



**AHA/ASA SCIENTIFIC STATEMENT
MANAGEMENT OF STROKE IN NEONATES
AND CHILDREN
A SCIENTIFIC STATEMENT FROM THE
AMERICAN HEART
ASSOCIATION/AMERICAN STROKE
ASSOCIATION**

American Heart Association

*The American Academy of Neurology affirms
the value of this statement as an educational
tool for neurologists.*



**SLIDE SET PREPARED BY MEMBERS OF THE STROKE
PROFESSIONAL EDUCATION COMMITTEE**

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OVERVIEW OF CHILDHOOD AND PERINATAL STROKE

INTRODUCTION AND DEFINITION

- Standard adult definition of stroke—an acute onset neurological sign or symptom attributable to focal brain infarction or hemorrhage—applies to children as reflected by the NIH Common Data Elements (CDE) definition
- Important for pediatric health professionals to be able to recognize stroke at different ages and to treat stroke to preserve brain function and promote repair and recovery.

CLASSIFICATION

- **By age**
 - stroke occurring from 28 weeks gestation to 28 post-natal days of life is broadly classified as *perinatal stroke*
 - stroke occurring after 28 days to 18 years of age is classified as childhood stroke
- **Perinatal stroke**
 - *Acute perinatal stroke* - newborn infants at or near birth and typically presents shortly after onset with focal seizures or encephalopathy
 - *Presumed perinatal stroke* - chronic infarcts, diagnosed in a delayed fashion, that are presumed to have occurred in the perinatal period
 - typically present with pathologic early handedness or seizures, leading to brain imaging and the diagnosis of a remote infarction

ISCHEMIC OR HEMORRHAGIC

Ischemic stroke

- arterial ischemic stroke (AIS)
- venous infarction
 - cerebral sinovenous thrombosis (CSVT)
 - may or may not be accompanied by hemorrhage
 - cortical vein thrombosis
- older infants and children, some literature uses the term 'silent stroke' when asymptomatic infarcts are found on neuroimaging
 - misnomer, as the definition of stroke includes a clinical event; we use the term "silent infarct" in this review.
 - silent infarcts are likely not truly silent; as in adults, a sufficient burden likely causes vascular cognitive impairment.

CLASSIFICATION

- **Adult stroke is related to the traditional risk factors for atherosclerosis,**
 - hypertension, dyslipidemia, obesity, diabetes and cigarette smoking
- **Newer risk factors**
 - Insulin resistance and inflammation
 - atherosclerosis generally *not* a cause of stroke in children and adolescence,
 - Atherosclerotic process that leads to a stroke in adulthood may begin in childhood and dyslipidemia tends to be more prevalent among children with ischemic stroke than in other children
 - Children and adolescents with stroke may be at particularly increased risk for recurrent strokes in later life related to these processes
 - Emphasizes importance of promoting ideal vascular health through good diet and physical activity and avoidance of tobacco products to protect them from recurrent strokes in adulthood

EPIDEMIOLOGY: PERINATAL STROKE

- Arterial ischemic infarction accounts for approximately 80% of perinatal strokes
- Remainder due to CVST or hemorrhage (excluding SAH and IVH in premature babies)
- Ischemic stroke occurs in up to 1/3,500 newborns, although some estimates are as low as 1/10,000 newborns.
- Ratio of ischemic stroke is almost six times higher in newborns than in older children

- Agarwal and colleagues identified 60 individuals with perinatal stroke among a cohort of 208,876 live births
 - represents a frequency of 29/ 100,000 live births, or 1/ 3,500 live births
- Their overall stroke rate for both ischemic and hemorrhagic stroke was 37/100,000 live births, or 1/ 2,700 live births

EPIDEMIOLOGY: PERINATAL STROKE CONT'D

- Armstrong-wells et al. identified 19 infants with hemorrhagic stroke and one with SAH among 323,532 live births in the Northern California Kaiser-Permanente medical care program, representing a population prevalence for perinatal hemorrhagic stroke of 6.2 per 100,000 live births
- Cole et al calculated the incidence of perinatal hemorrhagic stroke to one per 6,300 live births for both hemorrhage and hemorrhagic infarction

EPIDEMIOLOGY: CHILDHOOD STROKE

- Ischemic stroke affects an estimated 1.0-2.0/100,000 children annually in western developed countries
- Incidence varies by age and sex, highest in infants and children under age 5 years, and higher in boys than girls
- African-American and Asian children have a higher incidence than Caucasian children
- Most of the increased ischemic stroke risk in black children is explained by sickle cell disease, which amplifies stroke risk more than 200-fold.
- Hemorrhagic stroke in children can be intracerebral (ich), intraventricular (IVH) or (SAH)
- Hemorrhagic stroke comprise about half of pediatric stroke, with an incidence of ~1-1.7/100,000/year

EPIDEMIOLOGY: CHILDHOOD STROKE CONT'D

- Krishnamurthy et al used all available global data on stroke incidence, prevalence and mortality to evaluate differences in stroke between developed and developing countries and changes from 1990-2013
- 2013 - 97,792 prevalent cases of childhood ischemic stroke and 67,621 prevalent cases of childhood hemorrhagic stroke
 - increase of approximately 35% in the absolute numbers of prevalent childhood strokes since 1990
- Prevalence rates for childhood ischemic stroke and hemorrhagic stroke decreased significantly in developed countries, a decline was seen only in hemorrhagic stroke, with no change in prevalence rates of ischemic stroke in developing countries
 - significant global increase in the absolute number of prevalent strokes in children
- Mortality rate significantly declined, with males showing a trend toward higher childhood stroke death rates (1.5 (1.3-1.8) per 100,000) than females (1.1 (0.9-1.5) per 100,000 globally in 2013)

EPIDEMIOLOGY: RECURRENT STROKE

- Cumulative brain injury due to recurrent stroke is a major concern in older infants and children, and in neonates with cardiac stroke
- Fullerton et al evaluated the risk of recurrent AIS from an international perspective
 - cumulative rate of stroke recurrences was 6.8% (95% CI 4.6%-10%) at 1 month and 12% (95% CI 8.5%-15%) at 1 year with most children on antithrombotics
- Strongest predictor of stroke recurrence was presence of an arteriopathy → 5-fold increased recurrence risk
- Risk was present despite increased utilization of antithrombotic agents

PERINATAL STROKE

PERINATAL STROKE

Perinatal stroke

- Ischemic and hemorrhagic events resulting from disruption of either arteries or veins from 20 weeks' gestation through 28 days after birth
- Approximately 80% of these lesions are ischemic, remainder are due to CVST or hemorrhage
- Most presumed perinatal ischemic strokes are in an arterial distribution

ARTERIAL ISCHEMIC STROKE IN NEONATES

NEONATAL AIS: PRESENTATION

- Newborns often present with seizures - focal motor seizures involving only one extremity
- One study seizures at the time of AIS occurred in 94% of neonates versus only in 17% of older children
- Occasionally, perinatal AIS presents with encephalopathy leading to suspicion for hypoxic-ischemic injury rather than AIS
 - neuroimaging distinguishes the diagnoses
 - left cerebral hemisphere affected in 80% of neonates with unilateral infarctions
 - Individuals with presumed perinatal stroke may seem normal after birth, but later present with delayed motor milestones, epilepsy, asymmetric motor function or early handedness

NEONATAL AIS: PRESENTATION CONT'D

- Some of these children with presumed perinatal ischemic stroke may have had clinical or subclinical seizures that escaped detection in the neonatal period due to the challenges of distinguishing neonatal seizures from normal infant movements
- Single center cohort, majority affected were male and most of the lesions fell within MCA territories
 - proximal M1 segment infarction was most common
 - venous periventricular infarction next highest and accounted for 75% of subcortical injuries
 - Motor outcomes predicted by basal ganglia involvement including leg hemiparesis, spasticity, and need for assistive devices
 - Non-motor outcomes associated with cortical involvement, including cognitive/behavioral outcomes, visual deficits, and epilepsy

NEONATAL AIS: RISK FACTORS

- Maternal and neonatal factors
- Normal activation of coagulation factors in mother and low levels of factors in the infant just before and after the time of delivery may contribute to increased stroke risk
- Neonates sometimes have an inherited thrombophilia
- Other risk factors include cardiac lesions, coagulation disorders, infection, trauma, and asphyxia
- Porencephaly and intrauterine stroke linked to col4a1 mutation
 - subunit of type IV collagen and plays a role in angiogenesis

NEONATAL AIS: RISK FACTORS CONT'D

- Maternal factors for perinatal/presumed AIS include primiparity or a history of infertility, chorioamnionitis, oligohydramnios, premature rupture of membranes, vacuum extraction, emergency cesarean section, coagulation disorders, and pre-eclampsia
- Likelihood of neonatal AIS increases dramatically with an increasing number of risk factors, but in many individuals, no single etiology can be identified

NEONATAL AIS: EVALUATION CONT'D

- MRI should be performed to diagnose the stroke
- MRA & MRV should be performed as well, especially when venous thrombosis is suspected

NEONATAL AIS: MANAGEMENT

- Supportive care measures include control of seizures, optimization of oxygenation, and correction of dehydration and anemia
- Antiplatelet (i.e. aspirin) or anticoagulation with LMWH or unfractionated heparin rarely indicated due to low risk of recurrent stroke
- must be considered in neonates with high risk of recurrent AIS due to documented thrombophilia or complex congenital heart disease (not including patent foramen ovale)

NEONATAL AIS: MANAGEMENT CONT'D

- Hyperacute stroke therapies (thrombolytics and mechanical thrombectomy) rarely considered in neonates with AIS as there is no evidence for their use.
- Endovascular mechanical thrombectomy sometimes utilized in older children with an arterial occlusion, the small artery size of neonates precludes use of current endovascular devices.

NEONATAL AIS: OUTCOMES

MAJORITY OF NEONATES WITH AIS EXPERIENCE RESIDUAL NEUROLOGICAL DEFICITS

- Golomb et al summarized 111 children with perinatal stroke,: 67 presented as neonates and 44 discovered later
 - 76 (68%) children exhibited cerebral palsy and 55 of these individuals had at least one additional disability
 - 45 (59%) experienced cognitive or speech impairment
 - 36 (47%) had epilepsy
 - Detailed neuropsychological testing often documents cognitive dysfunction, especially related to attention and executive function

Functional deficits more likely to occur with a larger-sized infarction, with comorbid epilepsy, or with presumed perinatal stroke

Study from Switzerland corroborated findings → 2 years after birth, 39% diagnosed with cerebral palsy and 31% had delayed mental performance

NEONATAL AIS: OUTCOMES CONT'D

- Congenital heart disease (CHD) and other medical co-morbidities can impair brain growth and development even in absence of stroke and can be difficult to ascribe neurologic deficits to the stroke in individuals with these conditions
- Studies specific to presumed perinatal ischemic strokes shown a similar array of long-term deficits, and Kirton, et al, demonstrated imaging characteristics of the brain injury can predict outcomes

NEONATAL AIS: OUTCOMES CONT'D

- Likelihood of recurrence is low except in those with CHD
- Fullerton et al documented recurrent stroke in 1 of 84 (1.2%) neonates
- Lehman et al identified 6 individuals with a recurrent ischemic lesion among 215 neonates with AIS or CVST
- Neonates with cardiac disease may have a higher recurrence risk, similar to older infants and children with cardiac disease

NEONATAL AIS: REHABILITATION

- Early intervention program based on best available evidence of interventions that work in older children, game (goals activity motor enrichment) was evaluated in infants in a single randomized trial with promising results improving motor outcomes of game participants when compared to standard care (SC)
- Another study explored effectiveness of baby-CIMT (constraint-induced movement therapy) and baby-massage in infants for improving manual ability of infants <12 months with unilateral cerebral palsy (CP)
 - baby-CIMT improved unimanual ability more than massage

CEREBRAL SINOVENOUS THROMBOSIS (CSV T) IN NEONATES

CSV: PRESENTATION

- Clinical manifestations of CSV in neonates often nonspecific → lethargy, irritability, or seizures
- Symptomatic seizures common among neonates with CSV than in older individuals, but occurrence of seizures at the time of presentation does not predict the occurrence of long-term epilepsy

CSVT: RISK FACTORS AND ETIOLOGIES

- Associated conditions include gestational or delivery complications, dehydration, sepsis, meningitis, cardiac defects, and coagulation disorders
- No controlled studies have proven the associations although these factors are commonly thought of as risk factors

CSVT: MANAGEMENT

- Supportive measures: control epileptic seizures, correct dehydration and anemia, and treat underlying infections
- Institutional practices regarding anticoagulation are highly variable in the absence of definitive studies demonstrating safety and clinical benefit
- Anticoagulation routinely utilized at some institutions and appears to be generally well-tolerated, even with intracranial hemorrhage
- Jordan et al analyzed factors that affected the use of anticoagulation in 84 neonates with isolated CSVT from ten countries
- Presence of infarction, hemorrhage, systemic illness or dehydration did not alter likelihood of antithrombotic administration
- Individuals born in the us were significantly less likely to receive anticoagulants than from other parts of the world

CSVT: MANAGEMENT CONT'D

Moharir et al analyzed 83 neonates from single Canadian center

- 29 (35%) neonates received either standard heparin, LMWH, or warfarin
- major hemorrhage occurred in 3/21 (14%) treated with a pre-existing intracranial hemorrhage, and 0/17 without a pre-existing hemorrhage
- Follow-up imaging demonstrated thrombus propagation in 10/35 (28%) neonates who did not receive anticoagulation and only 1/22 (4%) of the neonates who were treated
- Thrombus propagation associated with a new venous infarction in 10% of neonates and a less favorable clinical outcome

CSV T: MANAGEMENT CONT'D

- Absence of a clinical trial → data suggest that anticoagulation is safe for use in neonates, especially in the absence of a brain hemorrhage, and provide preliminary evidence that such therapy is useful
- Those centers that do not routinely utilize anticoagulation for neonatal CSV T often consider anticoagulation for thrombus propagation on serial imaging or a deteriorating clinical status related to the CSV T
- No evidence for thrombolytic agents or endovascular therapy for neonatal CSV T

CSVT: EVALUATION

- Thrombophilia evaluation in the neonate has limited clinical utility because levels of protein C, S, antithrombin and factor XI are normally decreased to 30% of adults levels, and these levels only approach adult levels at various time points during childhood
- MRI/MTV should be performed to diagnose the thrombosis,

CSVT: OUTCOMES

- Reported frequency of long-term neurological dysfunction is variable
- Individuals with venous infarction and those with seizures at the time of diagnosis tend to experience more serious neurological sequelae
- Individuals with large venous infarctions more likely to experience neurodevelopmental impairment
- Fitzgerald et al summarized 42 neonates with CSVT, and detailed follow-up data were available for 27/41 survivors
 - 16 (59%) cognitive impairment, 18 (67%) cerebral palsy, and 11 (41%) epilepsy

CSVT: OUTCOMES

- Limited information about recurrence risk, but appears to be low
- Kenet et al investigated recurrence risk in a cohort of 396 children
 - 0/22 individuals who experienced recurrent thromboses were <2 years old at the time of initial thrombosis

HEMORRHAGIC STROKE IN NEONATES

NEONATAL HEMORRHAGE: PRESENTATION

- Tends to be nonspecific
- 20 neonates described by Armstrong-Wells et al → 65% experienced seizures and all exhibited encephalopathy
- More common than previously reported, $\geq 1/6300$ live births
- Asymptomatic ich found on brain MRIs of 15% of late preterm and term newborns
 - incidence of hemorrhagic stroke, clinically symptomatic ICH, is difficult to define

NEONATAL HEMORRHAGE: RISK FACTORS AND ETIOLOGIES

- Include coagulopathy, thrombocytopenia, trauma and, rarely, structural vascular lesions
- No specific etiology can be identified in the majority of neonates with hemorrhagic stroke, risk factors include post-maturity, emergency caesarean delivery, fetal distress, and male gender
- Mutations in col4a1 should be considered in neonates with cerebral hemorrhage, porencephaly, glaucoma, and/or cataracts
- Some hemorrhagic lesions, such as periventricular hemorrhagic venous infarction, may represent hemorrhagic conversion of an arterial or venous infarction

NEONATAL HEMORRHAGE: RISK FACTORS AND ETIOLOGIES

- Acquired or congenital coagulopathy may lead to ICH
- Hemorrhagic disease remains problematic in areas of the world where supplemental vitamin k not routinely administered to newborns
- In U.S., ICH has documented in babies whose caregivers refused vitamin k administration after birth
- Breastfeeding infants may also develop vitamin k deficiency
- Babies whose mothers ingested warfarin, phenytoin, or barbiturates during pregnancy sometimes develop a vitamin k-related coagulopathy
- ICH documented in neonates with hemophilia a and other hereditary coagulopathies

NEONATAL HEMORRHAGE: RISK FACTORS AND ETIOLOGIES

- Role for and timing of vascular imaging to rule out congenital structural vascular lesion (AVM or AVF) remain unclear for all cases
- MRA non-invasive but may miss smaller lesions
- Conventional angiography considered if clinical evidence of a congenital AVF (heart failure, pulmonary HTN, cranial bruit) or a family history suggestive of an autosomal dominant syndrome like hereditary hemorrhagic telangiectasia

NEONATAL HEMORRHAGE: MANAGEMENT

- Correct markedly low platelet counts and coagulation factor deficiencies
- Large doses of vitamin k may be needed to correct factor deficiencies from maternal medications
- Surgical evacuation of hematoma may reduce extremely high intracranial pressure, but rarely performed in neonates, and it is not clear whether surgery improves the eventual outcome
- Ventricular drainage and, if indicated, later shunting for progressive hydrocephalus due to IVH is appropriate

NEONATAL CONSIDERATIONS FOR CLINICAL PRACTICE

NEONATAL CONSIDERATIONS FOR CLINICAL PRACTICE

- Vitamin k routinely administered to newborns; larger doses may be needed to correct factor deficiencies resulting from maternal medications
- Aspirin, LMWH, or unfractionated heparin may be considered if at risk for stroke recurrence due to severe thrombophilia or cerebral embolism due to cardiac disease but generally not considered for first ischemic infarction
- No evidence for hyperacute stroke therapies (thrombolytic agents or embolectomy) with an arterial occlusion
- Anticoagulation with LMWH or heparin considered in CSVT, particularly with deterioration or evidence of thrombus extension on serial imaging
 - Serial imaging at 5-7 days considered to exclude propagation when a decision is made not to anticoagulate

NEONATAL CONSIDERATIONS FOR CLINICAL PRACTICE CONT'D

- Surgical evacuation of intracranial hematoma is rarely indicated, but may be considered to reduce extremely high intracranial pressure
- Ventricular drainage and, if indicated, later shunting for progressive hydrocephalus due to intraventricular hemorrhage is often appropriate

NEONATAL STROKE KNOWLEDGE GAPS

- Incomplete understanding of the causes of all forms of neonatal stroke limits ability to develop preventative strategies
- Some observational evidence that antithrombotic agents might benefit selected neonates with AIS or CSVT, clinical trial data lacking

CHILDHOOD STROKE

APPROACH TO A SUSPECTED STROKE IN A CHILD

CHILDHOOD STROKE: CLINICAL PRESENTATION

- Signs and symptoms similar to those in adults
- Most common: hemiparesis and hemi-facial weakness in 67-90%, speech or language disturbance in 20-50%, vision disturbance in 10-15%, and ataxia in 8-10%
- Children present with non-localizing symptoms such as headache in 20-50% and altered mental status in 17-38%
- Seizures at stroke onset more common in children than adults, affecting 15-25%, especially <6 years
- Clinical presentation varies according to age, setting (in-patient vs ed), and stroke subtype

CHILDHOOD STROKE: CLINICAL PRESENTATION CONT'D

- AIS due to cardiac disease occurs in the inpatient setting more often than the outpatient setting, and involves younger children, with a median age of 6 months-3 years
- These children present with seizures in up to 40%, hemiparesis in 36-75%, and clinically covert in 14-40%
- Braun et al found cardioembolic stroke may present with abrupt onset, as compared to stuttering or fluctuating presentation due to arteriopathy
- diagnosis often made when imaging is obtained for other reasons (cardiac arrest, ECMO cannulation)

CHILDHOOD STROKE: CLINICAL PRESENTATION CONT'D

- Moyamoya-type arteriopathies distinguished by high prevalence of TIA and large burden of “silent” infarction
- 7-year single center cohort study of 54 children with Moyamoya arteriopathy (median age at diagnosis of 7.5 years), TIAs occurred in 70%, and AIS in 48%
- TIAs often multiple and recurred over extended periods of time
 - Signs and symptoms include hemiparesis or hemisensory deficits most commonly (72%), often with chronic headache (52%), and occasionally seizures (<10%)
 - Imaging at initial diagnosis has shown evidence of prior silent infarct in 52%
 - another cohort of 60 with Moyamoya who initially presented with a TIA, 55 (92%) had recurrent TIAs and 14 (23%) went on to ischemic infarction
- Severity of Moyamoya arteriopathy at presentation corresponded with risk of subsequent stroke

CHILDHOOD STROKE: CLINICAL PRESENTATION CONT'D

- Posterior circulation stroke represents distinct pattern of clinical features
 - present at median age of 7-8 years, predominantly male (67-77%), and are previously healthy children in majority of cases
- Presenting signs and symptoms include localizing deficits referable to posterior circulation in 70-100%: hemiparesis, ataxia, dysarthria, visual field deficits, and oculomotor deficits
- Non-localizing symptoms in 60-70%: headache, vomiting and altered mental status
- Vertebral artery dissection most common cause (25-50%), especially younger boys, and frequently preceded by recent minor head/neck trauma
- Finding of multiple posterior circulation infarcts of varying age at time of initial presentation suspicious for vertebral artery dissection

CHILDHOOD STROKE: DELAYS AND CHALLENGES OF STROKE MIMICS

- Multiple studies investigating time to AIS diagnosis aim to identify strategies to improve access to hyperacute therapies
- Median time from symptom onset to parent seeking medical care is highly variable, from 1.7- 21 hours, though majority usually present ≤ 6 hrs.
- Median time to radiologic confirmation of diagnosis is 15-24 hours
- Children with onset of stroke during admission for other illnesses experience similar delays in radiologic confirmation of ischemic stroke
- Major causes of delays: delayed consideration of stroke among front line providers, and delays in accessing MRI, often related to the need for sedation or anesthesia. delays are greater on evenings and weekends

CHILDHOOD STROKE: DELAYS AND CHALLENGES OF STROKE MIMICS

- Accuracy and timeliness of diagnosis by frontline providers are important challenges
- ED providers correctly diagnose a stroke in ~60% of children → ~40% incorrect initial diagnosis of “stroke mimic”
- Studies of stroke mimics in ed have yielded several important observations
 - 60-90% of children presenting to ed with acute neurologic syndrome, or “brain attack”, have other condition than stroke
- Diagnoses that commonly mimic stroke, and may prompt an ed physician to activate a “stroke alert” pathway are numerous and diverse
 - migraine with aura, bell’s palsy, and seizure, especially with Todd's paresis
 - brain tumor, demyelinating disease, cerebellitis, encephalitis, epidural abscess, traumatic brain injury, syncope, intoxication, metabolic disease and psychogenic disorders
- Up to 40% of patients with stroke mimics have serious disease and/or time-sensitive treatment implications

CHILDHOOD STROKE: DELAYS AND CHALLENGES OF STROKE MIMICS CONT'D

- Clinical diagnostic strategies and tools used in adults to distinguish stroke from stroke mimics have limited utility in children - sensitivity ~60%
- Focal deficits more common in children with stroke than in stroke mimics, but there is overlap
- non-localizing symptoms such as headache and altered mental status are equally common in both groups

CHILDHOOD STROKE: CONSIDERATIONS FOR CLINICAL PRACTICE

MEDICAL EDUCATION

- Develop education programs to improve knowledge and skills in diagnosis and emergency management of pediatric stroke for frontline providers (pediatricians, ED physicians and emergency medical technicians)
- Similar programs for subspecialty providers who care for populations at high risk for stroke: cardiologists, hematologists, cardiac intensivists and pediatric intensivists, nursing staff

RESEARCH

- Develop and validate bedside clinical assessment methods for frontline providers to identify stroke in children with improved sensitivity and specificity
- Develop better imaging techniques for early and accurate diagnosis of stroke and cerebrovascular disease generally, including vertebral artery dissection

DEFINE MODIFIABLE STROKE RISK FACTORS TO BE INCORPORATED INTO SCREENING, EARLY DIAGNOSIS AND PREVENTATIVE TREATMENT STRATEGIES IN CHILDREN WITH HEART DISEASE

ARTERIAL ISCHEMIC STROKE (AIS) IN CHILDHOOD

- Irreversible brain tissue ischemia occurs within minutes to hours of arterial occlusion
- Time to irreversible tissue injury is shorter in the central 'core' of infarct and longer in surrounding 'penumbra' where collateral arterial supply can continue to perfuse tissue
- Neuroprotective strategies to balance metabolic substrate supply with tissue metabolic demand aim to increase brain tissue survival primarily in penumbra

CHILDHOOD AIS: HYPERACUTE STROKE THERAPIES IN CHILDHOOD

- Arterial recanalization therapy including IV alteplase (TPA), IA alteplase (TPA), or endovascular thrombectomy (EVT) has been shown to significantly benefit adults when implemented within discrete time windows
- Availability of recanalization therapy has dramatically changed time-frame for urgent diagnosis and management
- Whether and how to apply these therapies in childhood remains controversial

CHILDHOOD AIS: HYPERACUTE STROKE THERAPIES IN CHILDHOOD: IMPLICATIONS OF THROMBUS COMPOSITION

- Thrombus composition (erythrocytes, fibrin, platelets and leucocytes) is integral in determining susceptibility to mechanical and pharmacologic disruption and recanalization
- Thrombus composition directly affects physical properties → correlated to both effectiveness and complications of recanalization
- Recent meta-analysis reported that thrombi with high proportion of erythrocytes and less fibrin appear as “hyperdense sign” on CT and associated with increased recanalization rates
- In vitro data on composition of thrombi created in laboratory using adult and pediatric plasma suggest that children have a more loosely woven fibrin thrombus structure
- These data suggest that thrombolytic therapy could theoretically be more efficacious in children compared to adults
- no pediatric thrombolytic trials have been completed

CHILDHOOD AIS: HYPERACUTE STROKE THERAPIES IN CHILDHOOD: RECANALIZATION THERAPY: THROMBOLYTICS AND EVT

- When recanalization accomplished *prior to* tissue death, i.e. within hours of stroke onset, reperfusion reduces ischemic injury
- Beyond this time window, the increasing risks of recanalization including hemorrhagic transformation of infarct, 'reperfusion injury', and catheter and device related thrombotic and non-thrombotic complications, outweigh benefits
- In clinical trials of adults, optimal time window for recanalization therapy is within 4.5 for IV alteplase (TPA) treatment, 6 hours for IS alteplase (TPA), and 6 hours for EVT, but up to 24 hours for thrombectomy in a subgroup of patients
- Multiple trials demonstrate that among highly selected adults with AIS and large vessel occlusion (LVO), EVT improves 90-day survival without disability over standard medical therapy
- 2016 pooled analysis by Goyal, et al, of the 1287 adult stroke patients from the 5 EVT trials published by 2015, demonstrated robust clinical benefits for EVT across a broad spectrum of age and initial stroke severity (moderate or severe, with few minor strokes included), and a number needed to treat of 2.6 to reduce disability of one patient

CHILDHOOD AIS: HYPERACUTE STROKE THERAPIES IN CHILDHOOD: RECANALIZATION THERAPY: THROMBOLYTICS AND EVT CONT'D

- Two clinical trials published in early 2018 extended treatment window for select patients with smaller completed infarcts yet large penumbra territories at risk for infarction
- DAWN trial showed that EVT 6 – 24 hours post onset can be beneficial in adults with NIHSS >10 and core infarct volume <30 ml (equivalent to <5% of hemisphere volume) *or* NIHSS >20 and core infarct volume <51 ml (equivalent to 10% of hemisphere volume)
- Defuse 3 trial found benefit when EVT was performed 6 – 16 hours post onset in patients selected by perfusion imaging: initial infarct size <70 ml, and a ratio of the volume of ischemic tissue on perfusion imaging to infarct volume of ≥ 1.8
- Emergence of specialized pediatric stroke expertise, institutional pathways, and increased access to rapid stroke neuroimaging make hyperacute stroke therapies for children potentially feasible
- Study describing utilization of thrombolytics in a large, international pediatric stroke cohort provided impetus to design and initiate prospective thrombolysis in pediatric stroke study (tips)
- TIPS was an NIH-funded phase 1 clinical trial to determine safety and pharmacokinetics of IV alteplase (TPA) in children 2-18 years of age ≤ 4.5 hours of AIS, if vascular obstruction diagnosed on MRI

CHILDHOOD AIS: HYPERACUTE STROKE THERAPIES IN CHILDHOOD: RECANALIZATION THERAPY: THROMBOLYTICS AND EVT CONT'D

- TIPS closed due to low patient enrollment; multidisciplinary tips investigators succeeded in establishing systems for evaluation and care of a child with hyperacute AIS
- In absence of clinical trial data, one consensus opinion has suggested that, when IV alteplase (TPA) is considered in children, the adult dose of 0.9 mg/kg be utilized, which would likely be a conservative dose because developmental differences in plasminogen levels may actually make the effective dose for children higher
- EVT has potential appeal for childhood AIS over IV alteplase (TPA): longer post-stroke time window for intervention and concerns related to optimal pediatric TPA dose and developmental changes in plasminogen levels are moot
- 2015 aha guideline on EVT stated that EVT may be reasonable for some acute AIS patients <18 years of age, using adult parameters, while acknowledging that benefits and risks are not established in this age group

CHILDHOOD AIS: HYPERACUTE STROKE THERAPIES IN CHILDHOOD: RECANALIZATION THERAPY: THROMBOLYTICS AND EVT CONT'D

- >35 cases of recanalization therapy in pediatric AIS have now been reported and pooled in the published literature, most with successful outcomes
- Total number of children treated with EVT remains unknown, and those with treatment-related complications and adverse outcomes are likely under reported in the literature
- True safety profile of EVT in children remains unknown
- Special pediatric considerations
- smaller arteries (groin and cerebral), weight-based limitations for contrast, radiation-exposure in young children, and arteriopathies that cause AIS in children (e.g., concerns for introducing a catheter into an acutely inflamed artery, in cases of focal cerebral arteriopathy, or chronically stenosed cerebral artery (i.e. Moyamoya)
- Risk-benefit ratios of these interventions would differ if presumptions about better stroke recovery in children versus adults are correct
- Numerous studies indicate that a good outcome (no functional deficits) can be expected in 1/3 to 1/2 of children with AIS without any intervention
- Initial stroke severity measured by pediatric NIH stroke scale (PEDNIHSS) directly predicts outcome
- Risks of EVT may outweigh benefits in children with low initial stroke severity scores

CHILDHOOD AIS: HYPERACUTE STROKE THERAPIES IN CHILDHOOD: RECANALIZATION THERAPY: CONSIDERATIONS FOR CLINICAL PRACTICE

- In the absence of pediatric clinical trial data to guide treatment decisions, hyperacute therapies remain controversial
- Reasonable to limit consideration of intervention to children meeting these criteria
 - Persistent disabling neurological deficits (e.g., Ped-NIHSS ≥ 6 at time of intervention, or higher if DAWN trial criteria applied)
 - Radiographically confirmed cerebral LVO
 - Larger children, due concerns about introducing catheters into small groin and cerebral arteries, and size-based limitations on contrast dye and radiation exposure
 - Treatment decision made with neurologists with expertise in treatment of childhood stroke
 - Intervention performed by an endovascular surgeon with experience both in treating children and performing EVT in adult stroke patients

CHILDHOOD AIS: HYPERACUTE STROKE THERAPIES IN CHILDHOOD: RECANALIZATION THERAPY: CONSIDERATIONS FOR CLINICAL PRACTICE

- Establish systems and pathways for hyperacute pediatric stroke care
- Centers that choose to offer this therapy should pre-establish institutional pediatric hyperacute stroke pathways and consider current adult guidelines for these therapies
- Pathways should include criteria for consideration of EVT in children with acute AIS and LVO
- Establish referral networks connecting community hospitals and frontline providers to tertiary care pediatric stroke centers with specifically trained experts and technology in vascular neurology, neuroimaging, and neurocritical care
- Within pediatric stroke centers, multiple systems of care need to be structured through well-designed institutional care protocols that are staffed and equipped to provide 24/7 access to care from vascular neurologists, vascular neurosurgeons, neuroradiologists, neurointerventionalists, anesthesiologists and neurocritical care intensivists
- Consider "telestroke" or "telemedicine" as a specific way of bringing expertise to emergency providers who may have less experience with acute focal deficits and stroke in children. Telestroke has been effective in adult stroke medicine, and has been used in other settings in pediatric cardiovascular care.
- Pediatric stroke specific guidelines should be developed at local, regional and national levels. In order to leverage regional stroke expertise, partnerships between EMS, comprehensive stroke centers and pediatric tertiary care hospitals should be encouraged.

CHILDHOOD AIS: HYPERACUTE STROKE THERAPIES IN CHILDHOOD: RECANALIZATION THERAPY: KNOWLEDGE GAPS

- Safety and efficacy data for hyperacute stroke therapies in children are lacking
- Children treated with such therapies should be enrolled in existing registries: e.g., swiss neuropediatric stroke registry and the international pediatric stroke study registry
- No evidence to guide how young or how small a child may safely undergo EVT
- Analyses directly comparing post-AIS neurological outcomes in children versus adults, adjusted for confounders like stroke infarct and location, would help when considering risk-benefit ratios for adult stroke therapies applied to children

CHILDHOOD AIS: ACUTE MANAGEMENT OF CHILDHOOD AIS

- Current strategies for acute management rely upon both pediatric and adult data that explore the treatment of HTN, hypotension, hyperglycemia, and fever; as well as the surveillance strategies to prevent complications such as cerebral swelling and seizures
- Little is known about whether supportive care measures alter the effect of brain ischemia in children
- Traditional methods of neuroprotection are often employed, and recent data about specific management challenges, such as early hemicraniectomy in large strokes, are beginning to emerge

CHILDHOOD AIS: ACUTE MANAGEMENT OF CHILDHOOD AIS: BLOOD GLUCOSE, TEMPERATURE, BLOOD PRESSURE

- Hyperglycemia is a common and well-established risk factor for adverse outcomes in adult stroke, and likely a frequent and detrimental risk factor in children
- In both populations timing and goals of treatment of hyperglycemia are poorly understood, with only a single RCT examining efficacy of glucose control in adult stroke
- In this study, 933 patients were randomly assigned to two arms: insulin infusion to maintain euglycemia, and saline
 - stopped early due to slow enrollment; demonstrated no difference in 90-day mortality or other outcome measures
- Less data in childhood stroke
- Grelli et al. performed only study examining influence of hyperglycemia on outcomes in childhood stroke
 - retrospective multivariate analysis on 98 children with stroke examining the association between HTN, hypotension, hyperglycemia, fever and Pediatric Stroke Outcome Measure → hyperglycemia independently associated with adverse outcome
 - Hyperglycemia - 18%); hypoglycemia - 3%
- Given lack of data in children → reasonable to follow aha adult stroke guidelines for management of hyperglycemia and hypoglycemia
- Ongoing shine trial testing treatment of hyperglycemia in adults

CHILDHOOD AIS: ACUTE MANAGEMENT OF CHILDHOOD AIS: BLOOD GLUCOSE, TEMPERATURE, BLOOD PRESSURE CONT'D

- Pyrexia associated with adverse outcomes in adult stroke
- Impact of fever in children remains uncertain
- Single, multicenter, randomized, double-blind, placebo-controlled adult trial of patients with temperatures ranging from 36-39° c failed to show any difference in those treated with acetaminophen vs. placebo
 - post-hoc analysis demonstrated difference in expected MRS at 3 months
- Suggests treating fever may improve outcome, additional prospective adult evidence lacking
- Retrospective analysis of childhood stroke and impact of hyperglycemia, HTN, and fever, Grelli et al. found no influence of fever upon outcome in childhood stroke, although fever was found acutely in 38% of subjects
- Given the lack of pediatric specific data, reasonable to follow aha adult stroke guidelines when treating fever in children

CHILDHOOD AIS: ACUTE MANAGEMENT OF CHILDHOOD AIS: BLOOD GLUCOSE, TEMPERATURE, BLOOD PRESSURE CONT'D

- Current adult stroke AHA recommendations suggest, “in patients with BP \geq 220/120 mm/Hg who did not receive iv alteplase or EVT and have no comorbid conditions requiring acute antihypertensive treatment, benefit of initiating or reinitiating treatment of HTN within first 48-72 hours is uncertain”
- Might be reasonable to lower bp by 15% during first 24 hours after onset of stroke
- Several prospective randomized studies examining role of antihypertensive treatment in the acute management of adult stroke, results have been mixed
- Lack of consistent results in previous studies may have been the result of differing response to treatment across stroke subtypes, an important consideration when extrapolating these studies to childhood stroke, where etiology is often different from adult stroke
- Some evidence that acute antihypertensive treatment in adult stroke may have variable outcomes depending upon stroke presentation

CHILDHOOD AIS: ACUTE MANAGEMENT OF CHILDHOOD AIS: BLOOD GLUCOSE, TEMPERATURE, BLOOD PRESSURE CONT'D

- Early evidence in childhood stroke suggests that HTN in acute period following stroke is associated with worse outcomes
- Single-center retrospective study of 53 children with AIS demonstrated association between HTN in the first 3 days after stroke and in-hospital mortality
 - findings confirmed by examination of a large sample of children with stroke (n=2590) from large national database
- Grelli et al. demonstrated high prevalence of persistent HTN (2 consecutive measurements or more above 95th percentile) in childhood stroke (68%) at some point 5 days after stroke, but failed to establish an association with HTN (or hypotension) and adverse outcomes at 3 months

CHILDHOOD AIS: ACUTE MANAGEMENT OF CHILDHOOD AIS: BLOOD GLUCOSE, TEMPERATURE, BLOOD PRESSURE CONT'D

- While HTN in first 3-5 days after childhood stroke may be associated with in-hospital morbidity, the causal pathway is unclear
 - children with Moyamoya are often hypertensive at baseline, presumably as a compensatory mechanism to improve cerebral perfusion
- Up to 45% of children presenting with AIS will have an intracranial arteriopathy, like Moyamoya, and these children may be particularly sensitive to rapid decreases in blood pressure resulting in cerebral hypoperfusion
 - use of antihypertensive therapy in these children can trigger flow-related ischemia
- Hypotension in children with stroke should be treated aggressively, and in our experience patients with pressure dependent stenosis may need aggressive management and monitoring for even borderline hypotension
- Treatment may include laying head of the bed flat (recent adult data show no benefit), IVF and, in rare cases of a pressure-dependent lesion, salt tabs, fludrocortisone and/or pressors

CHILDHOOD AIS: ACUTE MANAGEMENT OF CHILDHOOD AIS: SEIZURE MANAGEMENT

- In acute childhood stroke, clinical seizures are common, occurring >20% of children with AIS
- Subclinical seizures found in patients with prolonged EEG monitoring, occurring acutely in 23% of all patients with clinical seizures and EEG monitoring in a single center study
- Detailed descriptions of protocols for seizure monitoring in pediatric brain injury are beyond the scope of this article
- Clinicians who take care of children with stroke should have a high suspicion for clinical and subclinical seizures in the acute setting, and should consider EEG screening and/or monitoring for children with altered mental status

CHILDHOOD AIS: ACUTE MANAGEMENT OF CHILDHOOD AIS: HEMICRANIECTOMY

- Hemicraniectomy rarely performed in treatment of childhood AIS—performed in 1% — remains a potentially lifesaving option in children with large supratentorial stroke
- Largest series of children who received hemicraniectomy following AIS, 95% (39/41) survived
 - of the survivors, 41% had no deficit, mild deficit or moderate deficit; while 59% had severe deficits. in a meta-analysis of the largest three randomized prospective trials comparing decompressive hemicraniectomy with medical management in adults, survival was improved with surgery from 29% to 78%
- Similar to pediatric population a significant number of survivors had severe deficits (45% had a MRS of 4/5)
- Recent analysis of large adult national inpatient sample demonstrated strong association between later decompression and poor outcome, using validated composite outcome variable
- Patients with decompression performed before herniation had better outcomes than those with surgery after
- Germane to pediatric population that has less brain atrophy to accommodate swelling

CHILDHOOD AIS: ACUTE MANAGEMENT OF CHILDHOOD AIS: HEMICRANIECTOMY CONT'D

- In children, as in adults, hemicraniectomy in large supratentorial infarcts are decided on a case-by case basis, and in consultation between the family and treatment team
- If hemicraniectomy is performed in pediatric patient, earlier intervention is likely preferable
- In children with large volume infarcts (>1/2 MCA territory), treatment teams should consider either performing early prophylactic hemicraniectomy within first 24 hours, or implementing serial imaging within first 72 hours to monitor swelling and need for surgical intervention
- It is reasonable to follow adult guidelines for surgical decompression
- Adult studies report improved outcomes and decreased mortality with decompressive craniotomy in patients with space-occupying cerebral edema secondary to large cerebellar infarctions
 - limited to case series, similar findings are seen in the pediatric population
 - poor outcomes from this intervention are rarely seen, ethical considerations are not as challenging as seen in malignant MCA syndrome

CHILDHOOD AIS: ACUTE MANAGEMENT OF CHILDHOOD AIS: CONSIDERATIONS FOR CLINICAL PRACTICE

- Children with AIS are usually monitored in an ICU setting for >24 hours post stroke, and general neuroprotective and neurocritical supportive care administered
- Evidence indicates that persistent in-hospital hyperglycemia during the first 24 hours, after stroke is associated with worse outcomes than normoglycemia, and thus, treat hyperglycemia to achieve blood glucose levels in a range of 140 to 180 mg/dl and closely monitor to prevent hypoglycemia (blood glucose <60 mg/dl) in patients with AIS
- Sources of hyperthermia (>38°C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke
- Caution should be employed in children with intracranial vascular stenosis such as Moyamoya, and in focal cerebral arteriopathies. In addition, hypotension in children with stroke should typically be treated aggressively.
- Decompressive surgery for malignant edema of cerebral hemisphere is effective and potentially lifesaving
 - patient/family valuations of achievable outcome states may affect decisions regarding surgery
 - consider decompressive surgical evacuation of a space-occupying cerebellar infarction early in preventing and treating herniation and brain stem compression

CHILDHOOD AIS: ACUTE MANAGEMENT OF CHILDHOOD AIS: CONSIDERATIONS FOR CLINICAL PRACTICE CONT'D

- In children with large volume infarcts ($>1/2$ MCA territory), treatment teams could consider either performing early prophylactic hemicraniectomy within first 24 hours, or implementing serial imaging and frequent clinical assessments within first 72 hours to monitor swelling and need for surgical intervention

CHILDHOOD AIS: ACUTE MANAGEMENT OF CHILDHOOD AIS: CONTROVERSIAL IN CURRENT PRACTICE

- Setting for treatment: should treatment occur only in centers with pediatric vascular neurologists?
- Hemispherectomy management.
- Blood pressure management.

CHILDHOOD AIS: ACUTE MANAGEMENT OF CHILDHOOD AIS: KNOWLEDGE GAPS

- Determining timing and appropriate candidates for hemicraniectomy
- Appropriate treatment of blood pressure since associations with worse outcome are not proven
- Appropriate treatment of hypoglycemia and hyperglycemia

CHILDHOOD AIS: RISK FACTORS AND ETIOLOGIES FOR CHILDHOOD AIS

- Etiologies of childhood stroke can be divided into multiple categories
 - cardiac, extracranial arteriopathies, intracranial arteriopathies, thrombophilia, sickle cell disease, and systemic causes such as systemic lupus erythematosus
- Several approaches to stroke subtype classification have been published, which may be useful in formulating management pathways and designing clinical research
- Many cases the etiology is multifactorial, and as such, the determination of a cause should typically include a systematic assessment of all potential causes

CHILDHOOD AIS: RISK FACTORS AND ETIOLOGIES FOR CHILDHOOD AIS: CARDIAC

- Cardioembolic stroke accounts for ~30% of all childhood strokes, and can occur from congenital heart disease (CHD), procedure related events, and/or acquired heart disease
- Three decade prospective evaluation of children with cardiac disease, 0.13% (132/100,000/year) had a stroke each year
- Increased utilization of assisted mechanical heart devices and improved survival of patients with CHD is likely increasing this incidence annually.
- Children requiring therapy from a Berlin heart EXCOR ventricular assisted device had highest prevalence of stroke (28-34% combined risk of ischemic and hemorrhagic stroke) among children with cardiac disease; children treated with extracorporeal membrane oxygenation (ECMO) (7-11%), Fontan (1.4-19%), and cardiac catheterization (0.38-1.3%), are also at high risk for stroke
- Prevalence of stroke in patients with endocarditis and cardiomyopathy is 5-10%, while children with CHD have a 19-fold increase risk of stroke as compared to the general population
- Data on recurrence risk of stroke after initial event are minimal
 - recent article from Canadian pediatric ischemic stroke registry reported a 27% recurrence risk of stroke at 10 years of age in CHD despite high usage of anticoagulation

CHILDHOOD AIS: RISK FACTORS AND ETIOLOGIES FOR CHILDHOOD AIS: CARDIAC CONT'D

- Pathophysiology of stroke in children with cardiac disease is usually thromboembolic, although associated anomalies of the head and neck vasculature may also play a role
- in cases of CHD, ventricular assisted devices and/or ECMO, thrombus can occur from stasis and/or paradoxical venous embolism
- role of arrhythmia in childhood stroke and clot formation is less clearly defined, although a recent report of increased risk of arrhythmia and stroke in adults with a history of congenital ASD raises the possibility that arrhythmia is an under-recognized cause for childhood stroke, especially in cases with a history of benign CHD
- role of PFO in childhood stroke remains uncertain
- several small studies have suggested that PFO with right to left shunt is more prevalent in children with cryptogenic stroke than in normal children, it is unclear when a PFO in childhood stroke is pathogenic, particularly given that the timing of normal, physiologic PFO closure is variable
- identifying PFO in childhood stroke may be important as increasing evidence in adults suggest that adults with larger PFOs and cryptogenic stroke may benefit from PFO closure

PRIMARY AND SECONDARY PREVENTION OF CHILDHOOD AIS

STROKE PREVENTION IN CHILDREN

CHALLENGES ASSOCIATED WITH PRIMARY PREVENTION

- Diverse underlying causes (compared to adult stroke etiologies)
- Sickle cell disease – chronic exchange transfusion
- Cardiac thrombus – anticoagulation or surgery

PREVENTION OF RECURRENT STROKE

- Addressing individual risk factors causing initial stroke
- Establish healthy behavior patterns to reduce adult stroke risk factors
- Antiplatelet agents or anticoagulation depending on etiology
- PFO closure remains controversial

STROKE PREVENTION CONT'D

RISKS OF RECURRENT STROKE

- Neonates have low risk aside from complex congenital heart patients
- >10% of older children have recurrent stroke within 1st year
 - 1/3 of children with arteriopathies
 - Posterior circulation strokes have higher recurrence rate than anterior strokes

MEDICATION OPTIONS

- Antiplatelets (ASA) or anticoagulants (LMWH, coumadin) should be used
 - Lowers risk of recurrent stroke 1.5-2x
 - No studies of DOACs in children with AIS
 - Consider hematology consultation for new thromboembolic stroke
- LMWH or warfarin for at least 3-6 months preferred for
 - Cardioembolic strokes
 - Prior thrombosis/known prothrombotic disorder
- ASA 3-5 mg/kg preferred for most others for 2+ years; consider GI prophylaxis

CONTROVERSIES IN CURRENT PRACTICE

- Anticoagulation vs antiplatelet therapy remains controversial – both appear safe
- Secondary stroke prevention strategies for specific etiologies
- Duration of therapy remains unknown
- Stroke prevention evidence nonexistent outside sickle cell population

STROKE PREVENTION IN CHILDREN WITH MOYAMOYA

IMAGING EVALUATION

- FLAIR/MRA sequences helpful; visualize chronic infarct burden, circle of Willis and differentiate between vasculitis and moyamoya
- DSA key for surgical planning

SURGICAL MANAGEMENT

- Indications: stroke/TIA, compromised blood flow or perfusion reserve
- Contraindications: very early stage arteriopathy, profound medical or neuro compromise
- Timing: as soon as feasible
- Indirect approach may be better but practice varies between institutions
- Improvements noted in white matter changes, CBF, ischemic symptoms, stroke, ICH risk and headache, functional and cognitive outcomes
- High volume centers with dedicated pediatric cerebrovascular team preferred

SPECIFIC POPULATIONS: DYNAMIC VERTEBRAL ARTERY COMPRESSION

PATHOPHYSIOLOGY

- Rotation/extension of neck → vertebral artery compression
- Patients with single vertebral physiology can experience brainstem/cerebellar ischemia
 - Vertigo, weakness, fainting, can lead to completed stroke
 - In children – seen as cause of recurrent posterior circulation AIS
- Dynamic compression means involved segment appears normal or mildly diseased when imaged with head in midline
 - Can see mild stenosis or dissection; typically left sided compression
 - Caused by congenitally narrow canals, ligamentous laxity w/hyper rotation, or structural lesions

SPECIFIC POPULATIONS: DYNAMIC VERTEBRAL ARTERY COMPRESSION

EVALUATION

- Dynamic TCD has high specificity, low sensitivity
- MRI/CT, MRA/CTA can demonstrate arterial anomalies
- Dynamic DSA is gold standard – must be performed with caution
- Pathologic compression demonstrated by recurrent posterior circulation strokes, arterial irregularity or dissection at level of compression

MANAGEMENT

- Decompression or fusion of the abnormal spinal segment
- Follow-up crucial to identify delayed instability that may require future fusion

STROKE AND SICKLE CELL DISEASE

BACKGROUND INFORMATION – STROKE IN SICKLE CELL DISEASE

GENETICS OF SICKLE CELL DISEASE (SCD)

- Homozygous = hemoglobin SS = sickle cell anemia
- Compound heterozygotes = hemoglobin SC, hemoglobin S β^0 thalassemia
- All SCD phenotypes have at least 50% hemoglobin S
- Trial literature includes children with hemoglobin SS and S β^0
 - These children have hemoglobin S levels of 85–95% with no hemoglobin A
 - These trials inform recommendations for primary and secondary stroke management

STROKE AND SICKLE CELL DISEASE – ACUTE MANAGEMENT

ACUTE MANAGEMENT OF FOCAL NEUROLOGIC DEFICIT/SEIZURE

- Acute neurology consult + MRI → MRA and/or MRV if infarct present
- Consider cerebral sinus venous thrombosis as an etiology
- Management principles include optimal hydration, correction of hypoxemia and hypotension
- Transfusion to goal hemoglobin of 10 - 11 g/dl within 6 hours of presentation
 - 10cc/kg of red blood cells increases hemoglobin 2.5-3.0 g/dl
 - Repeat hemoglobin 2 hours post transfusion
 - If hemoglobin is >10 prior to transfusion, initiate exchange transfusion prior to transfusion
 - Exchange transfusion goals: hemoglobin S level ~15%, hemoglobin ~ 10 g/dl
- Repeat MRI in 2-4 weeks may be needed
- DSA is warranted for SCD patients presenting with ICH

STROKE IN SCD – PRIMARY AND SECONDARY PREVENTION

PRIMARY PREVENTION OF STROKE IN SCD

- TCD screening (annually if normal) recommended; can repeat abnormal findings in 1-2 months
- Adams et al showed NNT of 7 for regular transfusions in patient with abnormal ICA/MCA TCDs (1998)
- TWiTCH subsequently showed noninferiority of hydroxyurea to continued transfusion after competing 1 year of transfusion (2016)
 - Excluded patients with vasculopathy on MRA
- No evidence that elevated TCD velocities obtained after treatment initiated confer increased risk of stroke

SECONDARY STROKE PREVENTION IN SCD

- Regular transfusion therapy to HbS <30% appears superior to hydroxyurea
- High rate of recurrent infarcts persists even after transfusion therapy begins; particularly with worsening arteriopathy burden on MRA (RR = 12.7)
- Hydroxyurea is an option in low-resource settings however optimal dose is unknown
- Bone marrow transplantation should be done in a clinical trial setting
- Surgical revascularization should be performed only as a part of team-based learning collaborative or long-term multicenter clinical study

STROKE IN SICKLE CELL DISEASE – SILENT INFARCTS

DEFINITION OF SILENT INFARCT AND IMPLICATIONS

- 33% of children with hemoglobin SS; normal TCDs have silent infarcts by 15 years of age
- Defined as: 3mm in 1 dimension, visible in 2 planes on T2-FLAIR imaging; absent neurologic deficit
 - 7 % of previously 'silent' infarcts were identified as strokes by pediatric neurologist
- Presence of silent infarcts associated with lower Full-Scale IQ; poor school performance
- Providers should consider screening MRI at least once; possibly every 1-2 years to identify progression
- Families should be informed of the risks of silent infarcts; benefits of transfusion therapy and implications for education and school resources (i.e. IEP)
- When identified, families should be offered cognitive assessment and initiation of regular blood transfusions

TREATMENT OF SILENT INFARCTS

- Regular transfusion therapy with goal of HbS <30% for at least 3 years
- NNT of 13 for children with silent infarcts and normal TCD velocities
- Initiation of transfusion associated with reduction in vaso-occlusive crises, acute chest syndrome
- Requires iron chelation after 1 year
- If post-transfusion Hb >12, phlebotomize to decrease Hb to <10 to avoid hyper viscosity syndrome

CONSIDERATIONS FOR CLINICAL PRACTICE

1. Acute management of ischemic stroke in SCD should include optimal hydration, correction of hypoxemia, and correction of systemic hypotension; Moyamoya-related management can be considered if such arteriopathy exists.
2. For primary stroke prevention, regular blood transfusions to reduce the percentage of hemoglobin s to a maximum of < 30% or offered hydroxyurea therapy after one year of regular blood transfusion therapy for children if there is no evidence of MRA-defined Moyamoya syndrome.
3. For secondary stroke prevention, children with hemoglobin ss or s β^0 thalassemia should be considered to receive regular blood transfusion therapy to reduce the percentage of hemoglobin s to a maximum of < 30% in conjunction with measures to prevent iron overload.
4. Screening for cerebral infarcts with an MRI of the brain using the sit trial criteria for detection can be considered for children with hemoglobin ss or s β^0 thalassemia.
5. If a silent infarct is identified in a child with hemoglobin ss or s β^0 thalassemia, then cognitive assessment is warranted and the caregivers can have the option for regular blood transfusion therapy for stroke prevention and consideration for special educational services.
6. For suspected acute cerebral infarction, prompt initial simple blood transfusion to get hemoglobin level to 10 g/dl or if the hemoglobin is greater than 10 g/dl an exchange transfusion is required. The goals of the exchange transfusion to reduce sickle hemoglobin to 15% total and the total hemoglobin to approximately 10 g/dl.

CONSIDERATIONS FOR CLINICAL PRACTICE CON'T

7. In children with SCD and an ICH, DSA to evaluate for a structural vascular lesion is warranted.
8. In children with hemoglobin ss or s β^0 thalassemia, it is reasonable to repeat a normal TCD annually and to repeat an abnormal study in 1 month). TCD values that are conditional and can be repeated within 2 to 6 months.
9. Hydroxyurea may be considered in children and young adults with SCD and stroke who will not or cannot continue on long-term transfusion or who live in low-resource settings where regular blood transfusion therapy is not feasible.
10. Bone marrow transplantation for children with CSD and strokes should be done in a clinical trial setting that has been registered in clinicaltrials.gov.
11. Surgical revascularization procedures may be considered in a subset of carefully screened children with SCD with ischemic strokes who continue to have recurrent cerebral infarcts (strokes or silent infarcts) despite optimal blood transfusion therapy (hemoglobin s level suppressed to less than 30%).
 - Neurosurgeons, neurologists and hematologists that elect to perform or recommend revascularization procedures in children with strokes, participate in a team-based learning collaborative or long-term multi-center clinical study.

OUTCOMES AFTER CHILDHOOD AIS

OUTCOMES AFTER CHILDHOOD AIS – MORBIDITY AND MORTALITY

IMPROVEMENT IN MORTALITY AFTER CHILDHOOD AIS

- Historical mortality of 20%
- Multiple recent cohort studies and stroke registries with mortality 4-10% over period up to 7 years

MORBIDITY OUTCOMES VARY BUT SUBSET OF PATIENTS MAKE COMPLETE RECOVERY

- Canadian Pediatric Stroke Registry – normal neurologic status in 30%; mild deficits in 36%
- British cohort study (n=94)- 50% excellent outcomes, mild to no impairments
- Swiss cohort study (n=95) – 27% normal long-term outcome, 28% with mild impairments (MRS 1)

OTHER OUTCOMES OF INTEREST

- Single study of perinatal stroke showed lower intelligence, verbal ability, working memory and processing speed; combined cortical/subcortical injury has more deficits than isolated injury to either area
- Poor attention, impulsivity and executive function can remain ongoing challenges
- Health-related QoL is lower than peer age group across all surveyed domains – largely driven by cognitive/behavioral deficits and Verbal IQ

PREDICTORS OF OUTCOME AFTER CHILDHOOD AIS

MULTIPLE PREDICTORS OF POOR NEUROLOGIC OUTCOME DESCRIBED

- Studied variables include infarct size, combined cortical and subcortical AIS, basal ganglia/internal capsule, presence of multiple infarcts, and post-AIS hyperglycemia or seizures
- Psychosocial/Cognitive function lower in larger infarcts, those with older age at time of AIS
- Poor mental health outcomes are described but risk factors, epidemiology remains challenging

TARGETED INTERVENTIONS AFTER CHILDHOOD AIS

- Rehabilitation should be multidisciplinary; age appropriate
- As children mature new physical/cognitive deficits may emerge requiring new rehabilitation needs
- Constraint therapy has level A evidence for improved function of hemiparetic hand
- Bimanual therapy may improve hand function
- Interventions under study include repetitive transcranial magnetic stimulation; botulinum toxin

OUTCOMES AFTER CHILDHOOD AIS - SUMMARY

CONSIDERATIONS FOR CLINICAL PRACTICE

- Age-appropriate rehab and therapy programs are appropriate after childhood AIS
- Psychologic assessment of cognitive and language deficits is useful for planning therapy/education following childhood AIS
- Consider constraint therapy in children with unilateral hand dysfunction after AIS
- Long-term follow-up is required for childhood AIS patients to assess for new concerns – ‘growing into deficits’

KNOWLEDGE GAPS

- Emotional and mental health outcomes in children with childhood AIS
- Newer rehabilitation approaches need further study

CEREBRAL SINOVENOUS THROMBOSIS (CSV T) IN CHILDHOOD

CSVT - BACKGROUND

CSVT - DEFINITION

- Thrombosis of superficial dural, deep venous system → impaired venous drainage, intracranial hypertension
- Can result in ischemia, infarction, hemorrhage if arterial flow is subsequently impeded

PRESENTATION

- Symptoms vary by age, can be gradual
- Neonatal CSVT – seizures or encephalopathy
- Older children – signs of increased ICP, focal signs/symptoms due to hemorrhage or venous infarct
- Cavernous sinus thrombosis – localized to CN III-VI (proptosis, CN palsies)
- Can be silent, incidental finding in postop head/neck surgery or in trauma

RISK FACTORS FOR CSVT

MODIFIABLE RISK FACTORS

- Fever
- Iron-deficiency anemia
- Dehydration
- Infection (Otitis media, other head/neck infections)
- Chemotherapy -induced hypercoagulable states
- Antithrombin deficiency
- Medications - Steroids, OCPs
- Mass lesions/mass effect

CHRONIC CONDITIONS ASSOCIATED WITH CSVT

- IBD
- SLE (with lupus anticoagulant, antiphospholipid antibodies)
- Behcet syndrome
- Homocystinuria
- Nephropathy
- Congenital heart disease
- Hepatic failure
- Enteropathy
- Thyrotoxicosis

EVALUATION OF CSVT

NEUROIMAGING

- Goals: identify thrombi; edema, ischemia and hemorrhage
- Modalities: Cranial US (neonates), CT < MRI
- CT Imaging:
 - NCHCT 60-80% sensitive
 - CTV usually needed to confirm diagnosis
 - Less specific/sensitive for non-hemorrhagic lesions
- MRI/MRV test of choice for pediatric CSVT
 - MRV requires 3D phase contrast, time of flight or administration of IV contrast
 - Contrast-enhanced MRV has fewer artifacts than other modalities
- Angiography rarely used for diagnosis

EVALUATION OF ETIOLOGY

- Comprehensive evaluation can help dictate acute management, timing of anticoagulation
- Thrombophilia workup – thrombophilia can increase risk of recurrent CSVT – present in up to 60% of cases
- CBC, Iron studies, infectious workup as indicated
- CT Head to evaluate for sinusitis/mastoiditis

MANAGEMENT OF CSVT

KEY POINTS OF MANAGEMENT

- Prompt recognition and treatment of risk factors
- Neuroprotective measures
 - Antipyretics
 - IV fluids – dehydration
 - Transfuse or supplement iron for anemia
 - Treat infection, headache
 - Surgical intervention for otitis media or mastoiditis may be needed
 - Head of bed to 30 degrees
 - Treatment of seizures, continuous video EEG may be necessary
 - Evaluate for increased ICP – consider acetazolamide, CSF diversion/monitor
 - Must balance risk of LP, ICP monitor, VP shunting with need for anticoagulation
- Anticoagulation has strong evidence base in adults, remains mainstay of pediatric treatment
 - Exception: septic CSVT arising from otogenic infection/sinusitis – typically requires surgical intervention
 - Anticoagulation may be contraindicated, recanalization rates after surgery and antibiotics are high

MANAGEMENT OF CSVT - 2

ANTICOAGULATION OPTIONS & DETAILS

- Treatment options include IV heparin, SQ low molecular weight heparin, warfarin
- No studies on direct thrombin inhibitors or factor Xa inhibitors in pediatric CSVT
- Generally safe in neonates, older infants, children
 - Expert opinion varies regarding anticoagulation of neonates with hemorrhagic lesions
- Heparin may be started when bleeding risks are a concern and is quickly reversed
- Transition later to LMWH or warfarin
- If no anticoagulation – consider repeat neuroimaging in 3-7 days
 - May need to reconsider decision if clot propagation or new venous infarct observe
 - Up to 1/3 of children w/o initial anticoagulation propagate thrombus in 1 week; of those 40% develop further venous infarct
- Most common duration of treatment is 3-6 months; repeat neuroimaging can be performed to evaluate response
- Endovascular intervention can be considered in rare circumstances – as a consensus decision among pediatric stroke experts, neurointerventionalists, and family
 - Circumstances include deep venous, multifocal or diffuse thrombus w/high risk of mortality despite anticoagulation

OUTCOMES AFTER CSVT

- Children fare worse than adult after CSVT
- Adverse outcome measurements vary widely (25-74%) in several studies
 - Heterogeneity of definition of 'adverse', no standardized measurement
 - Short follow-up duration
 - Comorbidities can confound
- Hemorrhage at diagnosis is associated with worse outcome
- Rate of recanalization or propagation may influence prognosis
 - Final outcome of recanalization does not
- We assume children without cerebral edema or venous infarction do better but has not been demonstrated in rigorous studies
- Remote seizure/epilepsy prevalence is 10-14%
- Mortality reported in 0-23% of cases

CEREBRAL SINUS VENOUS THROMBOSIS - SUMMARY

CONSIDERATIONS FOR CLINICAL PRACTICE

- Suspected CSVT requires MRV or CTV for confirmation; MRI can delineate ischemia/infarction size
- Evaluate for risk factors, thrombophilia. Treat fever, infection, anemia and dehydration
- Supportive care – IV fluids, O₂, seizure/headache treatment and HOB to 30 degrees
- Serial measurements/assessments for ICP issues are routine
- Anticoagulation is tailored to individual patients; multidisciplinary approach recommended
- In rare cases endovascular thrombolysis or thrombectomy can be an option

KNOWLEDGE GAPS

- Controlled clinical trial data of antithrombotic agents in children with CSVT
- Outcomes of anticoagulation in children with incidental post-operative CSVT
- Duration of anticoagulation remains uncertain

HEMORRHAGIC STROKE IN CHILDHOOD

ETIOLOGIES OF HEMORRHAGIC STROKE IN CHILDHOOD

COMMON ETIOLOGIES

- Nontraumatic, spontaneous ICH, IVH, SAH – 75% caused by structural lesions
- AVM most common
- 10% idiopathic

TABLE 3 Structural causes of hemorrhagic stroke in children

- Aneurysm
- Arteriovenous malformation (AVM)
- Arteriovenous fistulae (AVF)
- Cavernous malformation (CM)
- (Spontaneous hemorrhage into tumor)

Hematologic causes of hemorrhagic stroke in children

- Inherited
- Most common (90%)
 - Hemophilia A (FVIII deficiency) or B (Factor IX deficiency)
 - Von Willebrand's disease
- Rare (3-5%)
 - FVII deficiency
 - FII, FXIII deficiency (rare)
 - Vitamin K dependent clotting factor deficiency
- Acquired
 - Idiopathic thrombocytopenic purpura

ACUTE MANAGEMENT OF CHILDHOOD HEMORRHAGIC STROKE

INITIAL MANAGEMENT

- CT scan test of choice due to high sensitivity, availability
- Stabilize patient, diagnose, prevent secondary injury
- If known bleeding disorder – targeted therapy
 - Factor replacement for hemophilia
 - Specific protein deficiencies require specific therapies
 - Platelet transfusion for thrombocytopenia or platelet function deficit
- Urgent cerebrovascular imaging
- Neurology, hematology and neurosurgery involvement in treatment plan
- Airway/cardiovascular management as needed
- Head of bed to 30 degrees, isotonic fluids, normalize temp and blood glucose
 - Minimize hypotension, maintain cerebral perfusion
- Control seizures, prophylaxis controversial but typically given following any ICH
- Consider continuous EEG monitoring for prolonged altered mental status, suspected status epilepticus, or movements suggestive of seizures that routine EEG fails to capture

ACUTE MANAGEMENT OF CHILDHOOD HEMORRHAGIC STROKE

IMAGING AND EVALUATION OF ETIOLOGY

- MRI – allows detection of tumor, cavernous malformation but initial blood can obscure these
- CTA – rapid, easily available but carries radiation risk; contrast bolus timing can be difficult in small children
- MRA – better initial study if it can be obtained safely
- DSA – gold standard but often deferred if ICP issues are present
- Consider repeat imaging to evaluate re-hemorrhage; delayed MRI may be needed if initial MRI is confounded by bleeding

ICP MANAGEMENT

- ICP increases can occur due to mass effect or hydrocephalus
- EVD can drain, monitor and treat ICP but carries risks in placement; rehemorrhage
- Subdural bolts only measure ICP, cannot drain CSF
- Head of bed elevation, hyperventilation, hyperosmolar therapy and sedation can all reduce ICP or temporize ICP rise
- No role for steroids in ICP management in hemorrhagic stroke

ACUTE MANAGEMENT OF CHILDHOOD HEMORRHAGIC STROKE

SURGICAL MANAGEMENT

- STICH trial showed limited benefit of supratentorial evacuation in adults with spontaneous ICH but benefit may be larger in children
- Consider evacuation of symptomatic posterior fossa bleeds, large/symptomatic subcortical lobar hemorrhage
- Goals to reduce mass effect, prevent/relieve herniation
- Decompressive hemicraniectomy can be considered; limited data suggests most effective when performed in first 24-48 hours post-hemorrhage
- Small pediatric cohort had 3/22 in cohort requiring decompressive hemicraniectomy, all functionally independent

MANAGEMENT OF ICH ASSOCIATED WITH ANTICOAGULATION

- Children on anticoagulation with ICH have the drug held or reversed
- No guidelines for timing of resuming anticoagulation
- High risk of thrombosis may require a multidisciplinary discussion re: risk/benefit ratio of resuming anticoagulation (i.e. ECMO, VAD, PE, mechanical heart valves)
- Low risk situation – e.g. chronic VTE – may allow longer time off anticoagulation

CHILDHOOD HEMORRHAGIC STROKE - OUTCOMES

MORTALITY & MORBIDITY OUTCOME ESTIMATES VARY WIDELY

- Estimates from literature vary between 4-54%
- Largest population-based study (n=132) had mortality rate of 4%, 73% ICU admission rate
- Mortality predictors include older age (11-18), coagulopathy and coma
- Possible markers of poor outcome
 - ICH volume
 - AMS within 6 hours
 - Infratentorial hemorrhage
 - GCS \leq 7 at admission
 - Aneurysmal hemorrhage
 - Age <3 years
 - Underlying hematologic disorders
- Etiology remains a major factor influencing outcome, management and follow-up

CHILDHOOD HEMORRHAGIC STROKE - OUTCOMES

EPILEPSY AFTER ICH

- 4% of ICH patients developed epilepsy in 1 year after ICH; 13% at 2 years in prospective cohort study (Beslow et al)
- ICP requiring urgent intervention is risk for remote seizures/epilepsy

COGNITIVE OUTCOMES AFTER ICH INFREQUENTLY REPORTED

- Many studies demonstrate poor cognitive outcomes among ICH survivors
- Blom et al - 2003 - 17 of 31 children with cognitive impairment when evaluated 10 years after ICH
- Hawks et al - 2016 - ~1/2 of school aged children required education services in 1 year following ICH
- Yvon et al - 2016 - 40% prevalence of special education at a median follow-up of 43 months

HEMORRHAGIC STROKE IN CHILDHOOD – SPECIFIC ETIOLOGIES

CHILDHOOD ICH - ARTERIOVENOUS MALFORMATION (AVM)

IMAGING

- Most common cause of spontaneous ICH; hemorrhage risk ~6% per year with 25% of hemorrhages fatal
- Initial diagnosis typically made with CTA/MRA
- DSA gold standard – highest resolution study, needed for creation of treatment plan
- DSA very low risk, high yield as up to 15% of cerebral AVMs supplied by meningeal arteries (missed on MRA)
- DSA can help assess hemorrhage risk, outflow stenosis, venous drainage
- May need to be deferred/repeated after initial ICH until clot resolution permits mapping AVM anatomy

SCREENING

- Most AVMs are developmental lesions without genetic background
- RASA-1 mutations associated w/high-flow AV lesions, cutaneous capillary malformations in some families
- Hereditary hemorrhagic telangiectasia (HHT) – predisposition to AVMs in multiple organs
 - Mean age of diagnosis of HHT is 35 years however large proportion of intracranial AVMs are found in children
 - Consider in patients with known AVM, frequent nosebleeds, cutaneous telangiectasias or family history of AVM
- MRI Brain recommended at time of diagnosis of HHT; use of contrast recommended if >2 y/o
 - May wait 5+ years after first MRI to rescreen; low rate of novel AVM development in disease

CHILDHOOD ICH - ARTERIOVENOUS MALFORMATION (AVM)

TREATMENT, OUTCOMES AND FOLLOW-UP

- Varies based on AVM anatomy, location
- Options include surgery, radiation, embolization, or multimodality treatments
- Large lesions or eloquent location may carry unacceptable risk to treatment
- Surgical resection +/- embolization has >95% cure rate in low to moderate risk AVMs (ruptured and unruptured), remains first line in most cases of pediatric AVM
- No randomized trial to validate this approach; treatment of unruptured AVMs in adults remains controversial
- Radiation can be given as single dose or staged radiosurgery; cure rates of 63-85% reported
 - Deep lesions (i.e. thalamic or brainstem AVMs) have lower rate of cure (54%) but are higher risk cases
 - High grade lesions have only 35% rate of cure with radiosurgery
- Embolization alone in pediatrics is avoided due to increased rate of post-treatment hemorrhage
- DSA typically performed in perioperative phase and 1 year post-op; recurrence rates reported up to 11%
 - Consider annual MRI/MRA for up to 5 years even with negative 1 year DSA

CHILDHOOD ICH - ARTERIOVENOUS FISTULA (AVF)

IMAGING

- MRI/MRA limited and may be non-diagnostic or show secondary signs of AVF (sinus thrombosis, dilated vessels, effects of venous hypertension)
- DSA remains gold standard; can demonstrate arteriovenous shunting
 - ECA/ICA/Vertebral branches → dural sinus or pial vein

SCREENING

- RASA-1 and HHT related genetic mutations most common abnormalities
 - Multiple lesions, spinal AVM/AVF, hypercoagulable states and capillary hemangiomas can be seen

TREATMENT

- Consider treatment of symptomatic or high flow AVFs
- Endovascular or microsurgical techniques most commonly used; radiation therapy rare
- Case series demonstrate 85% success rate of dural AVF cure using endovascular approach
- Combined endovascular/open approach for pial AVFs carries 71% success rate

CHILDHOOD ICH - ARTERIOVENOUS FISTULA (AVF)

OUTCOMES AND FOLLOW-UP

- Children under 2 years of age have higher complication rates; need for repeat procedures
- Children >2 years – 72% w/good clinical outcome
- Complication rates up to 60% including mortality risk of 10-12%
 - Up to 85% complication rate in infants <1 year of age
 - Children >2 have ~33% rate of complications
- Technical success (lesion obliteration) reported in ~86% of cases with age-appropriate outcomes observed at average of 16 months post—procedure follow-up
- Hydrocephalus can develop due to changes in venous outflow, CSF dynamics or development of venous thrombosis

CHILDHOOD ICH - ANEURYSMS

IMAGING

- CTA or MRA useful in subarachnoid hemorrhage presentation
- MRI/MRA identifies SAH source in approximately 66% of cases
- DSA gold standard, 97% detection of lesion (80% detection w/o DSA)

SCREENING

- Familial syndromes very rare, <5% of cases in prepubescent children
- MRI/MRA screening of family members only for patients with multiple first-degree relatives affected or multiple aneurysms w/o infection (i.e. non-mycotic)

CHILDHOOD ICH - ANEURYSMS

TREATMENT

- Multidisciplinary team approach recommended
- Options include open surgery, endovascular treatment or combination
- Ruptured aneurysms, enlarging aneurysms or symptomatic lesions should be treated
- May consider lower threshold for treatment of unruptured aneurysms in children than adults
- Mycotic aneurysms can regress w/antibiotics and may not require further treatment
- Aneurysms proximal to AVM or other lesion may regress following treatment of primary pathology (i.e. AVM resection)
- In adults, lesions <2mm or outside subarachnoid space often receive surveillance only
- Anticipated lifespan, risk factors for aneurysm and etiology of aneurysms all different in pediatric population compared to adults

CHILDHOOD ICH - ANEURYSMS

OUTCOMES AND FOLLOW-UP

- Average mortality rates in series vary between 1-3%, morbidity ranges from 8-14%
- Sequelae include strokes, hydrocephalus, vasospasm, and electrolyte derangements
- Triple-H therapy can be used to reduce vasospasm risk following aneurysm treatment
 - Hypertension, hypervolemia, hemodilution
- Nimodipine efficacy in children unknown
- Ventriculoperitoneal (VP) shunts needed in ~14% of patients
- 91% of survivors regain independent living
- Annual MRI/MRA recommended for 5 years; possibly every 3-5 years for life to evaluate for recurrent or de novo aneurysms
 - New aneurysm burden seen in ~40% of patients

CHILDHOOD ICH – CAVERNOUS MALFORMATIONS (CM)

IMAGING

- CT or MRI required; DSA will not visualize CMs
- Clot burden may require repeat imaging weeks after bleed
- MRI signature – multilobulated lesion w/blooming on susceptibility sequences due to hemosiderin deposit
- Consider post-radiation or familial syndrome in cases of multiple CMs
- Can be associated with developmental venous anomalies (DVAs)

SCREENING

- Consider screening first degree relatives in patients with multiple CMs or family history of CMs
- CCM1, CCM2 or CCM3 mutations found in >90% of familial cases
- Extremely common in cases of multiple lesions on imaging (85%), rarer in cases of single lesion (16%)

CHILDHOOD ICH – CAVERNOUS MALFORMATIONS (CM)

TREATMENT

- Surgical resection vs observation
- Excision favored for symptomatic CMs; recurrent hemorrhage; high risk location (such as posterior fossa) or large lesion
- Brainstem CMs carry greater perioperative risks (6% mortality, 21% persistent deficits, 33% perioperative morbidity); decision to treat is challenging
- For patients with multiple CMs – only resect symptomatic or expanding CMs
- Radiation generally only for malignant CMs that are not amenable to surgery (inaccessible)

OUTCOMES AND FOLLOW-UP

- Resection of most common CM (supratentorial lobar location) carries 98% resection rate, 96% rate of seizure freedom, 5% complication rate
- CM can recur; especially in familial syndromes or post-radiation CMs
- Many obtain annual MRI for 3-5 years, then space out studies

CHILDHOOD HEMORRHAGIC STROKE - SUMMARY

CONSIDERATIONS FOR CLINICAL PRACTICE

- Acute management includes airway and cardiovascular management, seizure control, head of bed to 30 degrees, isotonic fluids, normoglycemia and normothermia.
- Rapidly correct any bleeding disorder
- MRA can be performed after stabilization.
- All pediatric hemorrhages should have DSA unless another alternative cause is identified in workup
- Assess symptomatic hematomas for evacuation
- Consider catheter angiography, multidisciplinary involvement for AVM, AVF and aneurysms

CONSIDERATIONS (CONTINUED)

- Unruptured AVMs – surgery typically first line for low grade lesions. Higher grade lesions – radiation or surgery.
- Observation may be appropriate in some AVM or AVF cases (large lesions, eloquent cortex)
- Most AVFs treated with embolization as first line; surgery for select cases.
- Surgical resection can be considered for symptomatic or enlarging CMs
- Careful skin examinations can identify vascular birthmarks; genetic syndromes

CHILDHOOD HEMORRHAGIC STROKE - SUMMARY

CONTROVERSIES IN CURRENT PRACTICE

- Brainstem cavernous malformations in children should generally be observed.
- Asymptomatic, incidentally discovered AVMs should be considered for treatment in most children.
- Genetic screening should be considered in children with the pial AVF, AVM, or cavernous malformations if there is a suggestive family history, multiple or unusually complex malformations, or vascular birthmarks on exam
- Screening for the presence of a thrombus should be performed for dural AVF not related to trauma
- Management of asymptomatic small aneurysms

KNOWLEDGE GAPS

- Utility of prophylactic anticonvulsants after ICH
- Long term outcome of conservatively treated AVM
- Role of biomarkers in diagnosis of cerebrovascular disease.
- Ideal timing of surgery
- Management of SAH-associated vasospasm