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ORIGINAL ARTICLE

Survey of practice patterns and preparedness for endovascular therapy in acute pediatric stroke

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Abstract

Purpose Endovascular therapy benefits selected adults with acute stroke while data are lacking for children. The purpose of this study was to assess physician practice and institutional preparedness for endovascular therapy in pediatric stroke.

Methods A link to an anonymous online survey was sent to members of the International Pediatric Stroke Study (IPSS) group about physician experience with endovascular therapy, likelihood of treatment for provided clinical vignettes, and institutional readiness for the delivery of endovascular therapy to children.

Results Thirty-one pediatric physicians with a mean of 11 years (SD 7.1) of experience responded. All but two would consider endovascular therapy in a child, and 20 (64.5%) had recommended endovascular therapy for a child in the preceding year. Most ($n = 19$, 67.9%) did not commit to an age minimum for endovascular therapy. Sixteen (57.1%) would consider treatment up to 24 h after symptom onset with 19 (67.9%) respondents reporting that their practice changed after the 2018 American Heart Association guidelines extended the time window for endovascular therapy in adults. Seventeen (60.7%) preferred imaging that included perfusion in children presenting beyond 6 h. Nineteen (70.4%) had institutional endovascular therapy criteria. Physicians in larger pediatric groups had more "likely to treat" responses on the clinical vignettes than physicians working in smaller groups (11.7 vs. 6.1, $p < 0.05$).

Conclusion Pediatric stroke physicians are largely willing to consider endovascular therapy with most changing their practice according to adult guidelines, though experience and selection criteria varied. These findings may help to inform consensus guidelines and clinical trial development.

Keywords Childhood stroke · Embolism · Critical care · Endovascular therapy

Introduction

Acute reperfusion therapies including intravenous tissue plasminogen activator (IV tPA) and endovascular therapy have become standard of care in adult stroke. These therapies are potentially beneficial when there is *mismatch*: the presence of ischemic but not yet infarcted tissue supplied by an occluded vessel. Mismatch is established by demonstrating difference

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between measurements of the infarct core and the critically hypoperfused tissue (infarct core + ischemic but not yet infarcted tissue). The core can be measured by the volume of abnormality on diffusion-weighted imaging, amount of hypodensity on head CT as measured by Alberta Stroke Program Early CT Score (ASPECTS, scored 0–10, with higher scores indicating less infarcted tissue), or perfusion imaging. The area of critically hypoperfused tissue can be measured by perfusion imaging and is reflected in the clinical deficit as measured by National Institutes of Health Stroke Scale (NIHSS, Fig. 1).

The 2015 American Heart Association (AHA) guidelines recommended endovascular therapy for adults with large vessel occlusion (LVO) presenting within 6 h, with an ASPECTS of ≥ 6 and an NIHSS of ≥ 6 [8]. These guidelines indicated that endovascular therapy may be reasonable for children within 6 h of stroke symptom onset, though no trials have evaluated the safety or efficacy of endovascular therapy in children. A review of 44 children treated with mechanical thrombectomy reported good outcomes in 80% [3], and another review of 29 cases reported good outcomes in 87% [10], though there was overlap between the studies. Publication bias, previously shown to be evident for pediatric tPA [2], is likely present in published pediatric endovascular cases as well.

Two randomized controlled trials, DAWN and DEFUSE 3, demonstrated efficacy of endovascular therapy up to 24 h after stroke onset by selecting adults using imaging and clinical criteria to demonstrate mismatch [1, 7]. These studies informed the 2018 AHA guidelines which extended the endovascular window to 24 h for some adults with stroke but did not specify whether the window should be extended in children [9]. The 2019 AHA pediatric scientific statement recommends that endovascular treatment should be limited to "larger children" with confirmed large artery occlusion if they have persistent severe deficit (NIHSS, score ≥ 6). No specific recommendations are made for implementation of perfusion imaging as a tool for endovascular treatment selection in children [4].

The goal of this study was to assess pediatric stroke physicians' practice patterns related to endovascular treatment of pediatric stroke and to determine reported institutional readiness across different types of pediatric facilities, to help frame the development of consensus guidelines or future trials.

Methods

We conducted an online survey of the International Pediatric Stroke Study (IPSS) physician members in March 2019. The IPSS includes 58 centers and 185 physicians from 20 countries. Participants were emailed a link to a REDCap electronic survey. We requested that only physicians who manage acute pediatric stroke respond. The survey was anonymous; however, respondents were asked to enter a code corresponding to

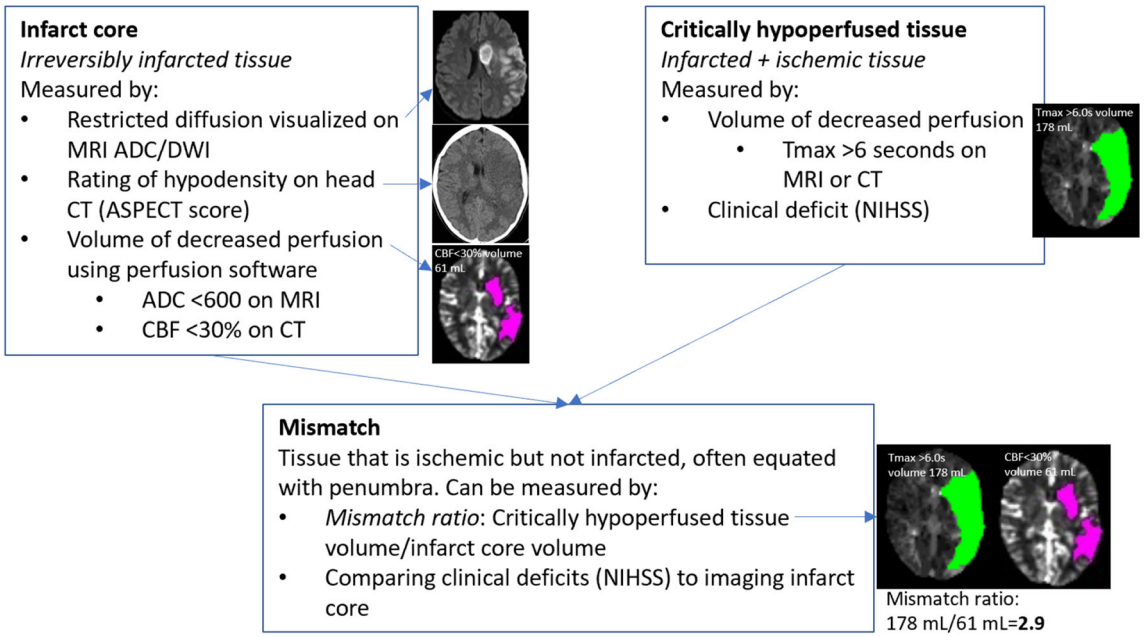

Fig. 1 Assessing infarct core, critically hypoperfused tissue, and mismatch. Methods of measuring the infarct core, critically hypoperfused tissue, and mismatch with example images from a teenager with acute stroke showing infarct core (pink), critically hypoperfused tissue (green), and calculation of mismatch ratio, using RAPID software®. ADC, apparent diffusion coefficient; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CBF, cerebral blood flow; CT, computed tomography; DWI, diffusion-weighted imaging; MR, magnetic resonance; NIHSS, National Institutes of Health Stroke Scale; Tmax, time to the maximum of the residue function (measure of perfusion delay)

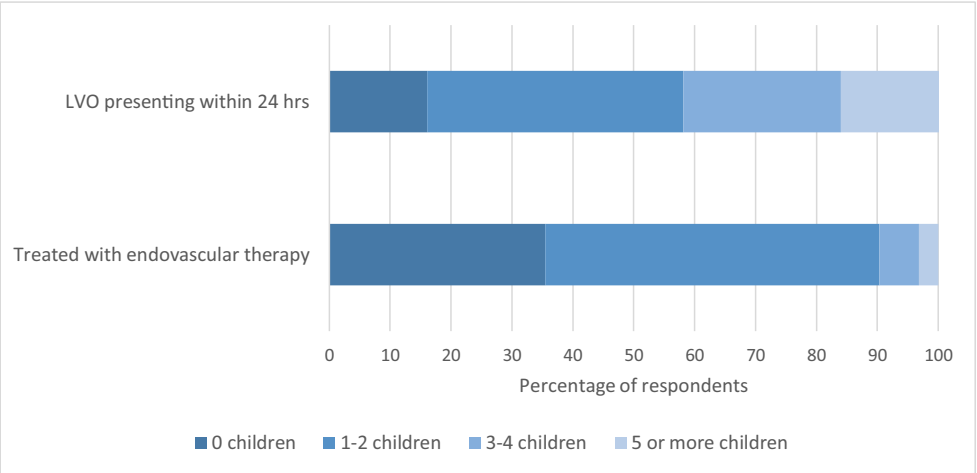

Fig. 2 Reported number of children presenting with large vessel occlusion and treated with endovascular therapy. Percentage of respondents reporting the number of children presenting to their institution from January 2018 to the time of the survey with large vessel occlusion within 24 h of symptom onset (top) and the number of children treated in that time frame with endovascular therapy (bottom). LVO, large vessel occlusion

their institution in order to determine how many institutions were represented.

Endovascular therapy was defined to include intra-arterial tissue plasminogen activator (IA tPA) or mechanical intervention to remove a clot. The survey contained 65 items covering physician background, physician experience with endovascular therapy, endovascular therapy criteria, institutional factors, and 27 clinical vignettes asking about likelihood of treatment with endovascular therapy using a 3-point Likert scale (unlikely, uncertain, and likely), in children of varied ages (2, 5, and 12 years), time since stroke onset (6 and 16 h), and perfusion mismatch ratio (1.5, 2.5), where mismatch ratio is the volumetric ratio of hypoperfused to infarcted tissue. These perfusion ratios were used as they fell below and above the 1.8 ratio used as a criterion for treatment in the DEFUSE 3 study [1]. There was an additional scenario of a child with congenital heart disease who presented within the adult IV tPA treatment window, which addressed the likelihood of subsequent treatment with endovascular therapy. Physicians were also asked if their practice regarding endovascular therapy in children had changed since DAWN/DEFUSE 3 and the 2018 AHA guidelines (see Online Resource 1 for complete survey).

The datasets generated during the current study are available from the corresponding author upon reasonable request. This study was approved by the Institutional Review Board at Oregon Health & Science University.

Statistical analysis

Standard descriptive analyses were used to describe results. Multiple choice responses were collapsed to dichotomous variables, and chi-squared analyses were used to explore associations. Fisher's exact test was used if cell counts were predicted to be less than 5. The number of vignettes for which a respondent marked "likely to treat" was summed for the total likely to treat responses. Student's *t* test was used to explore predictors of the likelihood to treat sum. Analyses were performed using STATA version 15.0 software (Stata Corp., College Station, TX). Study data were collected and managed using REDCap electronic data capture tools.

Results

Thirty-one responses were received; 22 of these were complete, 5 were complete except the vignettes, and 4 completed part of the survey and none of the vignettes. Eleven countries were represented, with 19 (61.2%) respondents from the USA, 2 (6.5%) from Canada, and 2 (6.5%) from Chile. The other countries represented had a single respondent (Argentina, Australia, Austria, Columbia, India, Serbia, Uruguay, and Spain). There were 30 institutions represented with two respondents from the same institution.

Physicians had a mean of 11.0 years (SD 7.1) of experience treating pediatric stroke. Twenty-six (92.9%) physicians would consider treatment of children with endovascular therapy. One physician would not consider treating, and one was uncertain. Since January 2018, 11 (35.5%) had not treated any children with endovascular therapy, 11 (35.5%) had treated 1 child, 5 (16.1%) had treated 2 children, and 4 (12.9%) had treated 4 or more. Figure 2 reports the number of children presenting to the respondent's institution since January 2018 with large vessel occlusion within 24 h of symptom onset and the number of children treated at the institution with endovascular therapy.

Of the 20 physicians who had treated a child with endovascular therapy from January 2018 to March 2019, 12 (60%) reported the use of both stent retrievers and aspiration devices, 2 (10%) reported use of just stent retrievers, 5 (25%) reported use of just aspiration devices, and 1 (5%) reported use of a stent for an intracerebral dissection. Three respondents reported use of IA tPA with embolectomy (3 total

Table 1 Physician background and preferences for endovascular therapy in acute pediatric stroke

Parameter	Physicians *n* (%) (*n* = 31)
Specialty	
Pediatric neurology	22 (71.0)
Pediatric neurointensive care	4 (12.9)
Pediatric neuroradiology	2 (6.5)
Hematology	3 (9.7)
Age minimum (years)*	
1	1 (3.6)
2	6 (21.4)
4	1 (3.6)
No age minimum or uncertain	19 (67.9)
Time window (anterior circulation)*	
< 6 h	3 (10.7)
< 8 h	2 (7.1)
< 16 h	1 (3.6)
< 24 h	16 (57.1)
No established time window	6 (21.4)
Time window (posterior circulation)*	
< 12 h	3 (10.7)
< 24 h	10 (35.7)
No established time window	15 (53.6)
NIHSS minimum†	
NIHSS minimum 4	2 (7.4)
NIHSS minimum 6	9 (33.3)
No minimum, but deficits must be significant	5 (18.5)
Depends on clinical scenario	9 (33.3)
Uncertain	2 (7.4)
Imaging preference within 6 h*	
CT/CTA	2 (7.1)
CT/CTA/CT perfusion	3 (10.7)
MRI/MRA	7 (25.0)
MRI/MRA/MR perfusion	10 (35.7)
Case-dependent	6 (21.4)
Imaging preference after 6 h*	
CT/CTA	1 (3.6)
CT/CTA/CT perfusion	6 (21.4)
MRI/MRA	3 (10.7)
MRI/MRA/MR perfusion	11 (39.3)
Case-dependent	7 (25.0)
Adult neurology involved in pediatric stroke†	
Sometimes	17 (63.0)
Never	10 (37.0)

Reported physician background and treatment criteria for endovascular therapy

CT computed tomography, *CTA* computed tomography angiography, *IV tPA* intravenous tissue plasminogen activator, *MRA* magnetic resonance angiography, *MRI* magnetic resonance imaging, *NIHSS* National Institutes of Health Stroke Scale

*3 missing values (28 respondents)

† 4 missing values (27 respondents)

Table 2 International Pediatric Stroke Study institutional characteristics

Parameter	*n* (%) (*n* = 27)
Type of hospital	
Stand-alone pediatric hospital	9 (33.3)
Pediatric, affiliated with adult hospital	17 (63.0)
Pediatric unit in adult hospital	1 (3.7)
Program size (number of pediatric neurologists)	
0–10	12 (44.4)
11–20	7 (25.9)
> 20	8 (29.6)
Location of endovascular therapy	
Children's hospital	15 (55.6)
Hospital adjacent to children's hospital	4 (14.8)
Off-site hospital (transport via ambulance)	6 (22.2)
Direct to adult hospital	1 (3.7)
Not offered	1 (3.7)
Post-endovascular therapy treatment location*	
Always children's hospital	15 (71.4)
Always adult hospital	0
Children's hospital or adult hospital	6 (28.6)
Endovascular therapy operator	
Pediatric neurointerventionalist†	7 (22.6)
Adult neurointerventionalist‡	20 (64.5)
Institutional endovascular therapy guidelines	
In place	19 (70.4)
In development	6 (22.2)
Neither in place nor in development	2 (7.4)
Institutional endovascular therapy workflow procedures	
In place	14 (51.9)
In development	11 (40.7)
Neither in place nor in development	2 (7.4)

Reported characteristics of the institutions of responding physicians

† Primarily/exclusively treat children

‡ Primarily treat adults with comfort treating children

*Out of 21 total respondents

children treated) since January 2018, one reported use of IA tPA without embolectomy (one child), three respondents reported use of IV tPA in addition to embolectomy (9 total children treated), and 7 reported using IV tPA without embolectomy (9 total patients treated).

When asked about reasons for not treating children who presented with LVO within 24 h, age was the most common reason (29.0%), followed by large infarct core volume (22.6%), patient comorbidities (22.6%), risk of treatment (16.1%), minor stroke symptoms/low NIHSS (16.1%), lack of preparedness or protocols (12.9%), lack data in children (9.7%), vasculopathy (6.5%), presentation beyond 6 h (3.2%), and lack of salvageable tissue (3.2%). When asked how the safety of endovascular therapy in children compares with adults, 18 (64.3%) were uncertain, 2 (7.1%) felt it was less safe in children, 7 (25.0%) felt the safety was equal, and 1 (3.6%) responded that endovascular therapy was safer in children. Four respondents commented on the risk of endovascular therapy in a child with vasculitis or focal cerebral arteriopathy and 5 commented on the importance of an experienced neurointerventionalist ("safety is in the operator").

Most (*n* = 19, 67.9%) respondents did not have a set age minimum. A majority (*n* = 16, 57.1%) would consider treating children with anterior circulation LVO up to 24 h after symptom onset, and 67.9% of respondents reported that their practice changed after the DAWN and DEFUSE 3 publications extended the time window for endovascular therapy in adults [1, 7]. Seventeen respondents (60.7%) opted for imaging that included perfusion in children who presented beyond 6 h (Table 1). Most responding physicians (63%) practiced in a pediatric hospital affiliated with an adult hospital. Physicians reported that children were most often treated with endovascular therapy at a children's hospital (*n* = 15, 55.6%). Institutional and workflow characteristics are presented in Table 2.

The 22 respondents who completed the vignettes did not differ in their years of experience or the number of cases treated in the previous year compared with those who did not complete the vignettes. When presented with a scenario of a 5-year-old, 8 months post-Fontan, 2 h after onset of acute hemiplegia with an NIHSS score of 10, 19 (70.4%) physicians reported being likely to give IV tPA. If this child did not improve at 3 h after symptom onset, with an ASPECTS of 8 and an M1 occlusion, 23 (85.2%) of physicians reported being likely to treat with endovascular therapy. When this scenario was presented with the child treated with low–molecular weight heparin, presenting at 3 h with the same ASPECTS, NIHSS score, and M1 occlusion, 16 (72.7%) physicians were likely to treat with endovascular therapy. Vignettes responses are shown in Fig. 3.

We explored predictors of the total number of "likely to treat" responses on the clinical vignettes. Physicians who had treated more children with endovascular therapy in the preceding year had a higher number of "likely to treat" responses on the vignettes (11.4 vs. 3.0, $p < 0.01$). Physicians working in larger pediatric neurology groups (> 10 neurologists) had more "likely to treat" responses than those working in groups of less than 10 (11.7 vs. 6.1, $p < 0.05$). Respondents who had established institutional endovascular criteria trended towards having more "likely to treat" responses (11.3 vs. 6.2, $p = 0.08$).

Discussion

This is the first reported survey of pediatric neurologists' views on endovascular therapy for acute pediatric stroke.

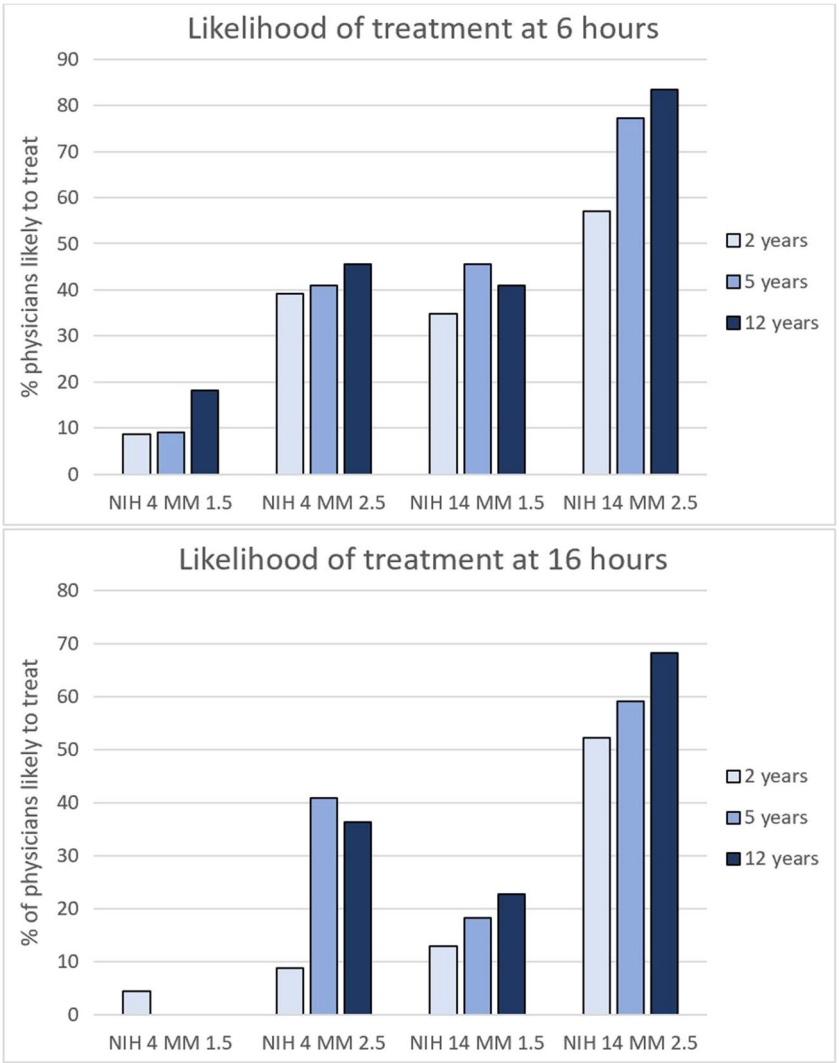

Fig. 3 Reported likelihood of treatment for clinical vignettes. Physicians were asked about likelihood of treating a child given age, time from presentation mismatch ratio on perfusion imaging, and National Institutes of Health Stroke Scale. The percentage who reported being likely to treat is reported. NIH, National Institutes of Health Stroke Scale; MM, mismatch ratio on perfusion imaging

Children infrequently presented with LVO within 24 h, with most physicians reported three or fewer such children presenting in the previous year. Responding physicians gain limited experience with endovascular treatment of children, with 35.5% referring no children for endovascular therapy in the preceding year. However, all but two respondents were willing to consider use of endovascular therapy in a child.

This study found that pediatric neurologists take into account a child's age, clinical deficit, time since symptom onset, mismatch ratio on perfusion imaging, capability of the neurointerventionalist, and stroke etiology, particularly vasculopathy when deciding about treatment with endovascular therapy. Decision-making was not generally altered if tPA had been given. Though most respondents did not commit to an age minimum for treatment with endovascular therapy, in the clinical vignettes, more than half of responding physicians reported being likely to treat a 2-year-old with a large perfusion mismatch ratio and high NIHSS score at 6 h. Eleven published reports exist of children under 5 years of age and as young as 9 months, treated with endovascular therapy from 2013 to 2018, with favorable outcome in 7 cases [11]. The size of pediatric cervical and intracranial large vessels grows rapidly at young ages, reaching 94% of adult size by age 5 [6]. While these reports suggest that very young children can be successfully treated, the overall safety and efficacy of endovascular therapy compared with natural history in very young children is unknown.

More than half of respondents reported willingness to consider endovascular therapy for a child presenting up to 24 h after onset of symptoms with an anterior circulation LVO, acknowledging a change of practice after the 2018 AHA stroke guidelines extended the time window [9]. The DEFUSE 3 study treated patients at 6–16 h with a mismatch ratio of 1.8 or more [1]. The DAWN study selected patients at 6 to 24 h with mismatch of clinical symptoms based on NIHSS and core infarct volume on imaging [7]. The strength

of the findings (NNT 2.8–4) argues for the importance of selecting adults with salvageable brain tissue. The clinical vignettes demonstrated that many responding physicians were willing to treat children with high NIHSS scores and perfusion mismatch ratios whether they presented at 6 h or 16 h. This contrasts to a previous survey distributed in 2018 to the IPSS members in which only 6% of respondents considered treating with endovascular therapy beyond 8 h [13]. The reliance on perfusion imaging to guide decision-making in an extended time window is problematic in children in whom perfusion imaging may not have the same meaning or for whom perfusion imaging is not obtained. Future research should focus on understanding the role of perfusion imaging in predicting outcomes and treatment decisions.

Responding physicians report increasing preparedness for endovascular therapy, though challenges and barriers remain. In the 2018 survey to IPSS members, 48.5% had institutional endovascular therapy guidelines in place, as compared with 70.4% in the current survey [13]. However, not every physician reported being able to offer endovascular therapy to children and the process of getting a child to endovascular therapy varied, with about 22.2% of physicians reporting that children would need an ambulance ride from the pediatric to adult facility for treatment. Furthermore, responding physicians raised safety concerns in treating children with endovascular therapy. Vasculopathies are a common cause of pediatric stroke [14], some of which may masquerade as LVO and could increase the risk of endovascular therapy. To safely and effectively offer endovascular therapy to children, it is important to consider pre-hospital triage [12], pediatric stroke center designations, and formation of multidisciplinary working groups including pediatric and adult neurologists [5].

Respondents often marked "uncertain" when asked about treatment criteria and only 22 of 31 respondents completed clinical vignettes. When endovascular therapy is being considered for a child, the decision is the result of a conversation between the neurointerventionalist, adult neurologist, pediatric neurologist, and other pediatric subspecialists, who are making a decision based on adult stroke data, clinical experience, and limited data about pediatric stroke. Pediatric stroke physicians are appropriately uncertain when deciding to treat a child with endovascular therapy. As we will continue to have unsatisfying data to drive these decisions, there should be efforts to improving the decision-making process and the conversations between clinicians.

These results should not be interpreted as consensus for treatment but rather reflect the self-reported practice and views of individual members who responded to this survey. Results are limited by the small number of respondents and low response rate. Pediatric neurologists may not have known or may not recall all the details of children who had been treated with endovascular therapy in the past, limiting the reliability of these results. Response bias may have overrepresented perspectives favorable towards endovascular therapy. Responses may not reflect the practice of pediatric neurologists who do not participate in the IPSS.

Conclusion

Pediatric stroke physicians are willing to consider endovascular therapy for acute stroke in children, with most changing their practice after recent adult guideline updates and increasing their preparedness, though uncertainties remain given the lack of pediatric-specific data. These findings may help to inform consensus guidelines and clinical trial development.

Compliance with ethical standards

This study was approved by the Institutional Review Board at Oregon Health & Science University.

Conflict of interest The authors declare that they have no conflict of interest.

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