Overview
Childhood “stroke” encompasses the following four broad, heterogeneous categories of cerebrovascular disorders that occur in newborns and older infants and children:

1. **Arterial Ischemic Stroke (AIS):** defined as presentation with a focal deficit or seizure localizing to an ischemic area of brain in a known arterial vascular territory.
2. **Cerebral Sinovenous Thrombosis (CSVT):** defined as thrombus within cerebral veins or dural venous sinuses, with or without venous infarction and hemorrhage.
3. **Hemorrhagic Stroke:** defined as spontaneous intracerebral hemorrhage with or without intraventricular extension, intraventricular hemorrhage, and non-traumatic subarachnoid hemorrhage.
4. **“Pre-symptomatic” Vascular Conditions:** including arteriovenous malformation (AVM), aneurysms, cavernomas, moyamoya disease/syndrome, and vein of Galen malformations.

Stroke is increasingly recognized as a major cause of morbidity and mortality in children around the world. The incidence of AIS in children (29 days of life to 18 years) is 2.3 to 13 per 100,000/year while CSVT is much less common, occurring in 0.34 to 0.67 per 100,000/year. The incidence of hemorrhagic stroke is estimated at 1 to 3 per 100,000/year. AIS and hemorrhagic stroke are far more common in neonates (≤ 28 days of life), occurring in 1 of 2000-4000 term births. There is a male predominance of stroke in all subtypes and at all ages, for reasons that are poorly understood.

Recent Advances in Childhood Cerebrovascular Disorders
The subspecialty of pediatric stroke has developed rapidly over the past two decades and considerable progress has been made in the diagnostic evaluation and treatment of children with cerebrovascular disease as well as in our understanding of stroke risk factors, pathophysiology and recovery processes in children. Many of these advances have been made as a direct result of the International Pediatric Stroke Study (IPSS), a consortium representing over 140 clinicians and researchers from 50 countries. With the emergence of primary “pediatric stroke centers,” children with stroke are now receiving earlier and more rapid neuroimaging diagnosis, and those with AIS are being considered for hyperacute stroke therapies widely available for adults, including tPA and mechanical thrombectomy.

Despite recent progress, challenges remain. Childhood stroke is rare and even tertiary care referrals centers that are knowledgeable and experienced in the field may still only see a limited number of cases per year. Further, while front line clinicians working in emergency departments are increasingly more aware of the presenting signs and symptoms of pediatric stroke, educational gaps persist. Stroke symptoms and signs can be subtle and harder to identify in children, especially in infants and toddlers. Complicating matters further are the number of conditions that “mimic” stroke in childhood, chiefly migraine with aura and seizure. When an adult develops a new, acute neurological deficit, an underlying stroke is assumed to have occurred until proven otherwise. A child with a similar presentation is often assumed to have a migraine with aura, or a Todd’s paresis secondary to seizure, even when no seizure has been witnessed or reported by caregivers. For this reason, stroke diagnosis in children is often delayed well-beyond the time window for acute thrombolytic therapies, even though most children with arterial ischemic stroke present for care within 6 hours of symptom onset. Unlike in adults, in hospital factors appear to contribute more to delays in diagnosis than pre-hospital factors.

Advances in the Diagnostic Evaluation of Stroke in Children
The differentiation of stroke from clinical mimics is critically important as decisions made early in triage and initial evaluation by nurses and physicians influence the speed with which neuroimaging is pursued for diagnostic confirmation, the initiation of anti-thrombotic therapy in AIS and neurosurgical intervention in hemorrhagic stroke.
Being healthy in the week before presentation, an inability to walk, and face or arm weakness at time of presentation are all associated with increased odds of stroke.\textsuperscript{23} In the past decade, tertiary centers with resident pediatric stroke specialists have developed pediatric stroke “teams” and alert systems to more rapidly triage children presenting to emergency departments with suspected stroke and to consider such children for hyperacute therapies.\textsuperscript{25, 26}

The care of children with acute stroke remains poorly coordinated in most health care facilities due to the limited number of cases seen and the need for considerable investment in training, education, and human and facility resources to establish pediatric stroke “teams” and alert systems. Childhood stroke diagnosis and treatment is a multidisciplinary effort that requires rapid and careful coordination of input from transport services, nursing, emergency medicine, neurology and neuroradiology, neurosurgery, anesthesiology and critical care, hematology, cardiology, and pharmacy. The development of stroke order sets and neuroimaging protocols can help to expedite the process, but intra- and inter-hospital, person-to-person communication is key.

The American Heart Association and the American College of Chest Physicians published consensus-based guidelines for the diagnostic evaluation and treatment of pediatric AIS in 2008 and 2012, respectively.\textsuperscript{9, 10} In the emergency department, most children undergo basic laboratory evaluation including CBC, PTT, PT/INR, electrocardiogram, as well as diagnostic testing for infection when appropriate. Additional investigations performed after stroke is confirmed typically include an echocardiogram (for AIS) and thrombophilia testing (for AIS and CSVT) even when other known stroke etiologies have been identified.

Older infants and children with suspected stroke often undergo non-contrast head computed tomography (CT) as the first imaging procedure because it can be readily accessed and does not require sedation. For similar reasons, newborns often undergo cranial ultrasound. While ultrasound and head CT can rapidly identify intracranial hemorrhage and ventriculomegaly, the sensitivity of these neuroimaging procedures for early ischemic infarcts and cerebral sinus venous thrombosis is considerably lower. Given this, MRI is considered to be the diagnostic modality of choice for confirmation of AIS and CSVT in neonates and children and some pediatric centers have developed hyperacute MRI protocols for stroke that can be performed in less than 20 minutes.\textsuperscript{9, 10} The IPSS Neuroimaging Consortium recently published consensus-based neuroimaging pathways for neonatal and childhood stroke (including AIS, CSVT and hemorrhagic stroke) to aid practitioners in choosing appropriate neuroimaging for children with present stroke.\textsuperscript{31, 32} In neonates, MRI is preferred, given its superior anatomic resolution and sensitivity for acute ischemia without need for irradiation. Recommended sequences include diffusion-weighted imaging and apparent diffusion coefficient mapping to diagnose acute ischemia, gradient-recalled echo or susceptibility-weighted imaging to detect intracranial blood and its breakdown products, and T1- and T2- weighted imaging to assess for myelination, extra-axial blood and edema. MR angiography of the brain may be useful to detect vascular abnormalities, with venography if CSVT is suspected. These sequences also apply to older infants and children, who additionally benefit from dedicated vascular imaging of the brain and neck.

**Advances in Childhood Stroke Pathophysiology**

Most children with ischemic stroke can be assigned to one of three broad pathogenic categories--cardioembolic, idiopathic or arteriopathic. Arteriopathy is present in about a third of children and can be progressive, leading to stroke recurrence. Historically, cerebral arteriopathies of childhood were further sub-classified as inflammatory or non-inflammatory, but a lack of a validated and reliable classification system has hindered childhood AIS research. Fortunately, recent progress has been made in our classification of arteriopathies\textsuperscript{11, 12} as well as in our understanding of underlying mechanisms.\textsuperscript{27-30}

The CASCADE (Childhood AIS Standardized Classification and Diagnostic Evaluation) criteria were developed by the IPSS.\textsuperscript{12} The classification system is based on the primary anatomic site of disease (the heart, the great vessels of the neck, or the intracranial vessels) and also includes secondary classification based on additional clinical data available. The CASCADE criteria can be used in both the acute and chronic phases of the stroke. The criteria were recently validated and shown to be reliable system for childhood AIS classification.\textsuperscript{11}

The NIH-funded Vascular Effects of Infection in Pediatric Stroke (VIPS) study\textsuperscript{27-30} has shed light on the important role that infection and inflammation play in childhood arteriopathies. The VIPS study found that infection—including common childhood viruses as well as herpesviruses—can act as a trigger for stroke in children. Moreover, elevated levels of inflammatory mediators—C-reactive protein and serum amyloid— at acute presentation appear to predict a higher risk of recurrent AIS. VIPS also found that rates of AIS recurrence were

higher in children with arteriopathy progression on follow-up neuroimaging. An improved understanding of the inflammatory processes underlying childhood arteriopathies will help the development of secondary stroke prevention strategies.

**Advances in Childhood Stroke Treatment**

**Supportive Care Measures**

The mainstay of children with stroke, regardless of subtype, is supportive care targeting the underlying etiology in addition to maintenance of cerebral perfusion, neuronal protection and salvage. This includes supporting the airway and oxygenation as needed, initiating maintenance IV fluids with normal saline (except in neonates and young infants), correction of anemia, and targeting physiologic homeostasis with normothermia and normoglycemia. Mild hypertension is prevalent in children after stroke. Optimal blood pressure management is under investigation as there is some data suggesting that hypertension may be an independent risk factor for AIS in children and contribute to increased mortality. At our institution, children are admitted to the pediatric intensive care unit for a period of observation, with the head of bed positioned flat for suspected AIS, and elevated to 30 degrees for suspected CSVT and hemorrhagic stroke. Children with congenital heart disease are carefully monitored for clinical changes related to head of bed positioning and volume status.

Given that most neonates and up to a third of older infants and children have acute symptomatic seizures at time of stroke onset, seizure identification and management is critically important to avoid exacerbation of pre-existing ischemic brain injury. Moreover, the increasingly widespread application of continuous video EEG monitoring has shown a high rate of subclinical seizures in both neonates and older children, supporting closer encephalographic monitoring of children after stroke. Remote symptomatic seizures and epilepsy develop later in much smaller, though noteworthy proportions, and while some appear to resolve their epilepsy in childhood, many report worse health-related quality of life than their counterparts who do not develop epilepsy.

**Acute Treatment of Cerebral Sinovenous Thrombosis and Hemorrhagic Stroke**

Cerebral sinovenous thrombosis typically results from the convergence of multiple risk factors, including fever, head and neck infections, dehydration, anemia, chronic systemic illness, and prothrombotic disorders. In addition to the supportive measures noted above, identification and treatment of the underlying risk factors is important to prevent thrombus propagation, venous ischemia and hemorrhage. CSVT can be a life-threatening condition, particularly when clots are large or extensive. Early activation of anticoagulation therapy has been the mainstay of treatment in both neonates and children, and continues to be the mainstay of CSVT treatment in both neonates and children. Anticoagulation is typically continued for 3-6 months, or longer when CSVT risk factors persist. There are no treatment trials in children to support this practice, though an anticoagulation trial in neonates is in development.

Vascular malformations, followed by brain tumors and coagulopathy are the most frequent reasons for pediatric hemorrhagic stroke. The acute treatment of hemorrhagic stroke is often under the purview of neurosurgery, though most children benefit from consultation with neurology, particularly when neurosurgical intervention is not required.

**Acute Treatment of Arterial Ischemic Stroke - Thrombolysis**

There are no randomized controlled trials of the acute treatment of pediatric stroke and no data about tPA safety and usage in childhood AIS upon which to base consensus guidelines. Thrombolytic therapy and intra-arterial thrombectomy are rarely mentioned in the AHA Stroke Council’s Management of Stroke in Infants and Children and are only recommended as a last resort due to lack of level I evidence. Only about 2% of children with acute AIS receive treatment with tPA in the United States, frequently outside of established safety guidelines used in adults.

In 2010, the NINDS funded the first prospective treatment trial in acute pediatric stroke, the Thrombolysis in Pediatric Stroke (TIPS) trial (NIH grant R01NS065848), at 22 IPSS centers. TIPS employed a multi-institutional design to determine the safety, optimal dose and feasibility of intravenous tPA treatment of children with AIS. Inclusion criteria were children 2-17 years of age evaluated within 4.5 hours of stroke onset, with radiographic confirmation of an acute infarct, evidence of partial or full vascular occlusion and PedNIHSS 4-24. Secondary aims were determination of tPA pharmacokinetics and assessment of 3 month clinical outcome. The trial was closed in December, 2013 for lack of patient accrual. Over the open enrollment phase of the trial, 93 patients were screened, of which 43 (46%) had confirmed stroke and the remainder had stroke mimics. Of those with confirmed stroke, half had medical contraindications to stroke and the rest either presented later than 4.5 hours or had a low

PedNIHSS. Ultimately, only one child was enrolled in the study before closure. While this outcome was a disappointment to the pediatric stroke community, the trial led to the development and refinement of primary pediatric stroke centers, and it is hoped that these centers will be represented in future trials of acute stroke intervention.

**Acute Treatment of Arterial Ischemic Stroke - Mechanical thrombectomy**

In light of recent consecutive strongly positive randomized controlled trials of mechanical thrombectomy in adults, intra-arterial treatment of AIS in the pediatric population is increasingly being considered. The challenges inherent in using tPA—delays in diagnosis, stroke mimics, and heterogeneous pathophysiology including arteriopathy—also apply to intra-arterial treatment. For this reason, the pediatric candidates most likely to be amenable to mechanical thrombectomy are those with cardioembolic stroke. These children comprise about a third of all those with AIS and they are often hospitalized in an intensive care unit setting where changes in neurological status are rapidly identified and investigated with neuroimaging. Moreover, they are often already anti-coagulated and therefore, not candidates for tPA. Endovascular therapy may be the only option in this subset of patients. Recent published cases series have highlighted the potential for intra-arterial treatment in children, but questions around safety and efficacy remain.

**Future Directions**

While great progress has been made in the field, pediatric stroke needs to continue to grow in the direction of multi-center treatment trials and research collaborations. Plans are underway for an anticoagulation trial of neonatal CSVT and given recent VIPS results, an anti-inflammatory trial of childhood arteriopathy (FOCAS) is under consideration. The recurrence risk of posterior circulation stroke is high, and this subtype of childhood AIS may be well suited to a trial of anti-thrombotic therapies. Future areas of neuroimaging include the role of perfusion weighted imaging in defining stroke onset and penumbra and the role of vessel wall imaging in diagnosing and characterizing arteriopathies. As dedicated, primary pediatric stroke centers continue to develop, diagnostic evaluation and treatment protocols should be standardized across these centers to inform treatment, clinical trials and evidence-based guidelines. Finally, the pediatric stroke community is working to ensure that if tPA and mechanical thrombectomy are used in childhood ischemic stroke, standard safety protocols are not only established, but followed, and outcomes are collected and used to guide further recommendations.

**REFERENCES**


