considered statistically significant. The statistical software program SAS (version 9.4; SAS Institute) was used for analysis.

Systematic Review

We conducted a systematic literature review in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines that analyzed data from studies reporting the treatment of hydrocephalus in newborns with MMC.²⁷ Using the PubMed database, we searched for articles published from January 1970 through June 2019 utilizing the terms (“cerebrospinal fluid shunts,” OR “hydrocephalus”) AND (“myelomeningocele”). The Rayyan systematic review app was utilized by 2 authors, who separately reviewed the search articles.⁴³ Additional papers were found through reference lists from pertinent articles. Full-text English cohort studies published in peer-reviewed journals were selected. The PRISMA flowchart is shown in Fig. 1.

Studies were excluded if MMC patients were a subset of the study. Studies were included and critically evaluated if they fell into 1 of the following categories: 1) MMC closure technique and hydrocephalus rate; 2) hydrocephalus treatment modality; and 3) timing of hydrocephalus treatment. Relevant information from papers was extracted.

Results

NIS Cohort Characteristics

Table 1 displays the NIS cohort characteristics stratified

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

FIG. 1. PRISMA flowchart of systematic review. Data added to the PRISMA template (from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group [2009]. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7):e1000097) under the terms of the Creative Commons Attribution License.

by hydrocephalic status. From 1998 to 2014, a weighted total of 10,627 inpatient MMC repairs were documented in the NIS, 8233 (77.5%) of which had documented hydrocephalus. Patient race ($p = 0.0051$) and patient insurance status ($p = 0.0004$) had a significant effect on hydrocephalus rates; white or Hispanic and Medicaid patients were most likely to be diagnosed with hydrocephalus. Level of MMC did not significantly affect hydrocephalus status and the number of patients coded for MMC with hydrocephalus versus without hydrocephalus did not change over time. Patients with hydrocephalus had longer median length of inpatient stay compared to those without the diagnosis.

NIS Hydrocephalus Treatment

Of the 8233 patients with MMC and hydrocephalus, 5876 (71.4%) were treated with VPS, 331 (4.0%) were

treated with ETV, and 2026 (24.6%) received no hydrocephalus treatment on initial inpatient stay. Treatment modality rates were stable overtime (Fig. 2, early vs late period, $p = 0.2595$) and did not differ based on academic hospital status ($p = 0.5938$), hospital region ($p = 0.5590$), patient race ($p = 0.5175$), or patient insurance status ($p = 0.1667$). When analyzing hydrocephalus treatment versus no treatment during inpatient stay using univariable logistic regression, patients in later years with hydrocephalus were less likely to receive hydrocephalus treatment during initial inpatient stay (odds ratio [OR] 0.974, 95% confidence interval [CI] 0.951–0.998, $p = 0.0331$). However, this difference was not significant when analyzed using early versus late time periods (76.9% vs 73.9%, $p = 0.1644$).

Of the 6208 patients who received treatment for hydrocephalus, the inpatient hydrocephalus treatment failure rate was significantly higher for patients who received

TABLE 1. NIS cohort characteristics

Characteristic	Overall (n = 10,627)	Hydrocephalic (n = 8233)	Nonhydrocephalic (n = 2394)	p Value
Female	5078 (47.8)	3965 (48.2)	1112 (46.5)	0.5132
Median length of stay (IQR), days	11.9 (11.3)	13.3 (12.1)	7.9 (6.6)	<0.0001
MMC level				0.5236
Lumbar	9041 (85.1)	7037 (85.5)	2004 (83.7)	
Thoracic	521 (4.9)	406 (4.9)	115 (4.8)	
Cervical	61 (0.6)	39 (0.5)	22 (0.9)	
Unspecified	1005 (9.5)	751 (9.1)	254 (10.6)	
Patient race				0.0051
White	4256 (56.6)	3396 (57.5)	860 (53.3)	
African American	718 (9.6)	551 (9.3)	167 (10.3)	
Hispanic	1777 (23.6)	1440 (24.4)	337 (20.9)	
Asian or Pacific Islander	118 (1.6)	78 (1.3)	40 (2.5)	
Zip code income quartile, \$				0.0886
1–24,999	2827 (27.2)	2284 (28.3)	543 (23.1)	
25,000–34,999	2852 (27.4)	2214 (27.5)	638 (27.2)	
35,000–44,999	2711 (26.0)	2074 (25.7)	636 (27.1)	
45,000 or more	2022 (19.4)	1491 (18.5)	531 (22.6)	
Insurance status				0.0004
Medicaid	5413 (51.2)	4373 (53.3)	1040 (43.5)	
Private insurance	4369 (41.2)	3189 (38.8)	1180 (49.4)	
Self-pay	315 (3.0)	247 (3.0)	68 (2.9)	
Hospital region				0.3039
Northeast	1406 (13.2)	1044 (12.7)	362 (15.1)	
Midwest	3242 (30.5)	2595 (31.5)	646 (27.0)	
South	3093 (29.1)	2358 (28.6)	735 (30.7)	
West	2886 (27.2)	2236 (27.2)	650 (27.2)	
Academic hospital status	9739 (92.6)	7506 (92.2)	2233 (93.8)	0.2394
Hospital bed size				0.6990
Small	1457 (13.8)	1094 (13.4)	363 (15.3)	
Medium	2053 (19.5)	1593 (19.5)	460 (19.3)	
Large	7028 (66.7)	5472 (67.1)	1557 (65.4)	

Weighted frequencies and column percentiles displayed unless otherwise stated. Some variables may be missing data from a few patients.

ETV (17.5% ETV failure rate vs 7.9% VPS failure rate; $p = 0.0028$).

NIS Timing of Hydrocephalus Treatment

Only 4551 of the patients treated for hydrocephalus had day-of-procedure information available for both MMC and hydrocephalus treatment. Treatment information stratified by time of treatment, ST versus DT, is displayed in Table 2. DT was more prevalent in the later time period (DT-late 77.9% vs DT-early 69.5%, $p = 0.0287$). This time trend is shown in Fig. 3. This trend was also significant when analyzed with a more accurate univariable yearly logistic regression (OR 1.06, 95% CI 1.019–1.102, $p = 0.0039$). DT was also more prevalent in patients with zip codes from poorer neighborhoods ($p = 0.0139$), and in medium-sized hospitals ($p = 0.0292$). The median number of days delayed before hydrocephalus treatment was 7 (IQR 7; distribution shown in Fig. 3).

Of the 4285 patients who received first treatment with VPS with procedure day available, 115 (2.7%) had documented shunt infection during initial inpatient stay. There was no significant difference in shunt infection rate and time of shunt placement (ST 1.3% vs DT 3.1%, $p = 0.1373$). Compared to patients with ST, those with DT were more likely to have shunt failure during the inpatient stay (10.4% DT failure vs 1.9% ST failure, $p = 0.0002$). In the univariable analysis we identified length of stay, shunt infection, jaundice, tachycardia, hematological diagnosis, respiratory distress, zip code income, and delayed treatment as correlating factors of inpatient shunt failure. However, the only significant independent correlating factors were length of stay, shunt infection, jaundice, and delayed treatment (Table 3). When days between hydrocephalus treatment and MMC repair was analyzed as a continuous variable, a longer duration between operations increased the likelihood of inpatient shunt failure (OR 1.10, $p < 0.0001$).

FIG. 2. Trend of treatment modalities for MMC-related hydrocephalus from 1998 to 2014.

There was no difference in ETV failure with regard to treatment time, although this was likely influenced by the low number of patients (ST 12.2% vs DT 21.4%; $p = 0.4388$).

Systematic Review

The systematic review identified 905 articles; 8 articles were from additional sources. A total of 48 articles met the inclusion criteria: 17 discussed hydrocephalus rates with regard to MMC closure technique,^{1,5–7,13,14,19–21,26,37,45,51,56–58,67} 16 involved MMC-associated hydrocephalus treatment modality and outcomes,^{3,4,9,22,24,28,36,39,42,46,50,53–55,61,62} and 15 the timing of hydrocephalus treatment.^{2,9,10,15,18,25,29–31,35,41,44,49,60,66}

Discussion

Rates of Hydrocephalus Following Different MMC Closure Techniques

Among the complications associated with MMCs, hydrocephalus is one of the most common and debilitating. Prior to the advent of CSF shunting, most hydrocephalic MMC patients did not survive beyond 2 years of age.^{14,47} Following the introduction of CSF shunts in the 1950s, many advocated for the indiscriminate, aggressive treatment of hydrocephalus in MMC patients, which resulted in a significant proportion receiving VPS at the same time as their postnatal MMC repair.^{6,47} Since then, many studies have evaluated the need for surgical intervention of MMC-related hydrocephalus following postnatal closure of MMC, with reported VPS rates ranging from 57% to 86%. The majority of patients with shunts placed ultimately require at least 1 VPS revision during their lifetime.^{6,8,14,19,26,37,48,59,63,65}

In 1998, the first human intrauterine MMC closure was reported and the following year the first prospective human study evaluating intrauterine repair of MMC was published.^{7,56} Their findings were the foundation for the MOMS trial, which concluded that prenatal closure of

MMCs resulted in significantly lower rates of postnatal hydrocephalus, with a reported prenatal repair VPS rate of 40% versus a postnatal repair rate of 82%. Fewer motor deficits were also observed at 30 months postdelivery ($p = 0.007$). However, these patients did exhibit higher rates of preterm delivery and uterine dehiscence when compared to the postnatal surgery group.¹

In 2016, the single-arm CECAM study demonstrated that using prenatal fetoscopic techniques resulted in similar rates of postnatal CSF diversion procedures (approximately 42%) with a lower likelihood of uterine dehiscence compared to the open technique used in MOMS; however, preterm delivery rates were no different.⁴⁵

Using rigorous criteria for VPS placement, which included tolerating some ventricular dilation in the absence of clinical findings, Chakraborty et al. demonstrated that rates of VPS placement following postnatal repair (51.9%) were close to those seen in MOMS and CECAM. However, these results were retrospective in nature and did not evaluate neurological function as an outcome measure.^{11,40}

Treatment of MMC-Associated Hydrocephalus

Ventricular Shunting

The standard surgical treatment for MMC-associated hydrocephalus is ventricular CSF shunt drainage, typically to the peritoneal cavity (VPS). However, shunts carry a risk of infection and malfunction that often necessitate revisions. In 1985, Liptak et al. evaluated 67 children with neural tube defects treated with VPS and found that 30% required at least 1 shunt revision and 22% required multiple revisions.²⁸ Additional investigations report shunt malfunction rates ranging from 14.7% to 64% and shunt infection rates ranging from 2.9% to 15.3%.^{3,9,55}

Studies have attempted to assess potential risk factors predisposing to shunt malfunction. Caldarelli et al. explored shunt complications over the first postoperative year in 170 children.⁹ They demonstrated that thoracic and cervical MMCs treated with VPS were more likely to have VPS complications, whereas age and surgical modality did not significantly influence shunt patency or overall complications. In the long-term follow up of 189 hydrocephalic MMC patients, Tuli et al. observed a 64% first-shunt failure rate due to obstruction (70%), infection (24%), or loculated ventricles (4%).⁵⁵ On multivariate analysis, these investigators found female sex and concurrent surgical procedure (including nonneurosurgical procedures) had a significant increase in subsequent shunt malfunction. Our NIS failed to find sex or MMC level associated with inpatient failure rates, likely due to our ability to only capture events during initial inpatient stay. However, we did identify surgical timing and specific comorbidities as correlates to higher risk of inpatient VPS failure.

With high rates of revision due to shunt-related complications, there has been effort directed toward optimization of shunt selection. In a retrospective review of 157 patients with neonatal MMC, patients were classified according to shunt system features, including valve type, valve size/contour, and catheter type. A total of 71 patients (45.2%) underwent early shunt revision due to various complications and there was no association between complica-

TABLE 2. Hydrocephalus treatment timing

Characteristic	Overall (n = 4551)	ST (n = 1167)	DT (n = 3383)	p Value
Female	2176 (47.8)	569 (48.7)	1607 (47.5)	0.7569
Median length of stay (IQR), days	14.7 (13.5)	11.6 (12.6)	15.6 (13.6)	0.0001
Shunt infection*	115 (2.7)	14 (1.3)	101 (3.1)	0.1373
Inpatient shunt revision*	353 (8.2)	20 (1.9)	333 (10.4)	0.0002
Time period				0.0287
Early (1998–2006)	1941 (42.7)	592 (30.5)	1349 (69.5)	
Late (2007–2014)	2610 (57.3)	575 (22.1)	2034 (77.9)	
First Tx				0.2700
ETV	265 (5.8)	87 (32.8)	178 (67.2)	
Shunt	4285 (94.2)	1080 (25.2)	3205 (74.8)	
Patient race†				0.9061
White	1974 (60.6)	493 (59.2)	1481 (61.1)	
African American	374 (11.5)	94 (11.3)	279 (11.5)	
Hispanic	909 (27.9)	245 (29.4)	66 (27.4)	
Zip code income quartile, \$				0.0139
1–24,999	1301 (29.3)	249 (19.1)	1052 (80.9)	
25,000–34,999	1230 (27.7)	300 (24.4)	930 (75.6)	
35,000–44,999	1143 (25.7)	342 (29.9)	801 (70.1)	
45,000 or more	768 (17.3)	240 (31.2)	528 (68.8)	
Insurance status†				0.7104
Medicaid	2413 (57.1)	623 (56.2)	1790 (57.4)	
Private insurance	1469 (34.7)	414 (37.4)	1055 (33.8)	
Hospital region				0.8160
Northeast	792 (17.4)	172 (21.8)	620 (78.2)	
Midwest	1001 (22.0)	253 (21.7)	747 (74.7)	
South	1423 (31.3)	367 (25.8)	1056 (74.2)	
West	1335 (29.3)	375 (28.1)	960 (71.9)	
Academic hospital status	4196 (93.3)	1034 (91.3)	3162 (94.0)	0.3146
Hospital bed size				0.0292
Small	693 (15.4)	193 (17.0)	500 (14.9)	
Medium	742 (16.5)	103 (9.1)	639 (19.0)	
Large	3062 (68.1)	837 (73.9)	2224 (66.1)	

Tx = treatment.

Weighted frequencies and column percentiles displayed unless otherwise stated. Some variables may be missing data from a few patients.

* Only in patients with shunts as first treatment.

† Only a portion of patients displayed due to smaller subsets.

tions and valve type or catheter type, although small-sized valves demonstrated significantly lower rates of wound complications.²⁴

ETV

ETV is an alternative method of hydrocephalus treatment and avoids many common infection and mechanical pitfalls associated with shunting. The first small series we identified that incorporated ETVs in MMC patients was documented in 1981 by Natelson. In a series of 20 neonatal hydrocephalic MMC patients, 9 received a shunt with ETV and 11 received a shunt alone.³⁹ No revisions were needed in the shunt-ETV group, but 54% of patients treated with a shunt alone required subsequent revision.

While Natelson demonstrated the feasibility of adjunct ETV treatment for MMC hydrocephalus, it was not until 1996 when the first large series of ETVs utilized as a singular treatment for hydrocephalus was published. In 64 patients with hydrocephalic MMC, Teo and Jones reported an overall ETV success rate of 72%, with a significant difference in success rate of infants younger than 6 months of age (12.5% success rate) compared to those over 6 months of age (80% success rate).⁵⁴ Rei et al. also observed an ETV success rate that correlated directly with older patient age. Importantly, a prior VPS malfunction or infection did not contraindicate ETV.⁵⁰ Our NIS results agree with the reported high rate of early-age ETV failure rates, with a 17.5% inpatient ETV failure rate. From

FIG. 3. Timing of treatment for MMC-related hydrocephalus. **Upper:** Trend of delayed inpatient hydrocephalus treatment (DT) over time. **Lower:** Histogram of days following MMC closure until hydrocephalus treatment among those patients who were delayed.

papers we identified, the reported success rates for ETV as a primary treatment ranged from 29% to 37.5%, whereas success rates for ETV after shunt failure ranged from 50% to 92%.^{22,46,50,54} Long-term ETV outcomes after 5 years

follow-up demonstrated ETV success rates of 53.3% and 64.3% when used as a first or second treatment modality, respectively.⁵³ Long-term neurocognitive outcomes between ETV and VPS groups are similar.⁵³

In 2008, Warf and Campbell evaluated ETV with CPC of both lateral ventricles, aiming to reduce CSF production.⁶² In 93 patients with MMC who received ETV-CPC, the procedure demonstrated a success rate of 76% with no need for additional surgery (mean follow-up 19 months). Multivariable analysis showed that scarring of the choroid plexus ($p = 0.026$) or of the cisterns ($p = 0.021$) resulted in a higher failure rate, but age was not a significant predictor. In a later study, Warf et al. compared neurocognitive outcomes in MMC patients, including 55 treated with ETV-CPC, 19 with VPSs, and 19 who received no treatment. The ETV-CPC and VPS groups were similar except in receptive communication, which was better in the ETV-CPC group.⁶¹

Comparing different hydrocephalus treatment modalities, Beuriat et al. evaluated 70 patients with MMC: 32 with ETV-CPC, 20 with ETV-VPS, and 18 with VPS alone.⁴ Failure rates were 28% in the ETV-CPC group, 35% in the ETV-VPS group, and 50% with VPS alone (mean follow-up 8.5 years). Causes of failure in the ETV-CPC group were due to insufficient drainage, with 3 cases found to have a closed stoma and 6 cases found to have an enlarged stoma.

Although ETV offers an alternative to conventional VPS treatment, use of this treatment varies across centers. MMC characteristics such as dysplastic ventricular anomalies, increased ventricular floor thickness, huge massa intermedia, narrow foramen of Monro, or a narrow prepontine cistern with posterior fossa crowding are all cited characteristics that interfere with treatment success.^{4,36} In our NIS data we hypothesized that ETV treatment would increase over the time period as this has been noted at individual centers,^{12,64} but there was no change in ETV treatment over time when analyzed. It is possible that even though some centers have embraced an increase in ETV, these trends are lost when assessing the national

TABLE 3. Univariable and multivariable logistic regression of inpatient shunt failure

Variable	Univariable			Multivariable		
	OR	95% CI	p Value	OR	95% CI	p Value
Length of stay	1.02	1.01–1.03	0.0002	1.02	1.0–1.0	0.0029
Shunt infection	23.0	8.5–62.4	<0.0001	15.4	5.3–45.0	<0.0001
Jaundice	3.6	1.8–7.0	0.0002	2.9	1.5–5.8	0.0022
Tachycardia	3.9	0.9–15.7	0.0508	3.0	0.9–10.4	0.0834
Hematological diagnosis	3.1	1.6–6.2	0.0014	—	—	—
Respiratory distress	4.4	2.1–9.3	0.0001	—	—	—
Zip code income, \$*				—	—	—
25,000–34,999	1.7	0.9–3.3	0.1100	—	—	—
35,000–44,999	1.1	0.5–2.3	0.7763	—	—	—
45,000 or more	0.6	0.3–1.5	0.3167	—	—	—
Same-day hydrocephalus Tx	0.2	0.1–0.5	0.0010	0.2	0.1–0.7	0.0076

* Reference: \$1–\$24,999.

TABLE 4. Identified studies investigating time of MMC hydrocephalus treatment and complications

Authors & Year	Patients		Shunt Revisions		Infection					
					Overall		Shunt		Wound	
	DT	ST	DT	ST	DT	ST	DT	ST	DT	ST
Khattak et al., 2018	49	49	—	—	10	6	—	—	—	—
Arslan et al., 2011	29	65	—	—	1	8	1	8	—	—
Yilmaz et al., 2010	27	38	—	—	5	4	—	—	—	—
Margaron et al., 2010	245	31	34	8	50	16	16	8	34	8
Wakhlu et al., 2009	135	110	—	—	5	0	2	0	3	0
Radmanesh et al., 2009	65	46	15	8	8	5	8	5	—	—
Oktem et al., 2008	63	31	—	—	14	16	9	6	5	7
Machado et al., 2004	7	11	0	3	1	2	0	1	1	1
Miller et al., 1996	48	21	4	4	2	1	2	1	—	—
Chaddock & Reding, 1988	11	22	2	3	1	1	1	1	—	—
Hubballah & Hoffman, 1987	0	10	—	—	—	0	—	0	—	0
Epstein et al., 1985	6	6	4	1	2	2	—	—	2	2
McDowell et al., 2018	31	14	15	5	12	2	4	2	8	0
Caldarelli et al., 1996	138	26	65	8	10	6	10	6	—	—
Totals	854	480	139/551 (25.2%)	40/177 (22.6%)	121/854 (14.2%)	69/480 (14.4%)	53/772 (6.9%)	38/387 (9.8%)	53/487 (10.9%)	18/213 (8.4%)
p Value			0.5805		0.9286		0.1047		0.3736	

trends, as many other centers have not adopted ETV. We observed no difference in treatment modalities between centers when stratified by size, academic status, or region. The NIS cannot select specifically for children's hospitals with pediatric neurosurgeons, so it is possible trends at smaller numbers of centers may be obscured by the overall population. Regardless, we can conclude based on NIS data that, nationally, patients treated over the time period had a stable rate of ETV.

Time of Hydrocephalus Treatment

After the initial introduction of VPS for MMC-associated hydrocephalus, many practitioners began repairing MMCs and placing shunts in patients simultaneously.^{6,47} Since the initial paper by Epstein et al. in 1985, numerous studies have been conducted that compare DT to ST with regard to shunt malfunction rate and MMC wound infection rate.¹⁵ Many surgeons delay shunting to ensure CSF sterility prior to VPS; however, in our NIS analysis there was no difference in infection rate between ST and DT. We observed that inpatient treatment timing for hydrocephalus became increasingly delayed between 1998 and 2014. Furthermore, the number of MMC patients diagnosed with hydrocephalus who were discharged without treatment increased over the time period. Together, these findings suggest that some patients in early years who were treated with ST may never have required hydrocephalus treatment on the initial inpatient stay if DT criteria were utilized. Unfortunately, the NIS is limited to initial stay, so we were unable to determine which patients discharged without hydrocephalus treatment ultimately underwent surgery versus those with no intervention.

Table 4 displays identified hydrocephalus treatment timing studies and their associated shunt malfunction and infection rates. A few studies did not distinguish VPS infection from wound infection, therefore an overall infection count is presented as well. A total of 1434 MMC patients were identified, 854 patients underwent DT and 480 ST. The aggregate rates of shunt malfunction, overall infection, VPS infection, and wound infection did not significantly differ between the two treatment times. These aggregate conclusions agree with the majority of the single-paper conclusions. Interestingly, our NIS data somewhat contradict these aggregate conclusions, with DT patients demonstrating a higher likelihood of inpatient shunt failure, defined as return to the operating room for hydrocephalus. When days between operations was analyzed separately, each additional day between operations increased failure likelihood by 10%. The majority of the identified studies followed the patients for a long period of time, whereas our NIS data are limited to the initial inpatient follow up. We do not hypothesize that our results suggest ST superiority, as we cannot assess more long-term failure, and some patients may be able to avoid shunt placement altogether. Our data do suggest that in those patients undergoing shunt insertion during their initial hospital stay, DT patients may experience earlier shunt failures compared to those who receive ST.

Many of the identified studies investigating timing of treatment are from countries other than America and cite a socioeconomically challenged population, in which ST is preferred due to its lower economic burden.^{49,60} As one may expect, the wealthier patients in the NIS comprised a smaller portion of MMC patients and had a lower incidence of associated hydrocephalus. Unexpectedly, when

treated, wealthier NIS-MMC hydrocephalic patients were more likely to receive ST treatment.

Strengths and Limitations

Our study draws strength from its utilization of a large nationwide survey consisting of a stratified-clustered sample from many insurers intended to accurately represent the annual US inpatient population. However, the hospital sampling is not biased on available subspecialties within each institution, and hydrocephalus management may vary drastically from institution to institution. Care at academic children's centers with pediatric neurosurgery may be different than at hospitals with less specialized care, and specific hospital trends may be diluted among overall treatment trends nationwide. The NIS data also precludes incorporation of prenatal management of MMC. The NIS does not include information on MMC severity, intention to treat, and imaging. NIS analyses are limited to inpatient data and are therefore unable to assess long-term results. Additionally, the NIS analysis relies on accurate ICD-9 coding, which is error-prone.

Conclusions

The management of MMC-associated hydrocephalus has evolved over time. In the US from 1998 to 2014, hydrocephalus treatment has become more delayed and the number of patients with hydrocephalic MMC not treated on initial inpatient stay has increased. Our NIS analysis suggests that delayed treatment of hydrocephalus during initial hospitalization resulted in a higher likelihood of inpatient shunt failure. However, a meta-analysis that incorporates longer follow-up demonstrated that shunt malfunction and infection rates do not differ between delayed and simultaneous hydrocephalus treatment.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: McCrea, McCarthy, Luther. Acquisition of data: McCarthy, Sheinberg, Luther. Analysis and interpretation of data: McCrea, McCarthy, Luther. Drafting the article: all authors. Critically revising the article: McCrea, McCarthy, Sheinberg. Reviewed submitted version of manuscript: all authors. Statistical analysis: McCarthy. Administrative/technical/material support: McCrea. Study supervision: McCrea, McCarthy.

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