pediatric stroke

Analysis of Shifting Trends in Pediatric Intracranial Aneurysm Care in the United States Using a National Cohort and an Institutional Cohort

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Abstract

Purpose

The natural history of intracranial aneurysms in children markedly differs from those in adults and management is not well reported. We seek to identify treatment trends and outcomes of pediatric intracranial aneurysm patients.

Methods

Using the United States 2000-2019 Kids' Inpatient Database, we investigated treatment patterns and the effect of treatment approach, and hospital volume on mortality, length of stay (LOS), hospital charges, and discharge disposition for children with intracranial aneurysms.

We identified children with intracranial aneurysms at our institution from 2010-2020. In cases meeting criteria, management was compared to adult strategies which would be applied based on expert consensus using the Unruptured Intracranial Aneurysm Treatment Score (UIATS).

Results

Of 3,697 children with intracranial aneurysms nationally (2,506 or 68% ruptured), 1,046 (28%) were treated. Endovascular treatment increased from 44.4% of treatments to 64.0% ($p=0.001$). Outcomes are primarily associated with rupture status and comorbidities. Of the modifiable factors, endovascular approaches had a shorter LOS while low aneurysm-volume hospitals were nearly twice as likely to send patients to rehabilitation or nursing facilities ($p<0.001$).

At our institution, 33 of 119 aneurysms (14 or 12% ruptured) were treated during the study period: 20 (60.6%) endovascularly. When considering the adult UIATS schema, 63% of the pediatric aneurysms couldn't be assessed using the model, highlighting the unique nature of this population.

Conclusion

Endovascular techniques are increasingly used to treat pediatric aneurysms, but there are key differences from aneurysms in adults. This underscores a growing need to train endovascular specialists in pediatric aneurysms. Furthermore, this work demonstrates– for the first time –better

outcomes for children with aneurysms when treated at high-volume centers, further supporting establishment of centers of excellence.

INTRODUCTION

Pediatric intracranial aneurysms constitute between 0.5% and 4.6% of all intracranial aneurysms treated in the United States each year.[1–5] This small but important cohort has been found to significantly differ from the adult aneurysm population in terms of presentation, clinical course, and patient demographics.[2,6,7] Previous groups have reported a significant male predominance in affected patients, a much higher rate of re-bleed, a greater incidence of seizure at presentation, and significant differences in the commonest locations of the aneurysms.[8] Due to the rarity of pediatric cerebral aneurysms, there is currently a lack of standardization for care and sparse data on long-term outcomes. As a result, there is currently no rupture risk scale designed specifically for use in the pediatric population. The Unruptured Intracranial Aneurysm Treatment Score (UIATS) was described by Etminan et al. 2015 as a multidisciplinary Delphi consensus of 69 specialists in the decision-making for conservative management or repair of an unruptured saccular intracranial aneurysm in adults without other cerebrovascular abnormalities or connective tissue disorders.[9] Children were specifically excluded from this score development, suggesting that adult aneurysm risk-benefit analysis is difficult to extrapolate to pediatric intracranial aneurysms.

Use of endovascular aneurysm treatments has significantly increased as experience and technology have advanced.[10] Large studies have compared open and endovascular treatment paradigms in adult cerebral aneurysms,[11,12] but not in children, whether ruptured or unruptured. Given the scarcity of pediatric intracranial aneurysms, most data have been limited to small case series from individual centers, which is subject to potential selection bias and limited volumes.[13,14] To address these limitations, we analyzed data collected from the Kids' Inpatient Database (KID) from 2000-2019.

This study's objective is to identify temporal trends in pediatric practice patterns nationally compared to adult practice, and the measure impact on clinical outcomes and cost. This is used to augment single-center experience from 2010-2020, which provides granular data about features of the patient and attributes of the aneurysm that are important in risk-benefit analysis for treatment decision-making; but which requires contextualization in national practice patterns.

METHODS

KID

The Kids' Inpatient Database (KID), Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality is the largest publicly accessible pediatric inpatient care database in the United States.[15] KID data were released in a batch every three years from 1997 through 2012, 2016, and 2019. The KID was not produced for 2015 because of the transition from ICD-9-CM to

ICD-10-CM/PCS coding. At the time of our analysis, 2019 was the most recent year with KID data available.

This study identified inpatient admissions for pediatric patients with intracranial aneurysms from 2000-2012, 2016, and 2019 using the KID. Patients from 2000-2012 were identified using codes for unruptured cerebral aneurysm (437.3) and subarachnoid hemorrhage (SAH, 430) (Table 1). Children with additional diagnoses of traumatic aneurysms (900.00–904.9), aneurysm of neck (442.81), traumatic SAH (852.0-6, 852.9, 800.20-6, 800.29), or arteriovenous fistula (447.0) were excluded.

All 2016 and 2019 pediatric aneurysm admissions were identified using ICD-10 codes for cerebral aneurysm, non-ruptured (I67.1) and most non-traumatic SAH (I6000-2, I6010-22, I602, I6030-2, I604, I6050-2, I606 and I607). Since ICD-10 codes are more specific than those of ICD-9, we excluded codes for non-traumatic SAH (I608) and non-traumatic SAH, unspecified (I609). Patients who harbored both ruptured and unruptured aneurysms (n=71) were only included in the ruptured cohort throughout our analysis since ruptured aneurysms drive the course of treatment.

Table 1. ICD-9 and ICD-10 codes used to include or exclude cases

	ICD-9 codes	ICD-10 codes
Intracranial aneurysm	437.3	
Traumatic aneurysm (excluded)	900.00-904.9	
Aneurysm of neck (excluded)	442.81	
Cerebral aneurysm, non-ruptured		I67.1
Subarachnoid hemorrhage	430	
Traumatic subarachnoid hemorrhage (excluded)	852.0-6, 852.9, 800.20-6, 800.29	
Non-traumatic SAH		I6000-2, I6010-22, I602, I6030-2, I604, I6050-2, I606 and I607
Non-traumatic SAH (excluded)	I608 and I609	

All included aneurysm cases were then classified based on whether they received a workup/test for their aneurysm diagnosis (Appendix A) and whether they received endovascular (Appendix B), open (Appendix C), or no surgical treatment for their aneurysm. Patients with both endovascular and open surgeries were excluded from analyses comparing the two modalities as the outcomes could not be attributed to one modality or the other.

Institutional study population

At Boston Children's Hospital, with institutional review board approval (P00005517, Cerebrovascular Disease in Children - Natural History and Outcomes, Initial Approval Date: 8/29/2012), reports of catheter angiography, magnetic resonance imaging (MRI), and computed tomography (CT) of the head and neck from 2010-2020 were searched for "aneurysm". Data from this period was chosen because with the deployment and broader institutional integration of electronic health records

including imaging, the data marshaled for clinical decision-making was of higher quality and more consistently available than data from 2000-2010. One pediatric neurosurgeon (AS) reviewed all the cases where “aneurysm” was indicated in a differential diagnosis or there was a possibility of aneurysm noted in the imaging report. Cases that were more likely aneurysms than anything else were included. Aneurysms associated with a primary arteriovenous shunt pathology (intranidal aneurysms and feeding artery aneurysms) were excluded from analysis. Considering imaging sensitivity, 3T MRI with MRA can detect lumen irregularity in patients who have low movement artifact or general anesthesia. Even under 3mm, detection is on the order of 90% or greater.[16–18] Thus, lesions <1.3 mm were not considered definitively an aneurysm, and infundibulum was considered an alternative explanation if a vessel originated from the apex of the protuberance. Aneurysms diagnosed in patients over the age of 18 were excluded because the UIATS defines pediatric patients as being 18 years or younger.

Aneurysms were evaluated on the Unruptured Intracranial Aneurysm Treatment Score (UIATS) described by Etminan et al. 2015 (figure 1).[9] We assigned scores based, in part, on the maximum diameter, morphology, location, complexity, and growth on serial imaging of each unruptured, saccular aneurysm. For patients with multiple aneurysms, each aneurysm was evaluated separately.

The clinical and operative reports of all patients were reviewed to identify treatment recommendations, which were categorized as continued medical therapy, open microsurgical therapy, or endovascular therapy.

Contributing variables

KID provides limited patient demographic data to allow analysis of socioeconomic differences that may impact outcomes. However, they do not provide granular information regarding the aneurysm morphology or vessel configuration which may impact treatment decision-making. The attributes that are described in UIATS are therefore not evaluable in KID data. These variables previously reported as important in the treatment decision making were included for analysis in the institutional study population.

Outcome measures

Available data reporting allowed analysis of gross clinical outcomes and the cost of care. The primary outcome measured the disposition of patients, specifically whether patients were able to discharge home, termed “routine discharge”, after aneurysm care, a surrogate for a relatively favorable outcome, contrasted with what is considered “non-routine” discharge including acute rehabilitation admission, skill nursing facility admission, or death.

Secondary outcomes measured the length of stay, and the charges billed for the admission. Subgroup analysis was used to account for the impact of aneurysm rupture on case complexity and patient presentation.

KID does not provide longitudinal relationships to investigate long-term outcomes. However, we investigated additional secondary outcomes in our institutional case series including periprocedural complications and long-term findings such as delayed hemorrhage. Growth on serial imaging is included as a contributing variable in UIATS scoring, but with available granular follow-up data, it also provides an outcome metric for untreated aneurysms.

Statistical analysis

Statistical analysis was done using R version 4.1.0. Variables included in multivariable models were selected if they had a p-value less than or equal to 0.1 in univariable models. P-values were generated using the glm function quantile regression for continuous outcome variables and binary logistic regression for categorical outcome variables. The exponential of the logistic regression coefficients provided the odds ratio for categorical outcome variables.

RESULTS

KID results

In the KID cohort, 3,697 patients had non-traumatic SAH or cerebral aneurysm. Of these patients, 2,506 (68%) had non-traumatic SAH, and 1,191 (32%) had unruptured aneurysms. A total of 1,046 (28%) patients received surgical treatment for their aneurysm(s) with either endovascular or open surgery, and 2,000 (54%) patients received a workup/test for their non-traumatic SAH or aneurysm(s). Of the patients who received a workup/test, 1,205 (60%) were not surgically treated. A proportion of the patients treated did not undergo a separate diagnostic workup during the given admission encounter, such as someone presenting for an elective aneurysm treatment.

Of the 2,506 ruptured aneurysms, a total of 598 (24%) were surgically treated during the same admission: 352 (59%) endovascularly and 248 (41%) with open surgery. In the unruptured aneurysm cohort (n=1,191), 448 (38%) aneurysms were surgically treated: 287 (64%) endovascularly and 162 (36%) with open surgery. Of the 1,046 aneurysms treated amongst both cohorts, 639 (61%) were treated endovascularly and 407 (39%) with open surgery (Table 2).

Table 2. National characteristics of pediatric patients treated with endovascular and open surgeries for intracranial aneurysms

	All Treated Children	Endovascular n = 639	Open n = 407	p value†

	n = 1,046			
Age (y)				
Median (IQR)	16 (11-18)	16 (11-19)	16 (11-18)	0.4
Groups				0.7
≤ 2	74 (7.1)	42 (56.8)	32 (43.2)	
3-12	263 (25.3)	161 (61.2)	102 (38.8)	
>12	704 (67.6)	433 (61.5)	271 (38.5)	
Sex				0.07
Female	484 (46.5)	311 (64.2)	173 (35.8)	
Male	557 (53.5)	326 (58.5)	231 (41.5)	
Race				0.09
White	407 (44.6)	247 (60.7)	160 (39.3)	
Black	176 (19.3)	107 (60.8)	69 (39.2)	
Hispanic	227 (24.9)	134 (59.0)	93 (41.0)	
Asian/Pacific Islander	37 (4.1)	29 (78.4)	8 (21.6)	
Native American	9 (1.0)	5 (55.6)	4 (44.4)	
Other	56 (6.1)	42 (75.0)	14 (25.0)	
Primary Payer				0.3
Private	530 (50.8)	325 (61.3)	205 (38.7)	
Public	388 (37.2)	240 (61.9)	148 (38.1)	
Self-pay	56 (5.4)	38 (67.9)	18 (32.1)	
Other	70 (6.7)	36 (51.4)	34 (48.6)	
Income by ZIP				0.3
0-25th percentile	275 (27.1)	170 (61.8)	105 (38.2)	
26th-50th percentile	221 (21.8)	127 (57.5)	94 (42.5)	
51st-75th percentile	269 (26.5)	177 (65.8)	92 (34.2)	
76th-100th percentile	249 (24.6)	148 (59.4)	101 (40.6)	
Rupture Status				0.1
Ruptured	598 (57.2)	352 (58.9)	246 (41.1)	
Unruptured	448 (42.8)	287 (64.1)	161 (35.9)	
Years				0.001*
2000 – 2003	126 (12.0)	56 (44.4)	70 (55.6)	
2004 – 2006	194 (18.5)	118 (60.8)	76 (39.2)	
2007 – 2009	187 (17.9)	117 (62.6)	70 (37.4)	
2010 – 2012	226 (21.6)	153 (67.7)	73 (32.3)	
2016	138 (13.2)	83 (60.1)	55 (39.9)	
2019	175 (16.7)	112 (64.0)	63 (36.0)	
Mortality	55 (5.3)	29 (52.7)	26 (47.3)	0.2
Length of Stay (d)	8 (3-16)	8 (2-15)	10 (4-17)	<0.001*
Total Hospital Charge ($1000)	146.1 (75.5-280.1)	142.0 (75.9-278.4)	154.1 (74.6-281.0)	0.8

Discharge Destination				0.5
Routine	754 (72.1)	465 (72.8)	289 (71.0)	
Rehabilitation	202 (19.3)	124 (19.4)	78 (19.2)	
Other†	90 (8.6)	50 (7.8)	40 (9.8)	

All categorical data are presented as n (%) and all continuous variables as median (interquartile range). *Statistically significant. † Home healthcare, against medical advice, died. Discharge destination percentages reflect column percentages per condition.

National temporal trends (KID)

Over fifteen years, the duration of hospitalization had some fluctuation, but remained largely the same; the main determinants of hospital stay were rupture status and age (Table 3). Subgroup analysis revealed that the length of stay for ruptured aneurysms may have increased more than for unruptured aneurysms, particularly among those treated with endovascular approaches. However, over time there was a clear increase in the cost of hospitalization, even when accounting for rupture status and treatment modality (figure 2). There was a clear difference in cost between patients with ruptured versus unruptured aneurysms. However, even accounting for that, cost increases were such that the median cost of a hospitalization for an unruptured aneurysm treated by any modality in 2019 was greater than that of a ruptured aneurysm in 2000-2003 (figure 2).

Table 3. Multivariable associations with outcomes

Outcomes	**Contributory variables (coefficient/odds ratio)**		**p value**
Length of stay	Number of comorbidities (per diagnosis)	1.2	<0.001
	Endovascularly treated	-2.3	0.01
	Primary payer (compared to Medicaid)	-	0.1
	Private insurance	-	0.09
	Self-pay	-2.6	0.008
	No charge		
	Age category (compared to <2years)	-7.5	<0.001
	3-12 years	-9.1	<0.001
	>12 years		
	Rupture status: ruptured	7.5	<0.001
Total charge	Number of comorbidities (per diagnosis)	20,668	<0.001
	Year (compared to 2003)		
	2006	-	0.2
	2009	87,144	0.006

	2012	104,972	<0.001
	2016	168,649	<0.001
	2019	162,345	<0.001
	Race (compared to white)		
	Black	-	-
	Hispanic	41,381	0.05
	Asian or Pacific Islander	-	-
	Native American	-	-
	Other	90,842	0.007
	Rupture status: ruptured	106,140	<0.001
	Hospital bed size (compared to small)	-193,945	0.005
	Medium	-224,513	<0.001
	Large		
Non-routine discharge	Number of comorbidities (per diagnosis)	1.2	<0.001
	Year (compared to 2003)		
	2006	0.34	0.002
	2009	-	0.06
	2012	0.33	<0.001
	2016	0.28	<0.001
	2019	0.20	<0.001
	Race (compared to white)		
	Black	-	0.3
	Hispanic	0.55	0.01
	Asian or Pacific Islander	2.60	0.04
	Native American	-	0.4
	Other	-	0.8
	Rupture status: ruptured	2.6	<0.001
	ZIP Income (compared to 0-25 percentile)	1.8	0.03
	26-50 percentile	-	0.1
	51-75 percentile	-	0.4
	76-100 percentile		
	Hospital aneurysm volume*: high	0.42	<0.001
Death	Number of comorbidities (per diagnosis)	1.12	<0.001
	Year (compared to 2003)		
	2006	0.19	<0.001
	2009	0.16	<0.001
	2012	0.15	<0.001
	2016	0.12	<0.001
	2019	0.06	<0.001

	Rupture status: ruptured	2.43	0.02

*High aneurysm volume hospitals are the 10% of hospitals with the highest number of aneurysm admissions. Reference groups for the categorical variables: open treatment, small hospital bed size, 2003, white, age ≤ 2, midwest urban/nonteaching, high aneurysm volume. Categorical response variables list odds ratios for predictor variables and continuous response variables list coefficients for predictor variables.

The total charge associated with treatment of aneurysms has increased over time. However, the cost of treating ruptured aneurysms is increasing at a faster rate than the cost of treating unruptured aneurysms (figure 2).

The LOS for patients treated for a ruptured aneurysm with either endovascular or open surgery has increased over time. LOS for patients receiving open treatment for an unruptured aneurysm has not changed over time. Conversely, the LOS for patients receiving endovascular treatment for unruptured aneurysms has decreased over time (figure 2).

Univariable analysis (KID)

The median age of the treated cohort was 16 years (IQR: 11-19) in the endovascular cohort and 16 years (IQR: 11-18) in the open cohort (p=0.354). Between 2000 and 2019, surgeons increasingly relied on endovascular techniques to treat pediatric aneurysms (44.4% in 2000-2003 vs. 64.0% in 2019; p=0.001). Demographic information including race, insurance carrier, family income approximated by Zone Improvement Plan code and rupture status were not significantly different between the two treatment cohorts (Table 2).

Fifty-five patients died during hospitalization in the treated cohort with an overall mortality rate of 5.3%, which was significantly higher in the ruptured aneurysm group (n=45, 7.5%) than in the unruptured aneurysm group (n=10, 2.2%; p<0.001). Compared to patients with unruptured aneurysms, patients with ruptured aneurysms were nearly three times less likely to discharge to home (RR = 2.90, 95% CI = 2.24-3.74 p<0.001). Patients with ruptured aneurysms also required longer hospitalizations (median 13 versus 3 days respectively, p<0.001) at a higher cost (median $210,437 compared to $95,860, p<0.001).

For all aneurysms, length of stay (LOS) was longer in the surgical clipping group than the endovascular group (median 10 vs. 8 days, respectively; p<0.001; Table 2). There was no significant difference in mortality rate, total hospital charge, or discharge destination between endovascular and open procedures.

Multivariable analysis (KID)

The multivariate analysis (Table 3) showed that open surgery had longer LOS (2.3 days, 95% CI 0.46-4.14, p=0.01), but did not significantly impact the cost, likelihood of discharge home, or risk of death.

Ruptured aneurysms were less likely to discharge to home (OR 2.60, p<0.001) and had longer hospitalizations (coefficient 7.5 days, p<0.001). As a surrogate for patient complexity, more comorbid diagnoses were associated with longer and more expensive hospital stays and a greater chance of non-routine discharge and death (p<0.001 for all outcome variables).

Younger patients had longer hospital admissions; compared to patients younger than 3 years old, patients aged 3 to 12 had stays 7.5 days shorter (p=<0.001), while children aged 13 or older stayed 9.1 days shorter (p=<0.001).

Larger hospital size was associated with lower total charge and hospital aneurysm volume (the 90% of hospitals in the KID database with the lowest number of aneurysm admissions versus the 10% of hospitals with the highest) impacted where patients were discharged: those treated at a high-volume hospital were more than twice as likely to go home.

Single institution aneurysm experience (BCH)

At our institution, 135 aneurysms in 107 patients were identified between 2010 and 2020. Sixteen aneurysms in unique patients were excluded because the patients were over the age of 18 at time of aneurysm diagnosis. Therefore, 119 pediatric aneurysms in 91 patients were analyzed with 14 (12%) of these aneurysms having been found in the setting of intracranial hemorrhage (Table 4). These patients were followed over a median of 3.4 years (IQR: 1.5-6.1 years).

Table 4. Clinical Characteristics of Aneurysms Included and Excluded from the UIATS Model at one high-volume institution

	All Aneurysms (n=119)	**UIATS Aneurysms (n=44)**	**Non-UIATS Aneurysms (n=75)**
Age at Diagnosis (y)	11.7 (7.9 – 15.2)	12.1 (7.9 – 16.1)	11.5 (8.2 – 13.5)
Females	62 (52.1%)	26 (59.1%)	36 (48%)
Race			
White	77 (64.7%)	28 (63.6%)	49 (65.3%)
Black or African American	8 (6.7%)	4 (9.1%)	4 (5.3%)
Asian	1 (0.8%)	1 (2.3%)	0 (0%)
American Indian or Alaska Native	4 (3.4%)	0 (0%)	4 (5.3%)
Other	12 (10.1%)	3 (6.8%)	9 (12%)

Unknown	17 (14.3%)	8 (18.2%)	9 (12%)
Follow-Up (y)	3.4 (1.5 – 6.1)	2.0 (0.7 – 4.1)	4.6 (1.6 – 8.1)
Lost to Follow-Up	7 (5.9%)	5 (11.4%)	2 (2.7%)
Ruptured	14 (11.8%)	-	14 (18.7%)
Aneurysm Features			
Maximum Diameter (mm)	4 (2.4 – 7.6)	2.4 (1.8 – 3.3)	5.8 (3.4 – 8.4)
Irregular shape/lobulated	27 (22.7%)	3 (6.8%)	24 (32%)
Growth on serial imaging†	28 (31.8%)	4 (13.3%)	24 (42.1%)
Ruptured	14 (11.8%)	-	14 (18.7%)
Mycotic	5 (4.2%)	-	5 (6.7%)
Dissecting	8 (6.7%)	-	9 (12%)
Location			
Cavernous	10 (8.4%)	6 (13.6%)	4 (5.3%)
ICA	33 (27.7%)	18 (40.9%)	15 (20%)
MCA	28 (23.5%)	3 (6.8%)	25 (33.3%)
ACA	12 (10.1%)	10 (22.7%)	2 (2.7%)
Vertebrobasilar	33 (27.7%)	6 (13.6%)	27 (36%)
PICA	3 (2.5%)	1 (2.3%)	2 (2.7%)
UIATS Recommendation			
Treat	-	8 (18.2%)	-
Observe	-	21 (47.7%)	-
Equivocal	-	15 (34.1%)	-
Treatment Received			
Endo	20 (16.8%)	5 (11.4%)	15 (20%)
Open	13 (10.9%)	1 (2.3%)	12 (16%)
Observed	86 (72.3%)	38 (86.4%)	48 (64%)
Concordant w/ UIATS*	-	24 (88.9%)	-
Discordant w/ UIATS*	-	3 (11.1%)	-

*The 15 equivocal aneurysms did not receive a definitive UIATS recommendation and so were neither concordant nor discordant. †Growth data was only available for 88 patients in total because 15 patients did not have repeat follow-up imaging, and 16 patients were treated so soon after presentation that repeat imaging was not obtained before treatment. The denominator for UIATS aneurysms is 30 and 57 for non-UIATS aneurysms. Abbreviations: UIATS = Unruptured Intracranial Aneurysm Treatment Score; ICA = internal carotid artery; MCA = middle cerebral artery; ACA = anterior cerebral artery; PICA = Posterior inferior cerebellar artery.

Thirty-three aneurysms (28%) were treated surgically or with endovascular techniques, 24 (73%) of which were treated within 3 months of diagnosis. Conversely, 95 aneurysms (80%) were initially observed for at least 3 months with 9 of these (9.5%) ultimately treated over a range of 1.4-5.8 years later. Of all treated aneurysms, 9 aneurysms (27%) were treated by coil embolization and 11 (33%) were treated with endovascular stent, flow diversion, flow reversal, and/or sacrifice. A total

of 5 aneurysms (15%) were clipped and 8 (24%) were treated with open bypass, flow reversal, and/or sacrifice.

Fourteen aneurysms presented with SAH, 13 (93%) of which were treated. Six (46%) ruptured aneurysms were treated using an endovascular approach and 7 (54%) with open surgery. A total of 105 aneurysms presented without rupture. Twenty (17%) unruptured aneurysms received treatment: 14 (70%) using an endovascular approach and 6 (30%) using an open surgery approach.

UIATS analysis (BCH)

In the pediatric cohort, a majority (63%) of aneurysms were excluded from the UIATS application because the aneurysm was ruptured (n=14), mycotic (n=5), dissecting (n=9), fusiform (n=37), or associated with moyamoya arteriopathy (n=11). Excluding the ruptured aneurysms, 58% (n=61) of unruptured aneurysms in children are atypical in that they fall outside the rubric of UIATS. 44 aneurysms (37%) met all inclusion criteria (excluding patient age) of the adult UIATS Model, and 29 (66%) of these cases would score on UIATS with a definitive management recommendation (Table 4). 8 (18.2%) had a UIATS recommendation of treatment. The model recommended conservative management for 21 (47.7%) aneurysms. The actual treatments administered were concordant with the UIATS recommendations in 24 aneurysms (89%) and discordant in 3 (11%). Two of the discordant aneurysms were treated conservatively. Of the 15 aneurysms with equivocal scores, 13 (87%) were treated conservatively.

Discordant case review

We reviewed the three cases at our institution where the management deviated from the UIATS treatment recommendation. One infant, with an elastin mutation and congenital heart disease, presented with a 5.2mm, partially thrombosed aneurysm of the left supraclinoid internal carotid artery. Although there was growth of the aneurysm over one month, the patient's young age and significant comorbidities led our surgeons to take a conservative approach while the UIATS model recommended surgical intervention. At last follow-up, the aneurysm has stabilized with no bleed.

The second discordant case was a patient in the second decade of life with sickle cell disease (SCD) whose 2.8mm, wide-necked aneurysm of the left superior cerebellar artery was diagnosed during screening for stem cell transplantation (SCT).[23,24] Posterior reversible encephalopathy syndrome (PRES) is a potential complication of SCD that is associated with systemic hypertension and potentially greater aneurysm rupture risk and is more common during SCT.[25,26] Therefore, we coiled the aneurysm in opposition to the UIATS recommendation to observe. In considering pediatric intracranial aneurysm care, it may be appropriate to modify the UIATS: similar to the "Aneurysm" features under the category "Other" in the UIATS model, there may be comorbid conditions or

treatments associated with a higher aneurysm rupture risk which could score in favor of aneurysm repair. Rapid advances may introduce uncertain risks: it is unclear if these concerns hold true with recently FDA-approved cell-based gene therapies (exagamglogene or lovotibeglogene autotemcel) for SCD.

Finally, a child in the first decade of life with a history of epilepsy, left middle cerebral artery (MCA) stroke and right posterior watershed infarcts was also found to have a 3.5mm, wide-necked aneurysm of the left MCA that had grown over time. While the UIATS model favored surgical treatment based on aneurysmal growth and epilepsy, our surgeons favored conservative management due the small size and positioning of the aneurysm on the same hemisphere as the stroke. We have observed decreased proximal artery caliber ipsilateral to large strokes due to flow-dependent constrictive vessel remodeling over time and postulate that this is associated with less flow-related mural stress on aneurysms of the constrictively remodeled parent artery. This aneurysm has not ruptured in over 9.5 years and has not grown in the past 2.9 years of follow-up.

Outcomes and follow-up (BCH)

Of the 95 initially observed aneurysms, 7 were lost to clinical follow-up and 81 had serial imaging. Twenty-three (28.4% of those with imaging) demonstrated growth on serial imaging and 9 (11.1%) were subsequently treated with either endovascular (n=7) or open surgery (n=2) over a median follow-up of 3.3 years (IQR: 1.4-5.8 years). None of the conservatively managed unruptured aneurysms bled during a median follow-up of 3.9 years (IQR: 1.6-6.1 years).

DISCUSSION

We have analyzed a wide range of granular factors influencing the management and outcomes of pediatric intracranial aneurysms using both a national clinical database and the detailed records from one pediatric institution. Our institution, and others across the country, often apply strategies similar to adult centers in assessing typical cerebral aneurysms, including increasing application of endovascular treatments. Of note, not all children need surgical treatment for their cerebral aneurysm.[19,20] We manage the majority of our aneurysms (~75%) with observation alone, which is similar to the national pattern for children, but higher than for adults.[12,18,21]

National differences in adult and pediatric aneurysm care

This work not only reinforces the intuition that pediatric intracranial aneurysms are different than intracranial aneurysms in adults, but – for the first time – provides clear delineation of these differences in a way not previously reported.

One of the key findings from this work is the importance of long-term follow-up in pediatric aneurysm patients, as 10% of aneurysms eventually undergo treatment for change in features. This is on the same order of magnitude as adult aneurysms, which have been observed with a 2-4% incidence of growth over each year follow-up.[26] Another important distinction between children and adults that was validated in this study is that nearly two-thirds of aneurysms in children are different in etiology from the typical saccular aneurysms most commonly present in adults, with distinct natural history and management considerations.

Common considerations in the management of adult aneurysms include the risks of treatment, structural features of the aneurysm, and comorbid disease that can alter the risk of procedures and life expectancy.[9] It is important to note that the types of comorbid disease identified in children in this study were found to be very different than those present in adults, such as autosomal dominant polycystic kidney disease, neurofibromatosis type I, Marfan syndrome, multiple endocrine neoplasia type I, pseudoxanthoma elasticum, hereditary hemorrhagic telangiectasia, and Ehlers-Danlos. However, in adults, aneurysms associated with these syndromes account for less than 1% of all aneurysms, compared to 10% in this pediatric cohort.[27]. This is critical to recognize, as different risk factors may correlate with different etiologies of aneurysm formation and natural histories of rupture risk. In particular, aneurysms in young children may occur from a developmental or embryological event that has a lower risk of ongoing pathogenesis, rather than from chronic mechanical or inflammatory stress observed in adults.[22]

Finally, treatment outcomes for aneurysms in children are not as well studied as in adults, and endovascular devices have not been formally evaluated in the rigorous manner applied to adults. Off-label use is a common practice and is applied at our center based on analogous indications from adult studies. Based on the data from our center reported here and the data we have analyzed from the KID database, it can be inferred that many US centers also utilize this approach to endovascular treatment in children. As a consequence, this report highlights the need to perform more coordinated study of this ad hoc approach in order to better characterize safety and efficacy.

A need for pediatric-specific risk assessment tools

This study found a 93.2% (41 of 44) rate of concordance between the recommended course of treatment at our institution and the UIATS recommendation for the one-third of patients who fit the inclusion criteria for the UIATS model. The impact of age on treatment decisions in children is non-linear and involves varying technical risk and device feasibility. Furthermore, children with aneurysms often have comorbid diseases or syndromic associations which can increase or decrease the aneurysm risk in various scenarios. The paucity of data on pediatric intracranial aneurysms precludes a pediatric-specific aneurysm grading scale but this study underscores that adult frameworks are poorly generalizable to children. The finding is important as it distinguishes

pediatric patients as a pathophysiologically distinct cohort that can benefit from subspecialization of pediatric-trained physicians.

Factors that impact outcomes in pediatric aneurysm care

Patient age and aneurysm rupture status

Similar to the care of adult patients, ruptured aneurysms in children require longer hospitalizations and have worse function at discharge. In addition, younger patients had longer hospital stays, an effect as significant as the rupture status.

Insurance effects on disposition and length of stay

There were no differences in race or hospital region with regard to insurance status in this cohort of patients. Although race had a significant impact on payer status, payer status did not impact disposition at discharge but did have a small impact on a patient's length of hospital stay. Patients reporting Hispanic race and other unspecified race had more expensive hospitalizations. Despite this, Hispanic patients had a lower rate of non-routine discharge, while Asians or Pacific Islanders had a higher rate of non-routine discharges. Hagerty et al. reported increased mortality in pediatric neurosurgery patients without insurance. Additionally, patients with private insurance had a shorter LOS and had higher rates of favorable discharge.[27]

Health equity initiatives at individual institutions such as the Center for Diversity and Health Equity at Seattle Children's Hospital are beginning to demonstrate the significant modifiable determinants of patient outcomes. In addition, there is a growing body of literature to suggest that centers of excellence focused on complex cerebrovascular disorders can not only improve clinical outcomes but also help to mitigate inequalities associated with race and socioeconomic status.[28] This data suggests similar factors exist in the care of children with intracranial aneurysms.

Hospital volume

Although the previously discussed features are not necessarily modifiable for an individual case, we did find that the treating hospital has an impact on outcomes. The top 10th percentile of hospitals, in terms of the annual number of intracranial aneurysms managed, were more than twice as likely to discharge patients directly to home when compared to lower-volume centers. Hospitals with more experience in treating pediatric aneurysms are significantly more likely to have a child have an uncomplicated return to home rather than requiring a transfer to a rehabilitation hospital or other outcome, including death.

Hospital volume has been associated with outcomes in other pathologies requiring elective cerebrovascular surgery and/or urgent hospitalization for intracranial hemorrhage. In 2016, Titsworth et al. found that patients at higher volume centers successfully discharged patients with

moyamoya routinely, back to home, whether or not a patient undergoes surgery, and with a shorter LOS and lower cost.[29] Similarly, for pediatric cerebral arteriovenous malformations, high-volume centers had fewer non-routine discharges, lower charges and fewer surgical complications.[30] Combined with the findings presented here, there is a growing body of evidence derived from national databases that strongly supports the development of centers of excellence for pediatric cerebrovascular disease.

This is one of the most critical findings of this work, as insurers often mandate in-network care as a (presumed) cost containing measure. However, it is increasingly apparent that regionalization of care in centers of excellence for complex conditions like pediatric cerebrovascular disease provides outcomes that are better – with shorter length of stay, fewer complications and lower death rates – and does so at a significantly lower cost than low-volume centers. This evidence supports care for children at high-volume[3,8,17,21,22,31–35] centers that give them the best chance at survival, while also providing significant cost savings to the insurer and family.

Strengths and Limitations

A key strength of this study is the comparison of findings in the national database to the practice patterns of a dedicated pediatric institution. The data from our institutional review strongly correlates with national patterns revealed in our KID analysis, which may support the generalizability of the findings.

However, this data set is composed of two distinct retrospective data sources and is therefore subject to the reliability and precision of reported data from each. Fortunately, several findings were similar between the two datasets, such as the proportion of aneurysms treated, and the proportion of aneurysms treated using endovascular techniques. Since the datasets were created with different techniques, they are less likely to be subject to the same systematic errors. For example, the national dataset is limited by the reliability of coding. However, the radiographic diagnosis of intracranial aneurysms from our institutional review of imaging is not dependent on coding.

The rarity of pediatric aneurysms means that any large cohort of aneurysms will be collected over a duration of evolving medical knowledge and advancing clinical technology. The data were collected over a period of 10 years at our institution, and 19 years for the national dataset.

Future Directions

Given the utility of the UIATS aneurysm treatment paradigm grading system in adults and its lack of applicability in the pediatric population, fruitful next steps would include the development of a grading scale analogous to UIATS for children and verification of such a scale.

CONCLUSION

Management of intracranial aneurysms in adults may not be generalizable to children, although trends in treatment reflect a similar benefit from advances in endovascular technology. For the subset of pediatric intracranial aneurysms that appear similar to saccular aneurysms in adults, similar management principles may apply, but for nearly two thirds of pediatric cases, management requires individualized consideration of risks and benefits. A mortality rate of 2.3% for the treatment of unruptured aneurysms supports and emphasizes this point. Importantly, there is a significant clinical benefit to management by high-volume centers with particular experience in the care of pediatric intracranial aneurysms.

STATEMENTS AND DECLARATIONS:

Statement of ethics:

Study approval statement: This study protocol was reviewed and approved by our local Institutional Review Board (IRB), protocol approval number IRB-P00027869.

Consent to publish statement: Local IRB determined this research met regulatory requirements necessary for waiver of informed consent/authorization.

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

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Data availability statement: The KID is the largest publicly available all-payer pediatric inpatient care database in the United States. The institutional data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants. Further inquiries can be directed to the corresponding author.

Abbreviations: SAH = subarachnoid hemorrhage; KID = Kids' Inpatient Database; LOS = length of stay; UIATS = Unruptured Intracranial Aneurysm Treatment Score; OR = odds ratio; CI = confidence interval; ICD-CM = International Classification of Diseases Clinical Modification; AVF = Arteriovenous fistula; RR = relative risk; IQR = Interquartile regression; MCA = middle cerebral artery. Posterior reversible encephalopathy syndrome (PRES).

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Figure Legend

Figure 1. Unruptured intracranial aneurysm treatment score including and quantifying the key factors for clinical decision-making in the management of unruptured intracranial aneurysms.[9]

Figure 2. Multivariate regressions of the total cost (left) and length of hospital stay (right) of all pediatric intracranial aneurysm admissions in the Kids' Inpatient Database separated by rupture status and treatment approach.