Emergence of the Primary Pediatric Stroke Center
Impact of the Thrombolysis in Pediatric Stroke Trial

Timothy J. Bernard, MD†; Michael J. Rivkin, MD*†; Kelley Scholz, MSW*; Gabrielle deVeber, MD, MSc*; Adam Kirton, MD, MSc*; Joan Cox Gill, MD*; Anthony K. Chan, MBBS*; Collin A. Hovinga, PharmD, MS*; Rebecca N. Ichord, MD*; James C. Grotta, MD; Lori C. Jordan, MD, PhD; Susan Benedict, MD; Neil R. Friedman, MBChB; Michael M. Dowling, MD, PhD; Jorina Elbers, MD; Marcela Torres, MD; Sally Sultan, MD, MS; Dana D. Cummings, MD, PhD; Eric F. Grabowski, MD, ScD; Hugh J. McMillan, MD, MSc; Lauren A. Beslow, MD, MSCE; Catherine Amlie-Lefond, MD*; on behalf of the Thrombolysis in Pediatric Stroke Study

Background and Purpose—In adult stroke, the advent of thrombolytic therapy led to the development of primary stroke centers capable to diagnose and treat patients with acute stroke rapidly. We describe the development of primary pediatric stroke centers through preparation of participating centers in the Thrombolysis in Pediatric Stroke (TIPS) trial.

Methods—We collected data from the 17 enrolling TIPS centers regarding the process of becoming an acute pediatric stroke center with capability to diagnose, evaluate, and treat pediatric stroke rapidly, including use of thrombolytic therapy.

Results—Before 2004, <25% of TIPS sites had continuous 24-hour availability of acute stroke teams, MRI capability, or stroke order sets, despite significant pediatric stroke expertise. After TIPS preparation, >80% of sites now have these systems in place, and all sites reported increased readiness to treat a child with acute stroke. Use of a 1- to 10-Likert scale on which 10 represented complete readiness, median center readiness increased from 6.2 before site preparation to 8.7 at the time of site activation (P≤0.001).

Conclusions—Before preparing for TIPS, centers interested in pediatric stroke had not developed systematic strategies to diagnose and treat acute pediatric stroke. TIPS trial preparation has resulted in establishment of pediatric acute stroke centers with clinical and system preparedness for evaluation and care of children with acute stroke, including use of a standardized protocol for evaluation and treatment of acute arterial stroke in children that includes use of intravenous tissue-type plasminogen activator.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01591096.

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Key Words: child ■ stroke ■ thrombolytic therapy

In adult stroke, clinical trials have resulted in 2 evidence-based acute stroke treatment guidelines that save lives and improve neurological outcome: the use of tissue-type plasminogen activator (tPA)† and the development of dedicated stroke units that provide standardized, best practice acute care.‡ Following the approval of tPA for the treatment

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From the Department of Neurology, Children’s Hospital Colorado, Aurora (T.J.B.); Departments of Neurology, Psychiatry and Radiology, Boston Children’s Hospital, MA (M.J.R.); Department of Neurology, Hospital for Sick Children, Toronto, Ontario, Canada (G.d.V.); Department of Neurology, Alberta Children’s Hospital Research Institute, University of Calgary, Calgary, AB, Canada (A.K.); Department of Pediatrics, Medical College of Wisconsin, Milwaukee, and BloodCenter of Wisconsin (J.C.G.); Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada (A.K.C.); Department of Pediatrics, Dell Children’s Medical Center, Austin, TX (C.A.H.), Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia (R.N.I.); Department of Neurology, Memorial Hermann Hospital, Houston, TX (J.C.G.); Division of Pediatric Neurology, Vanderbilt University, Nashville, TN (L.C.J.); Department of Neurology, Primary Children’s Medical Center, Salt Lake City, UT (S.B.); Department of Neurology, Cleveland Clinic, OH (N.R.F.); Department of Pediatrics and Neurology, UT Southwestern Medical Center, Dallas TX (M.M.D.); Department of Neurology, Stanford University, CA (J.E.); Department of Hematology and Oncology, Cook Children’s Medical Center, Fort Worth, TX (M.T.); Department of Neurology, Columbia University Medical Center, New York, NY (S.S.); Division of Child Neurology, Children’s Hospital of Pittsburgh of University of Pittsburgh Medical Center, PA (D.D.C.); Division of Pediatric Hematology/Oncology, Department of Pediatrics, Mass General Hospital for Children, and Massachusetts General Hospital, Boston (E.F.G.); Department of Neurology, Children’s Hospital of Eastern Ontario, Ottawa, Ontario, Canada (H.J.M.); Departments of Pediatrics and Neurology, Yale-New Haven Children’s Hospital, CT (L.A.B.); Department of Neurology, Seattle Children’s Hospital, WA (K.S., C.A.-L.); and Department of Neurology, University of Washington, Seattle (C.A.-L.).

†Members of Thrombolysis in Pediatric Stroke (TIPS) Steering Committee.
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†Drs Bernard and Rivkin contributed equally.

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Correspondence to Catherine Amlie-Lefond, MD, Department of Neurology, Seattle Children’s Hospital/University of Washington, MB 7.420, 4800 Sand Point Way NE, Seattle, WA 98105, E-mail Calefond@uw.edu
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2018
of acute arterial ischemic stroke in adults, the American Heart Association, American Academy of Neurology, and National Stroke Association have published guidelines that include its use for the care of adults with acute stroke.\(^4\) Requirements for designation as primary stroke centers (PSCs) and comprehensive stroke centers now exist to standardize acute stroke care in adults. Demonstration of considerable effort to achieve these requirements is needed to gain designation as an adult stroke center.\(^5\) Although most adults who present with acute stroke do not receive tPA, ensuring comprehensive stroke care assures that other elements of therapy are implemented and lead to improved outcomes, including evidence-based care management strategies, supportive care, prevention of complications, secondary stroke prevention, and rehabilitative care.\(^4\)

In contrast, the care of children with acute stroke has often been poorly coordinated and reflects a dearth of research on which to base treatment protocols. Only \(\approx2\%\) of children with acute stroke receive treatment with tPA in the United States.\(^6,7\) These strategies need to be well established to support children with stroke and to ensure that children with acute stroke receive care that improves their outcome.\(^5\)

In 2010, the National Institute of Neurological Disorders and Stroke funded the first prospective treatment trial in acute pediatric stroke, the Thrombolysis in Pediatric Stroke (TIPS) trial. TIPS trial was designed as a Phase I multicenter trial to determine the safety of tPA in childhood stroke, as well as the pharmacokinetics of tPA in the pediatric population. In preparation for site selection for TIPS, data were collected regarding the availability of emergency and intensive care services, emergent neuroimaging, pediatric anesthesia, pediatric neurosurgery, and pediatric hematologic availability from site principal investigators (PIs) seeking to participate. All potential TIPS sites required the involvement of a pediatric intensive care unit (PICU) in a tertiary hospital for care of patients after treatment with tPA, continual availability of urgent neuroimaging, either MRI/magnetic resonance angiography or computed tomography/computed tomography angiography, urgent pediatric anesthesia, and pediatric neurosurgery consultation. Based on these criteria, all centers participating in TIPS were well-established tertiary care pediatric centers with specialists dedicated to childhood stroke. Conversely, the site selection process demonstrated a significant variation among candidate centers in clinical, radiographic, and hospital readiness for management of children with acute stroke that highlighted the need for standardization of pediatric stroke care. Although each site had a PI with expertise in pediatric stroke, in the absence of published guidelines for pediatric stroke centers, many sites lacked an organized and systematic approach to stroke triage and early management.

Through the use of a complementary, multidisciplinary membership, the TIPS steering committee established criteria for the minimal clinical expertise and hospital systems necessary to execute an acute interventional stroke trial safely in the pediatric population. In addition to acute treatment with tPA, this included the ability to triage and diagnose stroke promptly, provide urgent care to children with stroke, and treat complications of stroke and stroke treatment. Furthermore, PIs and coinvestigators at each center were required to obtain certification in use of the pediatric National Institutes of Health Stroke Scale (NIHSS) which has been validated for use by pediatric neurologists.\(^14,15\) The pediatric NIHSS certification requires completion of the adult NIHSS certification (already established as a critical component of stroke care in adults), as well as a separate pediatric-specific module.\(^14\)

More importantly, the TIPS study coordinating center and steering committee were able to assist site PIs directly as they prepared their sites for enrollment. During this process, the TIPS trial served as a central repository for protocols and procedures from each site, allowing the ability to share ideas and expertise around the trial infrastructure. Many centers developed new systems for patient management in preparation for TIPS trial participation, often using experience gained from other participating sites. As such, each site expanded its ability to triage, manage, and treat acute pediatric stroke. The purpose of this study is to describe the emergence of these early PPSCs. In addition, we describe the resources necessary to establish acute stroke readiness for the pediatric population and compare the readiness of TIPS sites with the original adult PSC criteria.

### Methods

In 2010, the National Institute of Neurological Disorders and Stroke funded the TIPS trial (NIH No. R01 NS065818). The TIPS trial was designed to be a 5-year multicenter international safety and dose-finding study of intravenous tPA in children with acute arterial ischemic stroke to determine the maximal, safe dose of intravenous tPA among 3 doses (0.75, 0.9, 1.0 mg/kg) in children aged 2 through 17 years within 4.5 hours of symptom onset. The primary end point for TIPS trial was designed to determine the pharmacokinetics of tPA and its inhibitor plasminogen activator inhibitor (plasminogen activator inhibitor-1) in children receiving intravenous tPA for acute arterial ischemic stroke. In December 2013, the TIPS trial was closed secondary to low recruitment.

Potential site PIs were neurologists or hematologists with expertise in pediatric stroke who were identified primarily through participation in the International Pediatric Stroke Study (IPSS; https://app3. cch.sickkids.ca/cstrokestudy/) based at the Hospital for Sick Children in Toronto, Ontario, Canada. To establish site suitability for participation in TIPS, the PIs at each candidate site were queried for the incidence of pediatric stroke at their site as well as their ability to diagnose and treat acute pediatric stroke rapidly. Because of well-recognized delay in diagnosis of pediatric stroke,\(^11,12\) both were considered critical to study accrual. In preparation for site selection for TIPS, data were collected regarding availability of emergency and intensive care services, emergent neuroimaging, pediatric sedation and analgesia, pediatric neurosurgical and pediatric hematologic availability from sites seeking to participate. All sites were required to have a PICU in
a tertiary hospital capable to provide care to children after treatment with tPA, continuous availability of urgent neuroimaging, either MRI/magnetic resonance angiography or computed tomography/computed tomography angiography, and availability of urgent pediatric anesthesia and pediatric neurosurgery consultation. The TIPS trial leadership consisted of experts in pediatric stroke, hematology, pharmacology, and stroke imaging.

After site activation, each of the 17 participating TIPS centers were sent a questionnaire to complete at site activation regarding the process of achieving site readiness for treating acute stroke in children (Survey for Development of Pediatric Stroke Center in Appendix I in the online-only Data Supplement). The first section of the questionnaire asked to describe the timeline for development of (1) hospital-wide stroke systems, including development of systems for stroke triage; (2) a 24-hour/7-day per week (24/7) pediatric stroke service (ie, a team of pediatric stroke experts capable of administering tPA to children 24 hours a day, 7 days a week); and (3) emergency department (ED)/PICU stroke protocols. The second section of the survey asked about the evolution and timeline for development of outpatient care for pediatric stroke patients, including the establishment of a stroke clinic, as well as the extent to which a multidisciplinary team of clinicians was available to care for children with stroke: neurologist, hematologist, neuroradiologist, neurosurgeon, interventional neuroradiologist, cardiologist, rheumatologist, neuropsychologist, rehabilitation specialist, psychologist, vascular geneticist, social worker, or other subspecialist. The third part of the questionnaire surveyed readiness for vascular and neuroimaging, including stroke MRI capability and availability of anesthesia to sedate a younger or agitated patient for urgent MRI. In the last general quantitative section, sites were questioned about the resources necessary to conduct the trial, overall hospital support, quality initiatives, continuing medical education, as well as the impact of preparation on readiness for an acute pediatric stroke. Readiness was measured via a Likert scale (1=not ready at all to 10=completely ready), with the site PI answering the following question: Before preparing for TIPS, how prepared was your hospital to acutely treat a child with stroke? Finally, site PIs were asked for general qualitative comments about the challenges of creating a pediatric stroke center capable of participation in TIPS.

Results

All 17 TIPS sites activated by November 2013 completed the questionnaire and provided responses between September and November 2013. Responding site PIs reported that they spent 2.5% to 100% (mean, 62%; median, 70%) of their full-time equivalent on stroke activities, with 2.5% to 50% (mean, 22%) in stroke neurology clinical care, 0% to 10% (mean, 9%) in stroke-related administration, and 5% to 75% (mean, 31%) in stroke research. As of 2013, the majority of sites (16/17) had robust systems in place to identify, image, and treat children with acute stroke rapidly (Table 1). In addition, the stroke teams have a broad representation from multiple subspecialties (Table 2). Across the 17 sites, an average of 7 subspecialties with specialized expertise in pediatric stroke were available for care of children with acute stroke.

The majority of sites have had ≥3 subspecialists interested in stroke since 2004, but systems for acute stroke care were lacking at that time, with 18% of sites having a pediatric stroke team, 18% of sites having a 24/7 stroke team, 6% of sites having an ED order set, 12% of sites having a PICU order set, 24% of sites having acute stroke MRI capabilities 24/7, and 18% of sites having 24/7 acute sedated stroke MRI available...
from 6.2 to 8.7 after preparation for TIPS (P<0.001). The majority of respondents reported that readiness was increased because of 3 main factors: institution of stroke triage protocols, use of stroke alerts/stroke codes, and the use of stroke order sets. Almost all sites (13/17) reported that the site PI spent >40 hours preparing for TIPS trial. In reviewing the quantitative and qualitative responses to the questionnaire, the greatest challenges to attaining site readiness for TIPS were most related to limited financial resources, institutional review board approval, regulatory issues, and availability of study pharmacy resources.

Discussion

After preparation for the TIPS trial, TIPS site PIs reported a significant increase in readiness for treatment of acute childhood stroke, as indicated by formation and greater availability of pediatric-specific stroke teams, urgent neuroimaging, and specific stroke pathways in the ED and intensive care unit. Interestingly, although the majority of these sites reported ample availability of subspecialists related to care of children with stroke since 2004, a high degree of readiness to treat acute stroke rapidly was not reported at that time. Indeed, as illustrated by the Figure, the pace of development of site readiness increased markedly since funding for the TIPS trial in 2010. These data indicate that preparation for the TIPS trial has created an emerging network of PPSCs in North America, able to optimize the identification, imaging, and treatment of acute stroke in children.

Development of these emerging PPSCs required substantial resources, many of them supported by individual medical centers and local site PIs. Recruitment, education, and organization of support personnel were cited as the most time- and energy-consuming start-up tasks at most sites and were thought to have been critically important for institutional commitment to TIPS. Creation and expansion of the stroke service, MRI availability, and implementation of stroke order sets often required establishment of a stroke council with members from divisions across the hospital. In addition, PPSC creation required many meetings with numerous clinical services at each center including transport team, ED, PICU, cardiac intensive care, neurology, nursing, hematology, research pharmacy, cardiology, anesthesia, neuroradiology, research administration, and clinical and translational research support services. A mean of 10 formal lectures related to institutional preparedness to treat children with acute stroke were presented at each center in the process (of 17 responses, mean, 10; median, 9). Design and acquisition of institution approval of stroke order sets and care guidelines for triage, ED, intensive care unit, and post-thrombolysis care usually required 6 to 9 months to move through hospital committees.

The American Heart Association promulgates and maintains standards for hospital centers to attain certification as an adult PSC. In preparing for the TIPS trial, the majority of TIPS sites have met most of the primary criteria established by the Brain Attack Coalition in 2000 for adult PSCs. The initial primary criteria for adult PSCs in 2000 were divided into 2 areas: patient care areas and support services. The patient care criteria included acute stroke team composition, generation of written care protocols, organization of emergency medical care services, creation of a stroke unit, and neurosurgical services. The great majority of TIPS sites met these adult PSC requirements for the patient care areas criteria (Table 3). Importantly, 88% (15/17) of the TIPS sites have established relationships with adult PSCs within the same hospital or in adjacent adult medical centers. Existing certified adult PSCs provide invaluable modeling for nascent PPSCs. Although stroke pathogenesis differs between adults and children, close relationships between pediatric and adult stroke teams advance the development of the emerging PPSCs through shared conferences, clinical points of interaction, and exchange of patient care protocols. Support services included in the original adult Brain Attack Coalition criteria included a commitment by and support from the medical organization, a stroke center director, neuroimaging services, laboratory services, outcome and quality improvement activities, and continuing medical education. Remarkably, the majority of TIPS sites meet these criteria as well (Table 3).

Currently, designation as an adult PSC requires development of a stroke-focused clinical program administered by clinicians experienced in stroke care. Inclusion of an advanced practice nurse with expertise in neurovascular patient care, as has been done in many adult PSCs, would provide invaluable support in development and maintenance of care protocols for children who have had stroke. Such nursing leadership may be highly desirable for inclusion in criteria for pediatric PSCs, but is currently only available at 3 of the TIPS sites. In addition, care delivered must be tailored to meet the needs of the patients with stroke. Finally, the center must collect and use stroke data on outcomes and complications.
of managing and studying pediatric stroke with the same standards of care and alacrity that are found in adult stroke centers and by providing valuable resources for smaller surrounding pediatric centers that may encounter children who present with acute arterial ischemic stroke. These comprehensive pediatric stroke centers would clearly need increased hospital support in the form of advanced practice nurses and stroke team coordinators. Given the challenges of recruitment faced by TIPS trial, these Comprehensive Pediatric Stroke Centers will likely need to function as regional pediatric stroke telemedicine hubs, capable of interacting with multiple smaller PPSCs, allowing for the potential to administer acute therapies to an increasing proportion of children with stroke.

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**Disclosures**

None.

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on behalf of the Thrombolysis in Pediatric Stroke Study

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SUPPLEMENTAL MATERIAL

1- How long have you been at your current institution? ________ years
2- Name of primary institution:
3- What percentage of your time is spent doing:
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4- Is your pediatric stroke program affiliated with an adult stroke program? □ Yes □ No

HOSPITAL PROGRAMS

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CLINICAL EXPERTISE

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**IPSS**

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<td>What year did you join the IPSS?</td>
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<td>What year did you start enrolling patients in the IPSS?</td>
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<td>What year did you initiate planning for TIPS?</td>
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**IMAGING**

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<tr>
<td>What year did your institution acquire 24 hour MRI availability for stroke?</td>
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<td>What year did your institution acquire availability of 24 hour sedation for MRI for stroke?</td>
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**GENERAL:**

1. How much time do you estimate you spent on TIPS start-up as the PI?
   - [ ] 0-10 hours
   - [ ] 10-20 hours
   - [ ] 20-30 hours
2. During study start-up, did you have a research coordinator to assist you?
   - Yes
   - No

3. What has changed in your program (if anything) with establishing TIPS at your site?
   - Institution of stroke triage protocols
   - Use of stroke alerts/stroke codes
   - Use of stroke order sets
   - Identification of Stroke team
   - 24/7 neuroimaging for stroke
   - 24/7 availability of sedation for neuroimaging
   - Neuroradiology available to review imaging
   - Other ______________________

4. What were the 2 greatest challenges to get TIPS up and running?
   1.
   2.

5. Prior to preparing for TIPS, how prepared was your hospital to acutely treat a child with stroke?

   0 1 2 3 4 5 6 7 8 9 10
   Not at all prepared  Completely prepared
Emergence of the Primary Pediatric Stroke Center: impact of the Thrombolysis in Pediatric Stroke (TIPS) Trial

6. After your participation in TIPS, how prepared was your hospital to acutely treat a child with stroke?

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<tbody>
<tr>
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<td>Completely prepared</td>
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Follow-up Questions:

1. How many lectures/talks/seminars to services, RNs, pharmacy, etc did you give in preparation for TIPS?
2. Do you feel that your medical institution is committed to and supportive of an acute pediatric stroke program?
3. Does your pediatric stroke program have a director/co-directors? Are you that person?
4. Does your pediatric stroke program have formal outcome and quality improvement activities?
5. Does your staff receive CME training specific to pediatric stroke?