MMC/BBCH Stroke Clinical Practice Guideline – Emergent Evaluation

CLINICAL PRESENTATION: A pediatric patient (age < 18 years old) with focal neurologic deficit including any of the following:

- Lethargy, persistent mental status change or acute loss of consciousness
- Aphasia or dysarthria
- Severe headache
- Seizure with focal weakness
- Lower face weakness, unilateral extremity weakness
- Focal sensory disturbance such as numbness
- Acute ataxia

HISTORICAL RISK FACTORS FOR PEDIATRIC STROKE:

- History of congenital heart disease
- Sickle cell disease
- Diabetes
- Trauma
- Recent viral infection
- Hypercoaguable disorder
- Dehydration
- Malignancy
- Metabolic disorder (MELAS or other)

STAT page on-call pediatric neurologist (580-5917) to discuss appropriate imaging choices

Order labs, imaging, and initiate supportive care (as detailed below)

Obtain STAT labs:

- CBC, CMP and massive transfusion coagulation panel

When clinically appropriate add:

- Blood cultures, Troponin, βhCG, serum lactate, toxicology screen, ESR/CRP, reticulocyte count, % HbS, and type & cross
- EKG and telemetry

Obtain EMERGENT neuroimaging:

- **MRI brain/MRA head and neck** is the preferred first-line scan in pediatric patients, though may require sedation (neurology to call anesthesia floor walker at 662-4351)
- **Head CT/CTA** only if concern for ICH/SAH or potential acute intervention (i.e. off-label IV or IA tPA use)
- Add **gadolinium/venous thrombosis protocol** for suspected Central Venous Thrombosis (CVT)

Supportive care:

- Maintain ABCs with oxygen supplementation only if sats <95%
- Maintain euglycemia & euthermia
- Start IVF with NS at maintenance rate
- Permissive hypertension for ischemic stroke (allow SBP up to 95%)
- Keep NPO with aspiration precautions
- Treat seizures; consider cEEG
- Consider ECHO

Intracranial hemorrhage (ICH) or Subarachnoid hemorrhage (SAH)

- **Consult neurosurgery**
- Reverse coagulopathy
- Platelet transfusion for <50k
- May require angiography
- Monitor for signs of increased intracranial pressure (ICP)

Ischemic Stroke

ASA 3-5 mg/kg per rectum

Completed large MCA or large cerebellar infarct:

- **Consult neurosurgery** for possible ICP monitoring and decompressive hemicraniectomy
- Mannitol or hypertonic saline for patients awaiting surgery
- Head of bed at 15-30°

Thromboembolic arterial occlusion:

If within 3 hours of last known well and no other contraindications to tPA in an adolescent, **consider IV tPA[§] and/or interventional radiology consult (+/- CTA/CTP)**

- Carotid dissection: Consider IR endovascular procedure and LMWH
- Cardiac source of embolism: Consider aspirin vs anti-coagulation depending on clinical situation

Cerebral Venous Sinus Thrombosis (CVST)

- **Consult hematology**
- Initiate anticoagulation- (LMW heparin preferred)
- Consider serial imaging

Sickle cell disease:

- **Urgent hematology consultation**
- **Urgent intravenous hydration with normal saline** (avoid hypotonic saline)
- **Urgent exchange transfusion** to reduce the HbS fraction to <30 % of total Hgb
- Evaluate and treat any triggers for sickle crisis (infection, hypoxia, acidosis, dehydration)

§ **tPA** is not approved by the FDA for use in patients < 18 years of age with ischemic stroke. There are case reports, national registry data from the US and international registry data of IV or IA thrombolysis use in small numbers of children. However, the effectiveness, safety and dose have not been established. However, recognizing that safety and efficacy data are lacking in patients younger than 18 years of age, *it may be reasonable to consider thrombolytic treatment on an individual basis for older adolescents (age 15 and older) with acute arterial ischemic stroke*. Strict adherence to the accepted time limits and other eligibility criteria used in adults should be observed if thrombolytic therapy is employed for older adolescents.

BBCH Clinical Practice Guidelines for Pediatric Stroke
Diagnostic Work-up

The most common etiologies for ischemic stroke in children include cardiac abnormalities, vascular lesions, hematologic abnormalities, infection, head and neck trauma, and genetic conditions.

Table 1 - Causes of pediatric stroke

Vascular – non-inflammatory	Vascular - inflammatory	Cardiac
• Arterial dissection (traumatic, spontaneous or secondary to CTD) • Fibromuscular Dysplasia • Premature atherosclerosis • Focal cerebral arteriopathy of childhood • vasculopathy • Vasospasm (RCVS, migraine, post SAH) • HTN • Moyamoya -primary (disease) -secondary (syndrome)	• Primary CNS Vasculitis • Secondary - Takayasu - GCA - Kawasaki dz - PAN - other rheum disease • Infectious and Post-infectious -HIV -VZV -Bacterial meningitis -Syphilis -TB -Fungal -Lyme	• Congenital heart disease • PFO • Atrial myxoma • Afib, other arrhythmias • Cardiomyopathy • Myocarditis • MI • Endocarditis • Rheumatic heart disease • Mitral valve prolapse • Other valvular disease (congenital or acquired)
Hematologic	**Genetic**	**Iatrogenic/ingestion**
Inherted • Sickle cell disease • Thrombophilias • Hyperhomocystenemia • Elevated Lp(a) • Polycythemia vera Acquired • Fe-deficiency anemia • APLAS Prothrombotic states: • Pregnancy or OCPs • Occult malignancy • Protein-losing enteropathy Platelet dysfunction • thrombocytosis • DIC • HUS/TTP • HIT Neoplastic • Leukemia and other blood malignancies, including intravascular lymphoma	• MELAS • CADASIL • Fabry • Menkes' • Homocystinuria • MTHFR gene mutation • PHACE syndrome* • NF1, TS • Loewy-Dietz	• Cardiac surgery • Cardiac cath • ECMO • Prosthetic valves • OCPs • L-asparginase • Radiation vasculopathy • Cocaine • Amphetamines Possible causes may include synthetic marijuana ("spice") and tobacco abuse

* PHACE syndrome: congential arteriopathy. Dysplastic cervical and cerebral arteries – posterior fossa brain malformations, facial hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities.

Table 2 - Tiered approach to diagnostic testing

Tier 1 testing should be strongly considered in all pediatric patients with AIS (acute ischemic stroke). If an etiology is not found, Tier 2 testing should be pursued in specific patient populations. If no etiology is found, Tier 3 testing should be considered based on specific clinical findings and results of other testing.

	Tier 1	Tier 2	Tier 3
Labs	CBC, CMP, Troponin and coagulation panel, toxicology screen, fasting lipid panel, HbA1c Concern for infection: Blood cultures Childbearing potential: βhCG	Mitochondrial disease: serum lactate, amino acids, urine organic acids, carnitine Vasculitis: ESR/CRP, rheum panel Appropriate ethnicity: hemoglobin electrophoresis	Genetic testing
Cardiac	TTE with bubble ECG Telemetry	TEE with bubble Concern for arrhythmia: prolonged cardiac monitoring	
Vascular	MRA/CTA	Concern for vasculopathy not seen on MRA/CTA: Cerebral angiogram	
Hematological	Thrombotic risk panel[2], lipoprotein (a)		
Infectious/ Inflammatory	Lumbar Puncture[1]: Cell count, protein, glucose. Viral, bacterial and fungal cultures. VZV IgG and IgM in serum and CSF, VZV PCR in CSF. VDRL, Lyme; lactate		

1. LP is indicated for any pediatric stroke patient with concern for CNS infection, vasculitis, focal cerebral arteriopathy,
2. Thrombotic Risk Panel at MMC includes Protein C level, Protein S leve, Antithrombin III activity, Factor V Leiden gene mutation, Prothrombin gene mutations, Anticardiolipin antibodies (IgG and IgM), Beta2-glycoprotein I antibodies (IgG and IgM), Lupus anticoagulant, Homocysteine and D-dimer

MISCELLANEOUS

Secondary moyamoya: sickle cell disease, NF1, TS, Down syndrome, Williams syndrome, post-cranial irradiation, FMD, post-infectious vasculopathy, intracranial dissection, Transient cerebral arteriopathy of childhood (TCAC), vasculitis, viral or bacterial infx, cong heart dz (UpToDate)

Focal cerebral arteriopathy of childhood (FCA) is the term used by the International Pediatric Stroke Study (IPSS) group to describe an unexplained focal arterial stenosis in a child with AIS. This includes **Transient cerebral arteriopathy of childhood (TCAC)** is a clinical syndrome characterized by **unilateral focal or segmental stenosis of the distal carotid arteries and proximal Circle of Willis vessels (the middle, anterior, and posterior cerebral arteries).** The stenosis may worsen in the first three months after stroke, sometimes associated with new neurologic symptoms, but stabilizes and can even improve by six months after initial presentation. While the term "transient" implies complete resolution, many patients are left with some degree of residual arterial stenosis. Ischemic **stroke** associated with TCAC **typically occurs in the distribution of the lenticulostriate branches that arise from the proximal segments of the middle cerebral artery and anterior cerebral artery, supplying the basal ganglia and internal capsule**. In a subset of cases, this finding is associated with antecedent **varicella infection** and **other viral infections** may underlie the pathophysiology in idiopathic cases. The etiology is probably multifactorial. Possible causes are inflammation and vasculitis due to infection (eg, antecedent varicella infection) or autoimmune disease, thromboembolic arterial occlusion or stenosis followed by variable recanalization, intracranial dissection, arterial spasm, and prothrombotic factors.

Various connective tissue and vascular disorders that have been associated with dissection: Ehlers–Danlos syndrome type IV, Fibromuscular dysplasia, Marfan syndrome, Osteogenesis imperfect, cystic medial necrosis, Homocystinuria, Autosomal dominant polycystic kidney disease, Alpha-1 antitrypsin deficiency, Segmental mediolytic arteriopathy, Reversible cerebral vasoconstriction syndromes; Although supporting evidence is weak, a host of other conditions have been associated with cervicocephalic dissection, include recent infection, hypertension, migraine, longer styloid process length, aortic root diameter >34 mm, oral contraceptive use, smoking, elevated homocysteine levels, alcohol use, redundancy of vessels, higher body height, and lower body weight. Dissections have been noted in association with other vascular findings such as cerebral aneurysms and arterial fenestrations

BBCH Clinical Practice Guidelines for Pediatric* Stroke
Treatment for Secondary Stroke Prevention

	Therapies	Consults
Cryptogenic	Aspirin	
Cardiac		
High-risk for recurrent cardioembolic stroke Congenital heart disease Atrial myxoma Afib, other arrhythmias Cardiomyopathy Myocarditis Myocardial infarction Rheumatic heart disease with valvular dysfunction	Warfarin	Cardiology and in many cases cardiothoracic surgery
Low-risk for recurrent cardioembolic stroke Mitral valve prolapse PFO +/- ASA	Aspirin	
Endocarditis	Antibiotics	Infectious disease and cardiothoracic surgery
Vascular		
Non-inflammatory		
Arterial dissection (traumatic, spontaneous or secondary to CTD)	UFH or LMWH followed by warfarin for 3-6 months	
FMD	Aspirin	
Focal cerebral arteriopathy of childhood	Aspirin	
Vasospasm (RCVS, migraine, post SAH)	Calcium channel blockers; anti-migraine therapies	
Moyamoya -primary -secondary	Aspirin	Neurosurgery for possible endephaloduroarteriomyosynangiosis (EDAM) or other bypass procedure
Inflammatory		
- Takayasu, GCA, PAN, other rheum dz	Steroids, other immunosuppression	Rheumatology
Hematologic		
Inherited thrombophilias	Anticoagulation	Hematology
Sickle cell anemia	Hydroxyurea Monitor with TCD annually. If velocities > 200cm/sec, tx with exchange transfusion q3-6 wks to maintain HbS < 30%	Hematology Consider BMT from HLA-matched sibling
Antiphospholipid antibody syndrome:	Anticoagulation, possible immunosuppression	Rheumatology
Hyperhomocysteinemia:	B6, B12 and folate	
Lp(a)	Consider niacin	
PCRV	Keep Hct < 45%	
Infectious		
VZV HIV RPR	Acyclovir HAART PCN	Infectious disease
Genetic		
MELAS	Vitamins Avoid valproic acid	
Fabrys	Fabrazyme	

* Neonatal stroke (stroke occurring from 0 - 1 month-olds) has a very low risk of recurrence.; therefore, secondary stroke prevention measures are not recommended.

Monitor for the development of Reye's syndrome in patient's treated with aspirin & consider reducing/eliminating dose during febrile illness or around the time of influenza vaccination

Pediatric Medication Doses/Management:

Aspirin 3-5 mg/kg/d

Clopidogrel 1 mg/kg, max 75 mg/d

Intravenous unfractionated heparin (goal PTT 60 to 85). No bolus if there is infarction on MRI/CT. Maintenance dosing: under 12 mo – 28 U/kg/hr; oleder children 20 U/Kg/hr; adolescents 18 u/kg/hr (Therapeutic approaches and advances in pediatric stroke)

Low molecular weight heparin (eg, enoxaparin [1.5 mg/kg daily in infanct < 2 mo and 1 mg/kg dose every 12 hours or daily] to achieve a goal anti-factor Xa level of 0.5 to 1.0 U/mL)

Warfarin: initial dose 0.2 mg/kg/d followed by dose adjustment based on INR

Table 11. Warfarin Anticoagulation Protocol for Children*

Stage	INR	Action
Day 1	1.0–1.3	0.2 mg/kg orally
Days 2–4	1.1–1.3	Repeat day 1 loading dose
	1.4–1.9	50% of day 1 loading dose
	2.0–3.0	50% of day 1 loading dose
	3.1–3.5	25% of day 1 loading dose
	>3.5	Hold dosing until INR is <3.5, then restart according to stage III guidelines
Maintenance	1.1–1.4	Increase by 20% of dose
	1.4–1.9	Increase by 10% of dose
	2.0–3.0	No change
	3.1–3.5	Decrease by 10% of dose
	>3.5	Hold dosing until INR is <3.5, then restart at 20% less than last dose

INR indicates international normalized ratio. Adapted from Michelson et al,[524] with permission, and the experience of the Writing Group.

*The protocol is designed to maintain an INR between 2 and 3 with warfarin.

Table 10. Protocol for Using LMWH in Children

Preparation	Initial Treatment Dose	Initial Prophylactic Dose
Reviparin, body weight–dependent dose, units/kg per 12 h		
<5 kg	150	50
>5 kg	100	30
Enoxaparin, age-dependent dose, mg/kg per 12 h		
<2 mo	1.5	0.75
>2 mo	1.0	0.5
Dalteparin, all-age pediatric dose, units/kg per 24 h	129±43	92±52
Tinzaparin, age-dependent dose, units/kg		
0–2 mo		275
2–12 mo		250
1–5 y		240
5–10 y		200
10–16 y		275

Table 9. Protocol for Systemic Heparin Administration and Adjustment in Children

Stage	aPTT, s	Dose, units/kg	Hold, min	Rate Change, %	Repeat aPTT
I. Loading dose*		75 IV over 10 min			
II. Initial maintenance dose					
Infants <1 y		28/h			
Children >1 y		20/h			
III. Adjustment†	<50	50	0	10	4 h
	50–59	0	0	10	4 h
	60–85	0	0	0	Next day
	86–95	0	0	−10	4 h
	96–120	0	30	−10	4 h
	>120	0	60	−15	4 h
IV. Obtain blood for aPTT 4 h after heparin load and 4 h after every infusion rate change					
V. When aPTT values are in therapeutic range, perform daily CBC and aPTT measurement					

aPTT indicates activated prothrombin time; CBC, complete blood count. Adapted from Michelson et al,[524] with permission, and the experience of the Writing Group.
*Some physicians omit this step.
†Heparin was adjusted to maintain aPTT at 60 to 85 seconds, assuming that this reflects an anti–factor Xa level of 0.35 to 0.70.