ORIGINAL ARTICLE

Pediatric Hyperacute Arterial Ischemic Stroke Pathways at Canadian Tertiary Care Hospitals

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ABSTRACT: ***Background:*** Childhood acute arterial ischemic stroke (AIS) is diagnosed at a median of 23 hours post-symptom onset, delaying treatment. Pediatric stroke pathways can expedite diagnosis. Our goal was to understand the similarities and differences between Canadian pediatric stroke protocols with the aim of optimizing AIS management. ***Methods:*** We contacted neurologists at all 16 Canadian pediatric hospitals regarding AIS management. Established protocols were analyzed for similarities and differences in eight domains. ***Results:*** Response rate was 100%. Seven (44%) centers have an established AIS protocol and two (13%) have a protocol under development. Seven centers do not have a protocol; two redirect patients to adult neurology, five rely on a case-by-case approach for management. Analysis of the seven protocols revealed differences in: 1) IV-tPA dosage: age-dependent 0.75–0.9 mg/kg ($N = 1$) versus age-independent 0.9 mg/kg ($N = 6$), with maximum doses of 75 mg ($N = 1$) or 90 mg ($N = 6$); 2) IV-tPA lower age cut-off: 2 years ($N = 5$) versus 3 or 10 years (each $N = 1$); 3) IV-tPA exclusion criteria: PedNIHSS score <4 ($N = 3$), <5 ($N = 1$), <6 ($N = 3$); 4) first choice of pre-treatment neuroimaging: computed tomography (CT) ($N = 3$), magnetic resonance imaging (MRI) ($N = 2$) or either ($N = 2$); 5) intra-arterial tPA use ($N = 3$) and; 6) mechanical thrombectomy timeframe: <6 hour ($N = 3$), <24 hour ($N = 2$), unspecified ($N = 2$). ***Conclusions:*** Although 44% of Canadian pediatric hospitals have established AIS management pathways, several differences remain among centers. Some criteria (dosage, imaging) reflect adult AIS literature. Canadian expert consensus regarding IV-tPA and endovascular treatment should be established to standardize and implement AIS protocols across Canada.

RÉSUMÉ : Protocoles de prise en charge d'enfants victimes d'un AVC artériel ischémique cérébral hyper aigu qui sont soignés au sein d'hôpitaux canadiens de soins tertiaires. ***Contexte*** **:** Chez les enfants, les AVC artériels ischémiques (AVCAI) aigus sont diagnostiqués 23 heures (médiane) après l'apparition de leurs premiers symptômes, ce qui entraîne des délais dans l'administration d'un traitement. Des protocoles de prise en charge qui leur spécifiquement dédiés peuvent faire en sorte d'accélérer l'établissement d'un diagnostic. Notre objectif est ici de comprendre les similitudes et les différences entre divers protocoles canadiens de prise en charge des AVCAI chez les enfants, et ce, dans le but d'améliorer justement cette prise en charge. ***Méthodes*** **:** Pour ce faire, nous avons contacté des neurologues à l'œuvre au sein des 16 hôpitaux canadiens pour enfants. Nous avons analysé les protocoles de prise en charge en vigueur et cherché à faire émerger des similitudes et des différences dans huit domaines. ***Résultats*** **:** Notre taux de réponse a été de 100 %. Au total, sept établissements, soit 44 % d'entre eux, ont adopté un protocole de prise en charge des AVCAI alors que deux, soit 13 %, en avaient un en voie d'élaboration. C'est donc dire que sept établissements n'ont aucun protocole de ce type. Dans ce cas, deux d'entre eux redirigent leurs jeunes patients vers un service de neurologie pour adultes tandis que les cinq autres s'appuient sur une approche au cas par cas. Notre analyse de ces sept protocoles a révélé des différences en ce qui concerne : 1) le dosage de l'altéplase par voie intraveineuse : 0,75-0,9 mg/kg en fonction de l'âge ($n = 1$) contre 0,9 mg/kg en fonction de l'âge ($n = 6$) avec des doses maximales de 75 mg ($n = 1$) ou de 90 mg ($n = 6$) ; 2) la limite inférieure d'âge d'administration de l'altéplase par voie intraveineuse : 2 ans ($n = 5$) contre 3 ou 10 ans (chacun $n = 1$) ; 3) les critères d'exclusion d'administration de l'altéplase par voie intraveineuse : score < 4 à la *Pediatric NIH Stroke Scale* (PedNIHSS) ($n = 3$), score < 5 ($n = 1$), score < 6 ($n = 3$); 4) les première option pré-thérapeutique en matière de neuro-imagerie : TDM ($n = 3$), IRM ($n = 2$) ou les deux ($n = 2$) ; 5) l'utilisation intra-artérielle de l'altéplase ($n = 3$) ; et 6) les délais pour procéder à une thrombectomie mécanique : < 6 h ($n = 3$), < 24 h ($n = 2$), non précisé ($n = 2$). ***Conclusions*** **:** Bien que 44% des hôpitaux pour enfants du Canada aient établi un protocole de prise en charge des AVCAI, plusieurs différences subsistent d'un établissement à l'autre. Un certain nombre de critères, par exemple le dosage et le recours à la neuro-imagerie, reflètent davantage les observations qu'on trouve dans la littérature portant sur des cas d'AVCAI d'adultes. Un consensus parmi les experts canadiens en ce qui regarde l'administration d'altéplase et les traitements endovasculaires devrait être établi afin qu'on puisse standardiser les protocoles de prise en charge des AVCAI partout au Canada et les mettre en pratique.

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Background

Acute arterial ischemic stroke (AIS) is caused by an interruption of cerebral arterial blood flow due to thrombotic occlusion or arterial narrowing causing ischemic injury within an arterial territory.[1] Pediatric stroke occurs between 29 days and less than 18 years of age and affects approximately 2 in 100,000 children annually.[1,2] It is associated with an in-hospital mortality of 2.6%, with more than 50% of children with AIS suffering from long-term disability including persistent neurological deficits, seizures, and learning or developmental problems.[1,3–5] Childhood AIS is diagnosed with a median delay of 23 hours post symptom onset.[6] This has been attributed to several factors: a lack of awareness regarding childhood AIS among caregivers and health care professionals; barriers to accessing timely neuroimaging; and a high frequency of stroke mimics in children.[6]

Intravenous tissue-type plasminogen activator (IV-tPA) administered within 4.5 hours of symptom onset has been shown to significantly improve outcomes following acute ischemic stroke in adults.[7] The use of tPA in children remains controversial. Currently, neither IV nor intra-arterial (IA) tPA is approved for use in children with AIS.[8] In 2008, the American Heart Association Guidelines recommended that children with AIS should not receive tPA outside of a clinical trial, however consensus was not reached regarding tPA treatment for adolescents with AIS who otherwise met adult eligibility criteria.[9] Since that time, an increasing number of children have been treated off-label with tPA, with published case reports and case series reporting it to be well-tolerated in the vast majority.[10] The delay to diagnosis remains a barrier to tPA therapy given the recommendations for treatment within a 4.5-hour time window from symptom-onset. Accelerating the time to diagnosis is possible with the implementation of a stroke protocol in the pediatric emergency department, as shown in a 2016 study.[11] Children presenting outside the time window for IV-tPA may still benefit from endovascular treatment (EVT).[8] There is increasing evidence for EVT as a safe and effective treatment for childhood AIS.[12]

Little is known about the use or uniformity of stroke protocols and stroke management in pediatric centers across Canada.[13,14] The aim of this study is to describe the current practice of hyperacute stroke care across different pediatric institutions in Canada, specifically in centers that have a protocol for the management of stroke patients, and to descriptively analyze differences and similarities between protocols.

Methods

This was a cross-sectional, exploratory study designed to understand pediatric stroke management in Canada. As the study was deemed to be a quality improvement study, a Research Ethics Board approval was not required. A standardized email inquiring about the existence of a formal pediatric stroke protocol was sent to either 1) a pediatric neurologist at each Canadian pediatric hospital who has expertise or clinical interest in pediatric stroke or 2) the division or section head of pediatric neurology. All 16 Canadian pediatric tertiary care centers were approached and pediatric neurologists from those centers were eligible to participate. There were no exclusion criteria. The contact information of pediatric neurologists was obtained through each hospital's website.

We set out *a priori* to identify if there were center differences in eight pre-defined criteria. Pediatric AIS protocols were collected and analyzed for similarities and differences in the following domains: 1) initial suspected stroke screening questions; 2) lab workup and neuroprotective care for children presenting with suspected AIS; 3) pre-treatment neuroimaging; 4) age cut-off for IV-tPA treatment; 5) exclusion/inclusion criteria for IV-tPA; 6) IV-tPA dosage (mg/kg dosing and maximal dose); 7) alternatives to IV-tPA; and 8) post IV-tPA care. Neuroprotective care is defined as maneuvers prior to tPA administration to minimize the risk of expansion of the ischemic area (e.g. maintaining normoglycemia and normothermia) as well as to reduce the risk of complications with tPA therapy (avoiding excessively high or low blood pressures). Post IV-tPA care is defined as laboratory investigations, imaging, and patient care following IV-tPA treatment. Following the analysis, we interviewed pediatric neurologists from the seven institutions with a formal protocol to understand the site-specific rationale for differences in the above items. We contacted the same neurologists from our initial correspondence through a non-structured and non-standardized email. We posed open-ended questions to understand the reasoning behind the following protocol components: 1) pre-treatment neuroimaging choice; 2) age cut-off for IV-tPA treatment; 3) exclusion criteria for IV-tPA; 4) IV-tPA dosage; 5) alternatives to IV-tPA. Email interview questions were generated by study staff. A second, non-structured and non-standardized follow-up telephone interview was arranged to clarify ambiguous information.

Results

Childhood Stroke Protocols in Canada

Pediatric neurologists from each of the 16 pediatric tertiary care hospitals replied to our inquiry. Seven out of 16 centers (44%) have an established stroke protocol and 2/16 (17%) have a protocol that is under development. Of the seven institutions that do not have a protocol, two redirect their patients to adult neurology, and five rely on a collaborative local expert approach to manage stroke without a protocol. An overview of stroke management across Canadian pediatric institutions is illustrated in Figure 1. All seven established pediatric stroke protocols were included in our analysis and were kindly provided by the following institutions: Alberta Children's Hospital (Calgary), British Columbia Children's Hospital (Vancouver), Children's Hospital of Eastern Ontario (Ottawa), Centre Hospitalier Sainte-Justine (Montréal), Children's Hospital at London Health

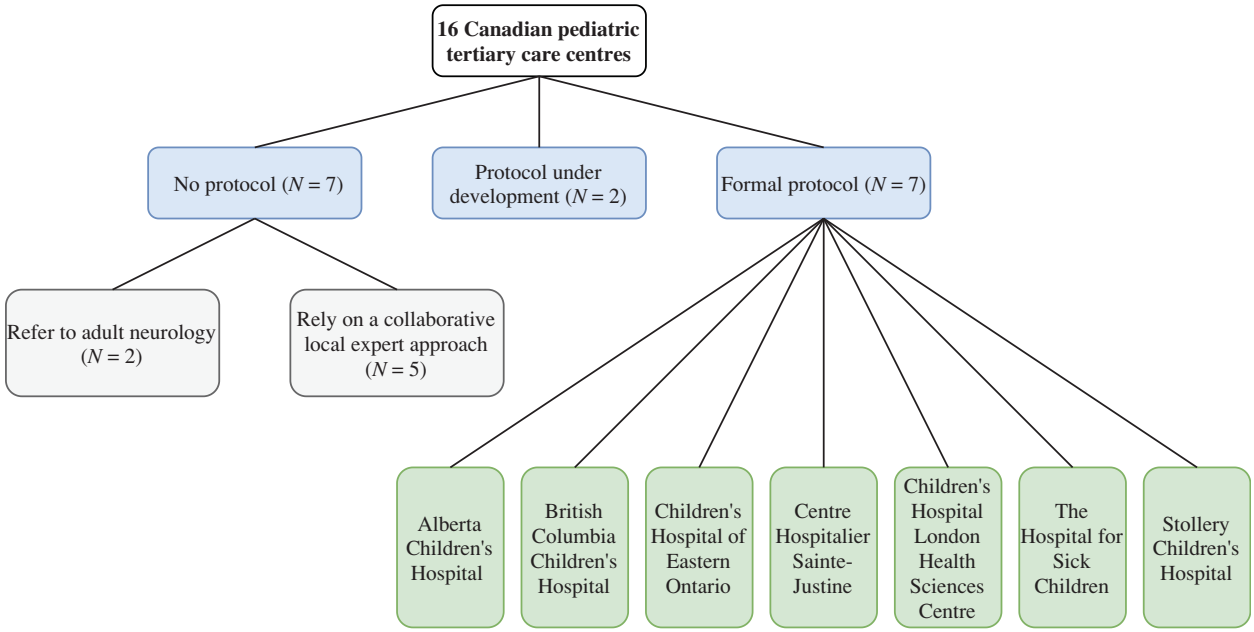

Figure 1: *Stroke management across 16 pediatric Canadian pediatric hospitals.*

Sciences Center (London), The Hospital for Sick Children (Toronto), and Stollery Children's Hospital (Edmonton).

Similarities Among Pediatric Stroke Protocols

The key recommendations presented in each protocol are similar and are explained in Table 1.

Differences in Pediatric Stroke Protocols

The differences noted in the seven protocols described below are illustrated in Figure 2 and explained in Table 2. The center-specific rationale for differences in stroke protocol criteria are outlined in Table 3.

Pre-Treatment Neuroimaging

The differences in neuroimaging are as follows: 3/7 centers (43%) use a computed tomography (CT) scan as their first-line choice; 2/7 centers (28%) use magnetic resonance imaging (MRI) as their initial neuroimaging; 2/7 centers (28%) use either a CT scan or MRI. The centers that use CT as first line do so because it is more accessible and does not require sedation ($N = 3$). The centers that use MRI as the first-choice do so based on the recommendations from the Thrombolysis in Pediatric Stroke (TIPS) study ($N = 2$).[13] The sites that choose either imaging modality do so because although their stated preference was to obtain an MRI, after-hours (evenings, weekends) studies are more limited due to the availability of an MRI technologist and anaesthesiologist, making a CT head available in a more timely manner ($N = 2$).

Exclusion Criteria for IV-tPA

We identified 3/7 centers (43%) to consider the Alberta Stroke Program Early CT Score (ASPECTS) when determining if a child is eligible for IV-tPA. The other 4/7 institutions (57%) do not use ASPECTS. ASPECTS is a 10-point qualitative score validated for adult AIS to evaluate the extent of early ischemic changes in the anterior circulation on non-contrast CT head.[15] Two centers that do not use ASPECTS scoring state that they do not because of their preference to obtain an MRI brain instead of a CT head. One center feels that ASPECTS scoring is redundant as ASPECTS correlates with the PedNIHSS score. One center explains that physicians are not comfortable with ASPECTS scoring in children.

We notice that 3/7 centers (43%) use a Pediatric NIH Stroke Scale (PedNIHSS) score of <4 as their lower cut-off, one center (14%) uses a cut-off of <5, and 3/7 centers (43%) use a cut-off of <6. The PedNIHSS is a tool that objectively quantifies the impairment caused by stroke, ranging from 0 to 42.[7] Institutions with <4 and <6 cut-offs indicate that they followed the TIPS study criteria when selecting this value. The TIPS trial initially indicated a <6 cut-off before revising it to <4.[13] The institute with cut-off of <5 indicates that this limit is not absolute and based on the discretion of the treating physician.

Age Cut-off for IV-tPA Administration

Five out of seven centers (72%) use IV-tPA starting at the age of 2 years, one center (14%) only administers IV-tPA starting at the age of 3 years, and one center (14%) only starting at age 10 years old. The five centers using a 2-year cut-off reference the TIPS study and the International Pediatric Stroke Study (IPSS) as their guideline. Avoidance of CT scans in younger children and lack of safety evidence for treating young children with IV-tPA are the rationale for protocols that have 3-year and 10-year cut-off ages, respectively.

IV-tPA Dosage

During our initial protocol analysis, 3/7 centers (43%) listed using an IV-tPA dose of 0.9 mg/kg, with a maximum dose of 60 mg. Two centers (28%) use a dose of 0.9 mg/kg, with a maximum dose of 90 mg. One center (14%) adjusts its dose based on age;

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Table 1: Overview of similarities between seven protocols

Similar domains among institutions	
Initial stroke screening questions	Focal neurological deficit present (unilateral weakness or sensory change, vision loss or double vision, speech difficulty, dizziness, or trouble walking)
	Symptoms started or worsened abruptly
	Focal neurological deficit has been present <4 hours
Neuroprotection and airway protection	Head of bed flat
	Patient kept *nil per os*
	Target systolic blood pressure to 50th–90th or 95th percentile for age
	Maintain normovolemia via normal saline with bolus as needed
	Maintain normoglycemia between 4 and 10 mmol/L
	Treat fever with acetaminophen
Initial lab tests for suspected AIS	Complete blood count (CBC) with differential
	International normalized ratio (INR)
	Activated partial thromboplastin time (PTT)
	Glucose
	Urea
	Creatinine
IV-tPA inclusion criteria	Clinical presentation consistent with AIS
	Stroke mimics unlikely based upon clinical and radiographical evidence
	Neuroimaging findings are consistent with AIS
	Time from symptom onset to IV-tPA treatment < 4.5 hours
	Informed consent obtained
IV-tPA exclusion criteria	Evidence of intracranial hemorrhage
	Recent intracranial surgery or intraspinal surgery
	Serious head trauma or previous stroke
	History of intracranial hemorrhage
	Uncontrolled hypertension
	Major surgery within 10–14 days
	Arterial puncture at non-compressible site within the previous 7 days
	Blood glucose <2.7 mmol/L or >22 mmol/L
	Known bleeding diathesis (such as platelet count <100,000/mm3)
Post IV-tPA care	Patient transferred to PICU for a minimum of 24 hours
	CT/CTA or MRI/MRA performed 24 hours post-treatment
	CBC, INR, PTT, fibrinogen checked 6 hours post-treatment or with any neurologic deterioration
	No arterial punctures, invasive procedures for 24 hours
	No antithrombotic medications for 24 hours
Endovascular therapy	Considered at all centers, although differences exist in time-windows among centers

children younger than 12 years old receive a dose of 0.75 mg/kg (maximum dose 75 mg) and children 12 years and older are administered 0.9 mg/kg (maximum dose 90 mg). However, during our teleconference discussion regarding protocol differences, 3/7 centers (43%) updated their maximum dosage from 60 mg to 90 mg to align with the best available evidence recently published in the medical literature.[16] This yields 6/7 centers (86%) using a dose of 0.9 mg/kg, with a maximum dose of 90 mg. All seven institutions referred to the TIPS study criteria and adult dosing when choosing their IV-tPA dosage.

Alternatives to IV-tPA

Only 3/7 centers (43%) use intra-arterial thrombolysis (IA-tPA) for a subset of their pediatric stroke patients. All seven institutions consider mechanical thrombectomy. Three centers

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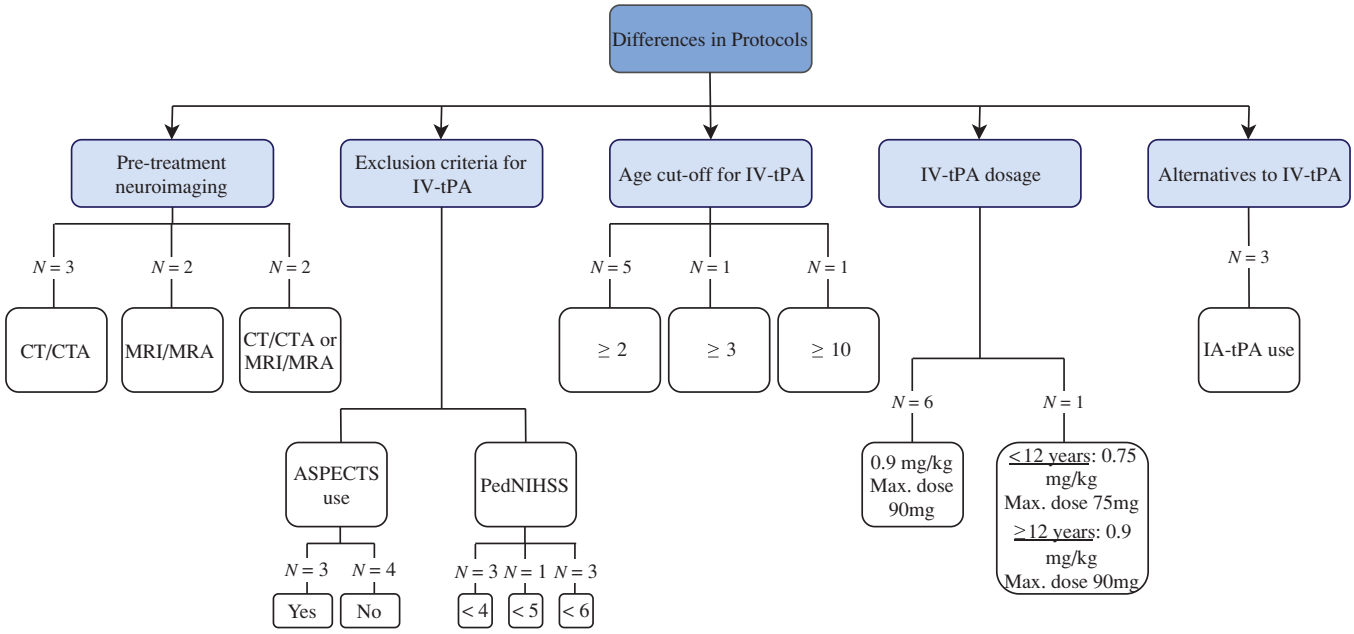

Figure 2: *Differences in stroke protocol domains.*

(43%) will perform mechanical thrombectomy within 6 hours of symptom onset. Two centers (28%) will extend their timeline of mechanical thrombectomy to 24 hours from symptom onset. Two centers (28%) will perform mechanical thrombectomy if the child presents outside of the 4.5-hour IV-tPA treatment timeframe, with no definite upper time limit for the thrombectomy procedure, ultimately leaving the decision to the treating team.

Discussion

This qualitative study shows that seven out of 16 Canadian pediatric tertiary care centers have established stroke protocols. Although these protocols have high concordance, several key differences were noted.

All protocols share initial neuroprotective measures, which require the normalization of temperature, blood glucose, oxygenation, blood pressure, and blood volume.

There were differences in age cut-off for IV-tPA use, ranging between 2 and 10 years of age. As there is no standardized guideline for IV-tPA use in children, centers referred to the TIPS and IPSS trial age criteria when creating their protocols.[13,14] Although there is evidence of successful IV-tPA use in children as young as 2 years, the majority of studies report IV-tPA use in older children, which may explain the higher age cut-off at some Canadian centers.[17]

The variability in IV-tPA dosage may be explained by the absence of randomized controlled trials for IV-tPA in the pediatric population. Recent published guidelines for childhood stroke management recommend a maximum dose of 0.9 mg/kg, with a maximum dose of 90 mg.[16] Notably, during our preliminary investigation, 3/7 centers initially listed a maximum dose of 60 mg, which was then changed to 90 mg after our first teleconference.

Only three centers use IA-tPA in pediatric stroke patients. The lack of randomized controlled trials for IA-tPA in the pediatric population and the need for an interventional radiologist may explain why not all centers offer this treatment option.[7] Numerous reports over the past two decades describe successful IA-tPA use in children.[18] Of note, a recent consensus statement recommends thrombectomy over the use of IA-tPA for adults.[19]

Our analysis revealed that the seven protocols differ in their choice of CT or MRI as the first-line imaging test to diagnose stroke. Given that AIS is a radiological diagnosis and the frequency of stroke mimics in children, timely neuroimaging findings must support the diagnosis of AIS prior to tPA administration.[20] Although the American Academy of Neurology guidelines recommend the use of a diffusion MRI to detect AIS due to its increased sensitivity, CT imaging is more readily available in most hospitals.[7] Access to an urgent MRI may be challenging in time-sensitive settings, particularly given the potential need for sedation in non-cooperative patients, including young, aphasic or anxious children. A non-contrast CT therefore remains the neuroimaging of choice if a diffusion-weighted MRI cannot be obtained within the appropriate timeframe for IV-tPA administration.[8] This difference in pre-treatment neuroimaging among pediatric centers reflects the current stroke imaging debate in the adult population; specifically, what is “best” (MRI) versus what is “more practical” (CT).[7]

All institutions indicate the use of mechanical thrombectomy in their protocols, though the timeframe for the procedure varies between 6 and 24 hours. Although mechanical thrombectomy has not been extensively studied in children, it is successfully performed within 24 hours of symptom onset in adults.[21] A recent systematic review with data from the last 20 years suggested that mechanical thrombectomy is an effective option for the treatment of AIS in patients aged 1–18 years.[22] Ultimately, pediatric neurologists we contacted agreed that mechanical thrombectomy is patient- and situation-dependent, and the decision should be at the discretion of the treating team.

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Table 2: Overview of discrepancies between seven protocols

Criteria that Differ Between Institutions	Alberta Children's Hospital	BC Children's Hospital	Children's Hospital of Eastern Ontario	CHU Sainte-Justine	Children's Hospital London Health Sciences Center	The Hospital for Sick Children	Stollery Children's Hospital
Age Cut-Off for tPA Administration (yrs)	≥2	≥2	≥2	≥10	≥2	≥2	≥3
tPA Dosage	0.9 mg/kg Max. dose 90mg	0.9 mg/kg Max. dose 90mg	0.9 mg/kg Max. dose 90mg	0.9 mg/kg Max. dose 90mg	0.9 mg/kg Max. dose 90mg	<12 years: 0.75 mg/kg Max. dose 75mg ≥12 years: 0.9 mg/kg Max. dose 90mg	0.9 mg/kg Max. dose 90mg
PedNIHSS Score	<6	<4	<6	<4	<6	<5	<4
Use of Intra-Arterial tPA	No	No	No	Yes	Yes	Yes	No
Choice of Imaging Prior to tPA Administration	CT/CTA or MRI/MRA*	CT/CTA or MRI/MRA*	MRI/MRA preferred**	CT/CTA	CT/CTA	MRI/MRA preferred**	CT/CTA
ASPECTS score inclusion for tPA exclusion criteria	Yes	No	No	No	Yes	No	Yes

*depending on which imaging modality is available quicker to qualify a child for IV-tPA in the 4.5-hour treatment window;depending on which imaging modality is available quicker to qualify a child for IV-tPA in the 4.5-hour treatment window;
**CT if MRI is contra-indicated or not accessible quickly enough to qualify a child for IV-tPA in the 4.5-hour treatment windows.

Table 3: Center-specific rationale for differences in stroke criteria

Differences in Stroke Criteria		Explanation
Pre-treatment neuroimaging	CT/CTA ($N = 3$)	More accessible and does not require sedation
	MRI/MRA ($N = 2$)	Based on TIPS trial criteria
	CT/CTA or MRI/MRA, depending on which modality is available quicker ($N = 2$)	MRI/MRA is not always readily available (especially after-hours such as weekends and weeknights), making CT/CTA a good alternative
Exclusion criteria for IV-tPA	No ASPECTS score use ($N = 4$)	Preference to obtain an MRI instead of CT head ($N = 2$)
		ASPECTS is redundant as it correlates with PedNIHSS ($N = 1$)
		Not comfortable with ASPECTS scoring in children ($N = 1$)
	PedNIHSS < 4 ($N = 3$)	Based on revised TIPS trial criteria
	PedNIHSS < 5 ($N = 1$)	Not an absolute limit, but rather based on the discretion of the treating physician
	PedNIHSS < 6 ($N = 3$)	Based on early TIPS trial criteria (before revision to PedNIHSS < 4)
Age cut-off for IV-tPA	≥2 years old ($N = 5$)	Used in the TIPS and IPSS trials
	≥3 years old ($N = 1$)	Avoidance of CT scans in younger children
	≥10 years old ($N = 1$)	Lack of safety evidence for treating young children with IV-tPA
IV-tPA dosage	0.9 mg/kg, max. dose 90mg ($N = 6$)	Based on TIPS trial criteria
	<12 years: 0.75 mg/kg	Based on TIPS trial criteria, which included doses of 0.75 mg/kg, 0.9 mg/kg, and 1.0 mg/kg
	Max. dose 75mg	
	≥12 years: 0.9 mg/kg	
	Max. dose 90mg ($N = 1$)	
Alternatives to IV-tPA	IA-tPA use ($N = 3$)	Only offered at institutions that have an interventional radiologist on-site
	Mechanical thrombectomy time window	Centers explained that the timeline is a rough guideline, but ultimately the decision is left to the treating team

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There are several limitations to our study. We did not inquire about the healthcare team and services involved in the initial triage of a patient with suspected AIS, the healthcare staff that trigger the stroke pathway, or the target time to neuroimaging at each institution. Additionally, our study did not examine the procedures performed post-tPA treatment to determine the cause of stroke. Furthermore, we did not investigate the frequency of stroke protocol use and the number of patients meeting IV-tPA criteria at the centers with a formal protocol. Future analyses of stroke protocols and response to management will be required.

Conclusion

Our study is unique as it describes the current landscape of childhood stroke management at Canadian pediatric hospitals. It is assuring that seven pediatric tertiary care centers have formal stroke pathways with extensive areas of agreement such as post-tPA care, though they differ in important aspects of diagnostic workup and treatment. Our work has already yielded amendments in stroke protocols at some centers – specifically regarding the maximum dosage of IV-tPA at three centers – and has sparked discussion regarding the need for further collaboration among Canadian institutions to optimize childhood stroke management. We advocate for a Canadian consensus regarding IV-tPA and EVT treatments with the goal of implementing and, where possible, standardizing pediatric stroke protocols.

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Disclosures

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Statement of Authorship

MG wrote the first draft of the manuscript and was responsible for study design.

HJM, DP edited the manuscript, provided data and were responsible for study design.

AA, CB, IB, JM, AM, MM, SP, and **JS** provided data and a critical review of the manuscript.

All authors reviewed and approved the manuscript in its final form.

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