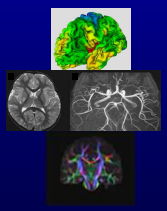
Pediatric Stroke: Acute Evaluation and Management

……or

To Thrombolysis and Beyond!



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Pediatric Stroke: Acute Evaluation and Management……or

To Thrombolysis and Beyond

Michael J. Rivkin, M.D.

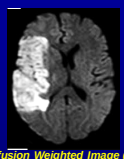
No financial relationships to disclose

Unlabeled or Unapproved Use Discussion:
Use of tPA for treatment of acute stroke in children

Developing an Acute Pediatric Stroke Program: Protecting the Child's Brain

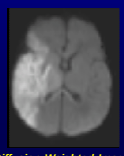
- *Time is brain*: review the epidemiology and clinical presentation of stroke in children.
- *What has been learned from the adult experience of defining care for patients with acute ischemic stroke*: the case for development of multidisciplinary, integrated acute stroke teams/programs for children in order to optimize care for children with acute stroke
- *Looking forward: work in progress to advance care of children with acute stroke.*

Time is brain.



Diffusion Weighted Image (DWI)

sudden onset; left hemiparesis; lethargic → Male, 62 years old; Smoker; high cholesterol



Diffusion Weighted Image (DWI)

focal left sided seizures, he was lethargic after, left hemiparesis present → Male, 5 years old, previously healthy

Adults and Children with Stroke Travel Different Paths during the Acute Phase of Their Illness

Adult with Acute Stroke

- Assessed in the field by EMS Team affiliated with a Primary Stroke Center
- Taken to a Primary Stroke Center

Child with Acute Stroke

- Often a delay before coming to the ED
- Delay in recognition of possibility acute stroke diagnosis
- Delay in acquisition of diagnostic neuroimaging

Studied Time Intervals in Children With Out-of-Hospital and In-Hospital Arterial Ischemic Stroke

Studied Time Intervals (in Hours)	N	Median	IQR‡
Out-of-hospital AIS			
Symptom onset to seek medical help	93	1.0	0.16–4.7
Symptom onset to initial assessment	85	1.6	0.4–6.4
Symptom onset to hospital arrival*	106	1.7	0.8–8.1
Symptom onset to initial neuroimaging	108	8.5	3.7–27.5
Symptom onset to diagnosis†	116	29	11.3–65.9
Hospital arrival to physician assessment	105	0.25	0.08–0.4
Hospital arrival to initial neuroimaging	95	3.1	1.5–7.4
Hospital arrival to diagnosis	95	12.9	5–31.1
Diagnosis to treatment, days	84	1	0–2
In-hospital AIS			
Symptom onset to initial assessment§	64	0.0	0.0–0.0§
Symptom onset to initial neuroimaging	75	10.5	3.8–25
Symptom onset to diagnosis	73	11.6	3.9–39.9
Diagnosis to treatment, days	25	2	0–5

*Prehospital delay.
†Total delay.
‡Interquartile range defined by the 25th to 75th percentile.
§Majority of in-hospital AIS occurred in an intensive care setting (eg, postcardiac procedure) while under close observation.
N indicates number of patients with available data.

N=209

n_{out}=132

n_{in}=77

Rafay et al ,Stroke. 2009;40:58-64; Srinivasan et al, Pediatrics. 2009; 124; e227-e234, Gabis et al, Pediatrics.2002;110;924-928

Adult Primary Stroke Center (PSC)

- Acute Stroke Team
- Pre-written stroke care protocols
- Field EMS Linked-in to PSC
- Neuroimaging services immediately available
- Pharmacy skilled in rapid preparation of thrombolytic
- Neurointerventional suite and team rapidly populated

Song S , and Saver J Stroke. 2012;43:1975-1978

The Effect of Protocol-Driven Primary Stroke Centers on Outcome for Adults

Unadjusted Outcomes by JC Primary Stroke Center Certification Status

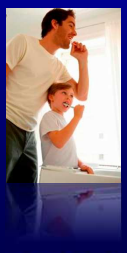
	Total		JC-Certified	Noncertified	
	N	Percent	Percent	Percent	*P* Value
Length of stay, mean±SD, days	5.0±4.3		4.6±4.0	5.1±4.4	<0.0001
In-hospital mortality	19 614	5.4	4.7	5.5	<0.0001
30-day mortality	40 421	11.0	9.8	11.3	<0.0001
30-day all-cause readmission*	48 628	14.5	13.8	14.6	<0.0001
30-day complications*†	26 158	7.8	7.3	7.9	<0.0001
Ischemic stroke	12 498	3.7	3.5	3.8	0.0003
Any stroke	13 346	4.0	3.7	4.0	0.0006
Pneumonia	2370	0.7	0.5	0.8	<0.0001
Peripheral arterial disease	19 176	5.7	5.4	5.8	0.0023
Urinary tract infection	1464	0.4	0.4	0.4	0.0759

JC= Joint Commission

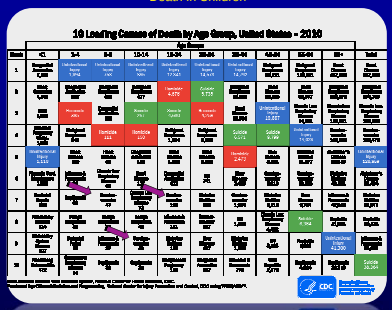
In adults, care by an acute stroke team and on stroke units decreased mortality, morbidity, dependency and increases frequency of living at home.

Lichtman et al. Stroke. 2009;40:3574-3579; Langhorne et al. Cochrane Rev, 2013

Why emulate the adult experience in pediatric stroke?



Cerebrovascular Disorders Rank Among the 10 Most Common Causes of Death in Children



International Pediatric Stroke Study (IPSS)

Initiated:
- Jan 2003, 11 co-investigators (Canada, US, UK)

Objective:
- Provide data and vehicle for clinical trials in paediatric stroke

Progress:
- >300 investigators, 200 centers (50 countries), 70 enrolling (25 countries)
- ~5,000 patients enrolled as of February, 2016
- 30 investigator meetings

IPSS Enrolling Centers

Centers Enrolling Patients

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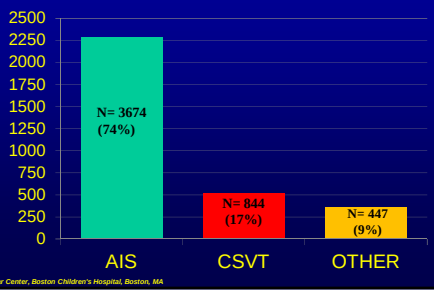
IPSS Patients – Stroke Subtype (N=4965)



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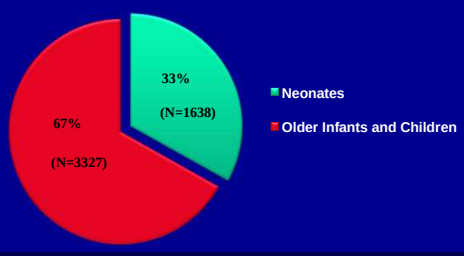
IPSS Patients – Age at Stroke (N=4965)



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Stroke in Children: Comparative Frequency

- Brain tumor in children: ~3/100,000
- Inflammatory Bowel Disease in children: ~2/100,000
- Arterial Ischemic Stroke in all children: 3-13/100,000 (1/7,700)
- Arterial Ischemic Stroke in Neonates 40/100,00 (1/2,500)

Stroke in Children: Epidemiology

Children > 1 month old

Frequency of occurrence greater than originally thought → 3-13/100,000

Males > Females

Blacks > Whites

75% as arterial ischemic stroke (AIS)

25% as cerebral sino-venous thrombosis (CSVT) and hemorrhage

Stroke in Children: Epidemiology

Neonates-

occurrence ~1 in 2,500 births

Males > Females

80% as arterial ischemic stroke (AIS)

20% as cerebral sino-venous thrombosis (CSVT) and hemorrhage

The Frequency of Stroke in Children

Age Group	Incidence of Stroke
Adults	175-200/100,000
Children	3-13/100,000
Neonates	25-40/100,000
Premature Infants	100/100,000

Mortality from Stroke

	Hemorrhagic	*Ischemic*
Adults	38%	23%
Children	11%	7%

Children live many more decades than adults following stroke and their aggregate cost of care is greater than for adults.

Gardner et al. Neurology, 2010:372-78; Statler et al,. Childs Nerv System, 2011:565-573; Grysiewiczet al, Neurol Clin, 2008:871-95; Lo et al. Stroke. 2008;39:161-165

Arterial Ischemic Stroke

Outcome after Stroke in Childhood

Neonatal Arterial Ischemic Stroke

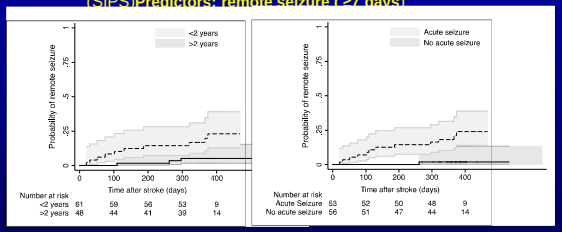
Motor deficits	30-50%
Cognitive deficits	up to 60%
Executive function	
Language	
Epilepsy	15-55%

Arterial Ischemic Stroke in Children > 1 month of age

Motor deficits	65%
Cognitive deficits	40-50%

Westmacott et al. DMCN, 2010
Kok et al. Pediatr Neurol, 2011
Lee et al. Ann Neurol, 2005
Ricci et al, Stroke, 2008
Wanigasinghi et al, DMCN, 2010
Ganesan et al, DMCN, 2000
De Veber et al, J Child Neurol, 2000

Preliminary Data: *Seizures in Pediatric Stroke Study* (SIPS)Predictors: remote seizure (>7 days)



Acute seizures (HR 12, CI 1.5 – 92)
Age less than 2 years (HR 4.3, CI 1.2-16)

International Paediatric Stroke Study
iPERF
Christine Fox, M.D. , P.I.

Presentation of AIS in Children

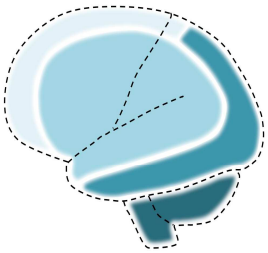
- Sudden-onset, focal neurologic deficits in 85% of non-neonates
  - Hemiparesis 60-80%
  - Speech difficulty 10-35%
  - Visual field defects 5-20%
  - Other 18%

Anterior cerebral artery
Weakness of contralateral leg
Behavior changes

Middle cerebral artery
Weakness of contralateral face and arm
Speech disturbance (aphasia, dysarthria)
Visual field deficit (hemianopia)
Inattention to stimuli (hemineglect)
Sensory deficits

Posterior cerebral artery
Visual field deficit (hemianopia)
Sensory deficits

Vertebrobasilar system
Dizziness, ataxia, impaired balance
Pupil and eye movement abnormalities
Changes in voice and swallowing
Weakness and sensory changes
Decreased level of consciousness



Cerebral veins and sinuses (not shown)
Decreased level of consciousness
Headache
Vomiting
Papilledema (late)

Arterial Ischemic Stroke

Clinical Signs

Headache
- Occurs in 45% of children who present with stroke
- Associated with arteriopathy, including inflammatory origin

Seizure
- Occurs in 30% of children who present with stroke
- In a child who presents with first time seizure with postictal lateralized paresis

Arterial Ischemic Stroke

Treatment of Arterial Ischemic Stroke in Children

- **Oxygenation** : ≥ 95%
- **Normothermia**:
  - Hyperthermia- ***treat fever!*** If present, each degree of ↓, improves outcome
  - Hypothermia - interest is high based on success with neonatal HIE
- **Euglycemia**:goal is 70-120 mg/dl; treat if >200 mg/dl
- **Blood pressure** adequacy:
  - Maintain cerebral perfusion to brain to avoid exacerbating infarct
  - Targets have not been proven- developmental increment in blood pressure with age
- **Anticoagulation:**
  - if cardioembolic origin or cervicocephalic arterial dissection is suspected

Use of tissue plasminogen activator to treat acute arterial ischemic stroke in children

Thrombolysis in Pediatric Stroke …it's about time

Goals of TIPS:
To determine safety,
To determine best dose of tPA
To determine treatment feasibility

→ IV tPA when used to treat children who present with arterial ischemic stroke (AIS), within 4.5 hours of onset of symptoms

Initial TIPS Sites

Australia:
Royal Children's Hospital, Melbourne, Victoria
Mark Mackay MD

Canada:
Children's Hospital of Eastern Ontario
Hugh McMillan MD, MSc, FRCPC, FAAN
University of Calgary/Alberta Children's Hospital
Adam Kirton MD MSc
Hospital for Sick Children, Toronto, Ontario
Gabrielle deVeber MD MSc

United Kingdom:
Evelina Children's Hospital, London
Nomazulu Dlamini MD

United States:
Children's Hospital Boston, Boston, MA
Michael Rivkin MD
Children's Hospital, Denver, CO
Timothy J Bernard MD
Children's Hospital of Philadelphia, PA
Rebecca Ichord MD
Children's Hospital of Pittsburgh of UPMC
Dana D. Cummings MD PhD

Children's Medical Center at Dallas
Michael M Dowling, MD PhD MSCS
Cleveland Clinic, Cleveland, OH
Neil Friedman MBChB
Loma Linda University School of Medicine
Stephen Ashwal MD
Massachuetts General Hospital
Eric Grabowski MD, DSci, Ferdinando Buonanno MD,
Ronald Thibert DO
Medical College of Wisconsin
Osama O Zaidat MD MSc
Nationwide Children's Hospital,
Columbus, OH
Warren Lo MD
Rainbow Babies and Children's Hospital, Cleveland, OH
Max Wiznitzer MD
Stanford University, Palo Alto, CA
Paul Graham Fisher MD
Texas Children's Hospital
Lisa Michael Nassif MD
University of Texas Medical School at Houston
James C Grotta MD
University of Utah, Salt Lake City, UT
Susan Benedict MD
University of Washington, Seattle, WA
C Amlie-Lefond MD, S Gospe MD, PhD
Vanderbilt University Medical Center
Lori Jordan MD PhD

TIPS: Changes in approach to acute pediatric stroke

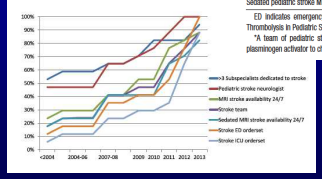


Table 1. TIPS Sites Readiness for Acute Stroke

Readiness Parameter	Percentage of Sites Attaining Parameter
24/7 Pediatric stroke team*	94%
Pediatric stroke ED order set	100%
Pediatric stroke ICU order set	88%
Pediatric stroke MRI available 24/7	88%
Sedated pediatric stroke MRI available 24/7	82%

ED indicates emergency department; ICU, intensive care unit; and TIPS, Thrombolysis in Pediatric Stroke.
*A team of pediatric stroke experts capable of administering tissue-type plasminogen activator to children 24 hours a day, 7 days a week.

Bernard, Rivkin et al, Stroke, 2014

TIPS: Emergence of the Pediatric Primary Stroke Center

Table 3. Comparison of the Original 2000 Adult Criteria With the Proposed Pediatric Equivalent

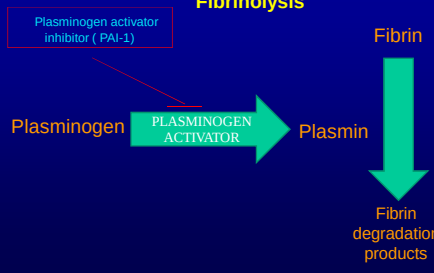
Adult PSC Criteria	Proposed Pediatric PSC Equivalent	Percentage of TIPS Sites Attaining PPSC Equivalent
Patient care areas		
Acute stroke teams	24/7 Pediatric stroke team; same as adult criterion	94%
Written care protocols	Pediatric stroke ED and ICU order set; same as adult criterion	100%
Emergency medical care services	Emergency medical care services; same as adult criterion	100%
Neurosurgical services	Neurosurgical services; same as adult criterion	100%
Stroke unit	Pediatric ICU	100%
Support services		
Commitment and support of the medical organization	Commitment and support of the medical organization; same as adult criterion	88%
Stroke center director	Stroke center director; same as adult criterion	100%
Neuroimaging services	Sedated pediatric stroke MRI available 24/7	82%
Laboratory services	Laboratory services; same as adult criterion	100%
Outcome and quality improvement activities	Outcome and quality improvement activities; same as adult criterion	35%
Continuing medical education	Continuing medical education; same as adult criterion	35% (but not meeting the rigorous definition used in the article by Alberts et al[9])

ED indicates emergency department; ICU, intensive care unit; PPSC, primary pediatric stroke center; PSC, primary stroke center; and TIPS, Thrombolysis in Pediatric Stroke.

Bernard, Rivkin et al, Stroke, 2014

Medical Noninvasive Treatment

Tissue Plasminogen Activator and Fibrinolysis



Developmental trajectory of [tPA]/[PAI-1] ratios

- From 1 to 16 years of age, baseline tPA concentrations in blood are about 50% lower than in adults
- Plasminogen activator inhibitor-1 (PAI-1) concentrations overall are increased in children compared to adults

Child, < 18 y.o.	Adult
tPA↓/PAI-1↑	tPA↑/PAI-1↓

tPA Treatment of Pediatric Stroke

Dose: 0.9 mg/kg,IV

Time: Within 4.5 hrs from onset of symptoms

Absence of intracranial hemorrhage

tPA contraindications:
- > 4.5 hrs from last seen well
- Patients in whom time of symptom onset is unknown
- Mild deficit (PedNIHSS <4) at start of tPA infusion
- Stroke 2° to SBE, SCD, meningitis, bone marrow, or fat embolism, or moyamoya disease.
- Stroke, major head trauma or intracranial surgery in the last 3 mo
- Symptoms suggestive of SAH even if CT or MRI of head are normal
- Patient who would decline a blood transfusion if indicated.
- History of prior intracranial hemorrhage
- Any prior ICH or known AVM, aneurysm, or neoplasm
- Persistent systolic blood pressure > 15% above the 95th percentile for age while sitting or supine
- Glucose < 50mg/ml (2.78 mmol/ll) or > 400mg/dl (22 mM)
- Bleeding diathesis including Platelets < 100,000, PT>15 sec (INR>1.4) or elevated PTT > upper limits of the normal range.
- Clinical presentation c/w acute myocardial infarction or post MI pericarditis that requires evaluation by cardiology before treatment
- Major surgery or parenchymal biopsy within 10 days
- GI or GU bleeding <21days
- Arterial puncture at noncompressible site or lumbar puncture w/in last 7days. Patients who have had cardiac cath via a compressible artery are NOT excluded.
- Patient with malignancy or within one month of completion of treatment for cancer.
- Patients with underlying significant bleeding disorder. Patients with mild plt dysfunction , mild vWillebrand disease or other mild bleeding disorders are not excluded.
- Children and families with limited English proficiency not eligible for TIPS
- Severe deficit suggesting very large territory stroke w/pre-tPA PedNIHSS>25, regardless of infarct volume seen on neuroimaging
- CT with hypodensity / sulcal effacement > 33% of MCA territory or ASPECTS ≤ 7
- Previousl dx'd primary angiitisof the central nervous system or secondary arteritis.
- Intracranial cervicocephalic arterial dissection.

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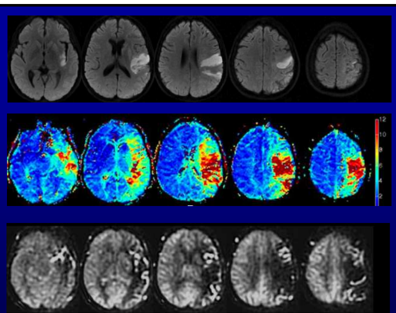
DWI

Bolus PWI

ASL PWI



Zaharchuk et al, Stroke , 2012

Does the penumbra found in adults with stroke exist in children with stroke?

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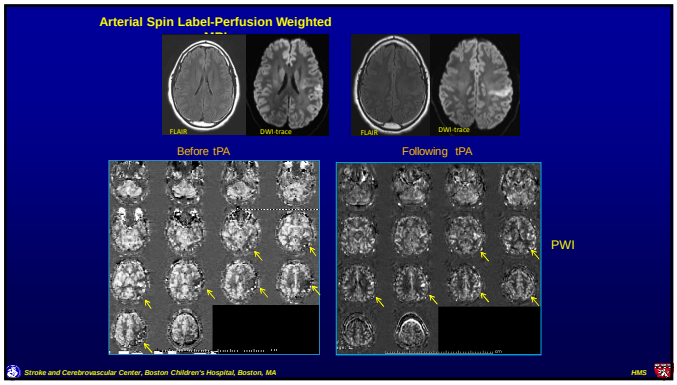
Arterial Spin Label-Perfusion Weighted
FLAIR
DWI-trace
FLAIR
DWI-trace
Before tPA
Following tPA
PWI
Stroke and Cerebrovascular Center, Boston Children's Hospital, Boston, MA
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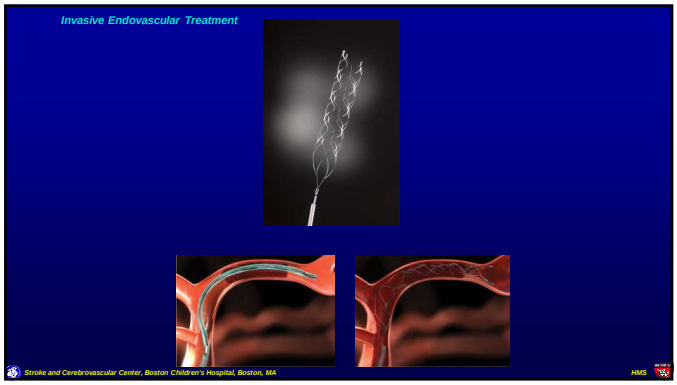
Invasive Endovascular Treatment
Stroke and Cerebrovascular Center, Boston Children's Hospital, Boston, MA
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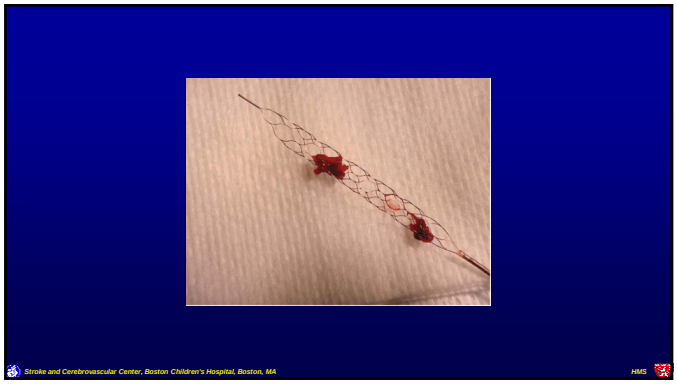
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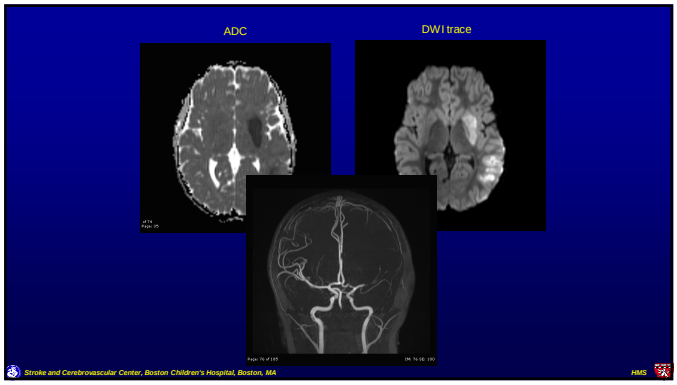
ADC
DWI trace
Stroke and Cerebrovascular Center, Boston Children's Hospital, Boston, MA
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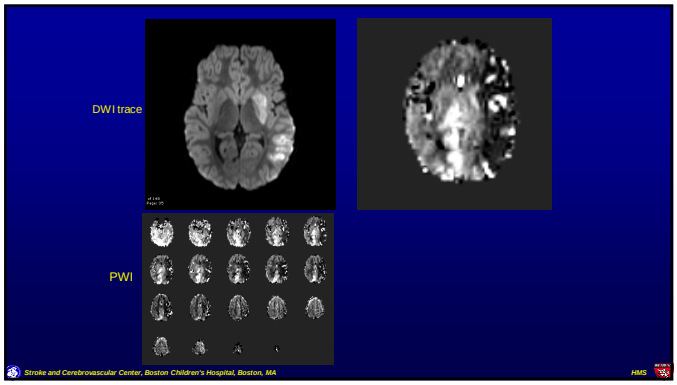
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PWI
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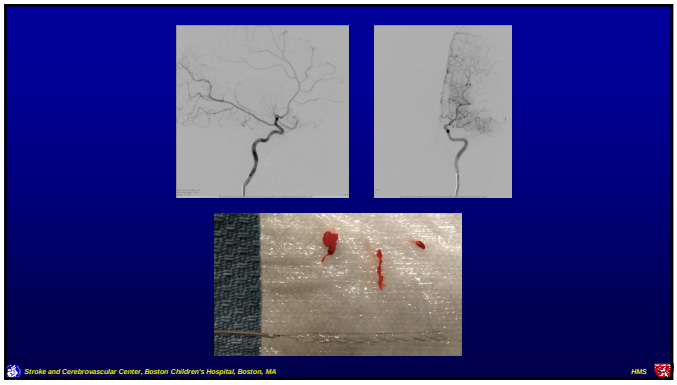
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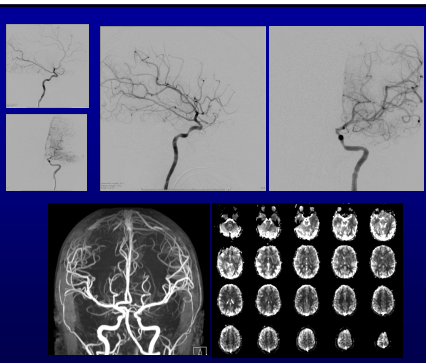


Pediatric **H**yper**A**cute **S**troke **T**rial (***PHAST***) NINDS-NIH

Specific Aim 1: Determine final volume of infarction seen initially at presentation , 3 days later and at 6 months.

Specific Aim 2: Measure biomarkers in serum to identify indicators of stroke that correlate with outcome

Specific Aim 3: **To** ascertain the predictive value of neuroimaging, serum biomarkers and clinical assessment individually and together to predict outcome at 6 months

25 centers in North America to participate

Specific Aim 1: Evolution of the arterial ischemic stroke lesion by MRI

- DWI }
- ASL-PWI; SWI} @ presentation, 3-5 days later, 6 months
- FLAIR/T2W }
- Use of a standardized imaging protocol across participating centers

Specific Aim 2: Ascertainment of serum biomarkers of stroke

- Inflammatory markers } Collected at initial presentation and
- Activators of coagulation } 3-5 days later

Specific Aim 3: Predictive value of MRI, biomarkers and initial outcome for outcome at 6 months

- Neuroimaging
- Biomarkers
- Pediatric Stroke Outcome Measure (PSOM)

Conclusions

1. Pediatric stroke has learned from the adult experience of acute stroke clinical team development
2. Children with acute stroke can present with lateralizing features similar to those of stroke in adults. However children commonly present with symptoms not usually found in adults---seizure and headache.
3. Pediatric acute stroke centers established for TIPS now can treat children with acute with IV thrombolysis or endovascular thrombolysis or thrombectomy

BCH Departments

Scott Pomeroy (Neurology)

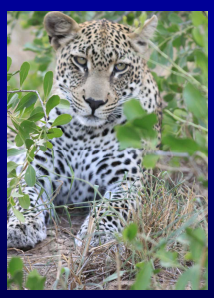
Monica Kleinman (Anesthesia)

Boston Children's Hospital
Until every child is well

Stroke and Cerebrovascular Center, Boston Children's Hospital

Cameron Trenor (Hematology)
Michael Rivkin (Neurology)
Laura Lehman (Neurology)
Ed Smith (Neurosurgery)
Rebekah Mannix (Emergency Dept.)
Amy Danehy (Neuroradiology)
Lindsay Simmons (Nursing)
Darren Orbach (Neuro IR)
Christine Mrakotsky (Neuropsychology)
Annette Correia (OT)
Marykay Nutini (Physiatry)
Lyndsay Handell (Coordinator)

http://www.childrenshospital.org/cerebrovascular-disorders-and-stroke



Thanks, for your attention.