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TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
Diagnosis and Management of Acute Arterial Ischemic Stroke In Children
Evidence-Based Guideline

Definition: Acute ischemic stroke (AIS) is defined as rapidly developing signs of focal cerebral disturbance observed as cognitive, sensory and/or motor changes, with symptoms lasting ≥1 hour. [1,3,9] Clinical signs and symptoms are often subtle. When AIS is suspected, optimal treatment requires rapid assessment and early intervention to prevent significant neurological deficits. Patients presenting within 6 hours of clinical stroke (last time child seen normal) or severe stroke symptoms should be evaluated expeditiously, with rapid triage and emergent evaluation by a neurologist.

Epidemiology: AIS is uncommon in children; however, the incidence for pediatric stroke ranges from 2-8 per 100,000 children per year in the United States. [11] Morbidity is high, with persistent neurological deficit found in up to 70% of patients. [12,13,22] AIS is more common in boys than girls. [33]

Etiology: The most common risk categories for acute ischemic stroke (AIS) are listed in Table 1 below. [1,3,9,22-35] Heart disease (congenital or acquired) is the most common risk category for AIS in children. Vasculopathies may be acquired (such as dissections or post-viral arteriopathies) or genetic and may place children at risk for AIS or may be related to clinical syndromes (resulting in congenital anomalies or progressive arteriopathy). Other risk categories include systemic vasculitis, hemoglobinopathies such as sickle cell disease, disorders of coagulation, and metabolic disorders. Approximately 30% of children have no identifiable risk factor present at stroke presentation. [1,12,14] However, children at risk often have multiple etiologies related to AIS. [1,12,15] See Appendix 1 on p. 10 for a more extensive list of AIS risk categories.

Table 1. Common Risk Categories for AIS [22-35]

Category	Description
Cardiac- **Congenital** **Acquired**	Complex cardiac anomalies involving both valves and chambers, and artificial devices are collectively the largest risk category, but any cardiac lesion may place a child at risk for AIS.
Vasculopathy **Acquired** **Traumatic** **Structural**	Examples include traumatic or spontaneous tear of the arterial intima resulting in dissection, Moyamoya syndrome that causes stenotic or occluded arteries.
Hemoglobinopathy	AIS rates in children with sickle cell disease are much higher than children in general.
Prothrombotic	Several hereditary disorders of coagulation promote thrombosis and increase the risk of AIS, especially in the setting of comorbid conditions such as vasculopathy. Certain cancer therapies increase the risk for AIS.
Vasculitis	Vasculitis of the intracranial vessels promotes occlusion and thrombosis. Vasculitis may be secondary to other immune diseases such as lupus, or rarely may be primary CNS vasculitis. Infectious causes may include varicella, human immunodeficiency virus, tuberculous meningitis or bacterial meningitis.
Metabolic	Mitochondrial disorders such as MELAS as well as inborn errors of metabolism may cause increase risk of AIS.

Inclusion Criteria:
≥1 month of age with rapidly developing signs of focal cerebral disturbance, within 72 h of symptom onset

Exclusion Criteria
<1 month of age, hemorrhagic stroke, traumatic brain injury, cerebral venous sinus thrombosis (CVST), suspected stroke with symptom onset >72 h

Differential Diagnosis
- Seizures
- Meningitis
- Tumors and other space occupying lesions such as brain abscess
- Hypoglycemia
- Hypertensive encephalopathy
- Complicated or hemiplegic migraine
- Focal encephalitis including cerebellitis
- Traumatic extradural or subdural hemorrhage
- Demyelinating conditions e.g. acute disseminated encephalomyelitis (ADEM)
- Postictal paralysis (Todd's paresis)
- Idiopathic intracranial hypertension
- Musculoskeletal disorders
- Functional / Medically Unexplained / Psychogenic symptoms
- Drug toxicity

Diagnostic Evaluation: Symptoms may be subtle and neurologic signs may be minimal in infants 1-12 months of age. Seizures may accompany neurologic signs and symptoms, especially in children <1 year of age. Signs and symptoms related to age are found in Table 2.

History: Assess for
- Time of onset- when was patient last awake and symptom-free
- Recent trauma, head pain, neck pain, or head or neck irradiation
- Recent viral infection (e.g., varicella infection or vaccination, upper respiratory infection)
- Heart surgery or cardiac anomaly
- Sickle cell disease
- In older children- oral contraceptive use, amphetamine or cocaine use
- Family history for recurrent miscarriages, lupus, autoimmune disease, early stroke, heart attack, pulmonary embolism, DVT
- Baseline developmental function

Table 2. Signs and Symptoms of AIS [22-35]

Signs and Symptoms **Children ≥1 month of age**
Focal Motor Deficits • Monoparesis or hemiparesis **Focal Neurologic Deficits** • Vision changes- diplopia, visual field cut • Dysarthria • Aphasia • Numbness • Ataxia
The following signs and symptoms may accompany motor and neurologic deficits listed above: • Headache • Seizures • Altered mental status • Vertigo • Cranial nerve palsies

Physical Examination: Assess for

- Level of consciousness, orientation, response to commands
- Gaze and visual fields
- Facial paresis
- Motor function- arms and legs
- Limb ataxia
- Sensory loss
- Language (naming, repetition) and articulation
- Carotid or head bruits, skin lesions or neurocutaneous disorders, and signs of cardiac problems (e.g., peripheral edema)

Early assessment should be performed by clinicians who are experienced in recognition, diagnosis, and management of AIS.

A detailed neurologic exam should be performed. The *PediNIH Stroke Scale* may be completed by the neurologist on call in the case of suspected or confirmed stroke.

Emergency Management: Suspected Stroke [1,3,15,17,20,42-60]

Children presenting with symptoms of stroke require immediate medical attention and rapid assessment. Notify the neurologist on call immediately. Key components of emergency management:

- Maintain airway, breathing, and circulation
- Monitor vital signs including pulse oximetry, continuous cardiac monitoring, and neurologic checks every 15 minutes until stable, then every 1 h
- Monitor oxygen saturation, administer humidified oxygen if room air O_2 ≤95% or mental status is depressed
- Establish IV access and draw laboratory studies
- Initial laboratory studies:
  - CBC with differential and platelets
  - PT, PTT, Fibrinogen, INR
  - Chem 10 (Electrolytes, glucose, BUN, creatinine, Calcium, Magnesium, Phosphorus)
  - Blood Glucose check by Accu-Chek® at time of blood draw
  - Type and Screen
  - Hemoglobin profile (if indicated)
- Initial diagnostic studies:
  - Diffusion-weighted Imaging (DWI) sequence (when feasible): (TCH policy DI-405 Safety for Magnetic Resonance Imaging)
    - Obtain an MR DWI if available and if MR is not immediately available or contraindicated, obtain a CT scan of the head and neck and a CTA.
    - Contraindications include electrically, magnetically or mechanically activated implants (e.g., cardiac pacemaker or defibrillator; implanted neural stimulator, cochlear implant), insulin pump, metal shrapnel or bullet)
    - Suspected foreign body metal in eyes or other body parts needs plain x-rays or CT imaging for confirmation.
    - Case by case determination for patients with metallic implants (e.g., aneurysm clips, surgical clips, sutures, pins, screws, dental braces), pregnant, unconscious or morbidly ill
    - MRI limited by artifact when metallic dental implants present
  - Noncontrast Brain CT
    - initiate a CT scan (or MRI) within 25 minutes of arrival and to complete interpretation of the CT scan within 45 minutes of arrival to exclude intracranial hemorrhage for patients who are candidates for intravenous rt-PA.
  - 12 Lead EKG
- For children ≥1 year, begin IV fluids with 0.9% normal saline at 1600 mL/m^2/24 h; avoid overhydration but correct for dehydration; monitor electrolytes
- For infants <1 year, begin IV fluids with D_5NS at 1600 mL/m^2/24 h; avoid overhydration but correct for dehydration; monitor electrolytes
- Obtain blood glucose check (Accu-Chek®) STAT every 2 h; if initial glucose is <80, correct hypoglycemia and add dextrose to IV fluids. Otherwise, avoid the addition of dextrose
- Maintain normothermia - administer acetaminophen for temperature >100ºF (38.3ºC)
- If seizures occur, administer nonsedating anticonvulsant such as IV fosphenytoin or leveTIRAcetam at standard loading doses
- Adhere to strict bedrest with head of bed (HOB) flat and neck midline
- Maintain NPO status

Initial Management for Confirmed Stroke [1,3,15,17,20,72-97]

Continue with emergency interventions discussed above. Supportive measures for AIS include airway maintenance and breathing, control of fever, monitoring of blood pressure, and normalization of serum glucose levels (Table 3, p. 3)

Critical Points of Evidence*

Evidence Supports

- Risk categories for AIS that include heart disease (congenital or acquired), vasculopathy (acquired, traumatic), hemoglobinopathy, vasculitis, disorders of coagulation, and metabolic disorders.[21-35] (As many as 30% of children have no identifiable risk factor present at stroke presentation. [1,3]) – Strong recommendation, low quality evidence
- Signs and symptoms associated with AIS include focal motor deficits (paresis), focal neurologic deficits (vision changes, dysarthria, aphasia, numbness, and ataxia), headache, seizures, altered mental status, vertigo and cranial nerve palsies. [21-35] – Strong recommendation, low quality evidence
- MRI DWI should be first choice for imaging because of its optimal sensitivity to detect early acute ischemic stroke. Obtain an MR DWI if available, and if MR is not immediately available or contraindicated, obtain a CT scan of the head and neck and a CTA. The MRI or CT scan should be initiated within 25 minutes of arrival. The interpretation of the MRI or CT scan should be completed within 45 minutes of arrival to exclude intracranial hemorrhage for patients who are candidates for intravenous rt-PA. [7,44-68] – Strong recommendation, moderate quality evidence
- Use ECG and telemetry monitoring as initial cardiac evaluation tools. Continuous cardiac monitoring during the acute/subacute phase is recommended. Routine Holter monitoring should be ordered AFTER initial stroke management. [3,69-71] – Strong recommendation, moderate quality evidence
- Supportive measures for AIS that include airway maintenance and breathing, control of fever, control of systemic hypertension, and normalization of serum glucose levels. [3,13]

- Normothermia maintenance for at least the first several days after an acute stroke. [72-77] – Strong recommendation, low quality evidence
- Maintain serum glucose concentrations at <140 mg/dL and treat hyperglycemia with insulin for patients with serum glucose concentrations >140 mg/dL. [78-84] – Strong recommendation, moderate quality evidence
- Maintain a blood pressure goal of the 50th-95th percentile for age and height, with permissive hypertension up to 20% above the 95th percentile. If a blood pressure–lowering agent is used, care should be taken to avoid a precipitous drop in blood pressure that may worsen cerebral ischemia. Persistent, significant hypertension should be treated with labetalol or ACE inhibitor to lower blood pressure by approximately 25% over 24 hours. [3,75,85-97] – Strong recommendation, moderate quality evidence
- Intravenous tissue Plasminogen Activator (IV tPA) should be initiated for patients 2 to 17 years of age who present to the EC within 4.5 h of last seen well and whom IV treatment can be administered within 4.5 hours from known symptom onset; radiologic confirmation of arterial stroke with absence of hemorrhage; pediatric stroke severity score ≥4 and ≤24; and no contraindications (see Table 3). [1,3,64,98-106] – Strong recommendation, low quality evidence
- Consider mechanical thrombectomy on a case by case basis for children presenting with AIS within 24 hours or less of onset in discussion with a multidisciplinary team (including neurosurgery, neurointerventional radiology, and neurology). [107-113] – Weak recommendation, very low quality evidence
- Antiplatelet therapy with aspirin while stroke etiology determined. [6] – Strong recommendation, low quality evidence
- Administer unfractionated heparin or low molecular weight heparin (LMWH) or aspirin as initial therapy until dissection and embolic causes have been excluded. Prescribe and deliver 5mg/kg of aspirin up to a maximum of 300mg within 24 hours of diagnosis of AIS in the absence of contraindications (e.g. parenchymal hemorrhage). After 14 days reduce dose of aspirin to 1mg/kg to a max of 75mg. Continue antithrombotic treatment initiated acutely in children and young people with AIS. Reduce dose of aspirin from 5mg/kg to 1mg/kg after 14 days. Treat all children and young people with AIS with aspirin, unless they have SCD or are receiving anticoagulation e.g. for a cardiac source of embolism. In children where an arterial ischemic stroke is NOT caused by cardioembolism or dissection, daily aspirin is recommended for a minimum of 2 years. In children with arterial ischemic stroke secondary to cardioembolism treatment with low molecular weight heparin or Vitamin K antagonist is recommended for a minimum of three months. In children with arterial ischemic stroke secondary to dissection, treatment with low molecular weight heparin or Vitamin K antagonist is recommended for a minimum of 6 weeks. Ongoing treatment should be dependent on neuroradiological assessment of stenosis severity and recurrent ischemic episodes. [6,114-117] – Strong recommendation, low quality evidence
- Consider the addition of steroids to antiplatelet therapy for children with infection and arteriopathy related etiologies, and AIS that is NOT cardioembolic or dissection. [6,119,120] – Weak recommendation, very low quality evidence
- Revascularization surgery for moyamoya patients when no contraindications to surgery present. [1,3,6]
- Consideration for early surgical intervention in those who have depressed or deteriorating level of consciousness or other signs of increased intracranial pressure. [121-123] – Weak recommendation, very low quality evidence
- Initiate for ALL children presenting with AIS, a clinical assessment of a child's body structures and functions and activities with consideration of the child's age and developmental abilities by a multidisciplinary team (including physical therapists, occupational therapists, speech and language therapists) as soon as possible after diagnosis to determine stroke severity and rehabilitation needs. [124-128] – Strong recommendation, low quality evidence
- Initiate rehabilitation for all patients with AIS that addresses physical, functional, cognitive and emotional domains; and individualized for age, developmental abilities and patient/family values and preferences. [129-133] – Strong recommendation, low quality evidence
- All patients admitted with AIS to be mobilized early (between 24 h and 48 h of stroke onset) if there are no contraindications. Contraindications to early mobilization include, but are not restricted to, patients with an arterial puncture for an interventional procedure, unstable medical conditions, low oxygen saturation, and lower limb fracture or injury. [129-133] – Strong recommendation, low quality evidence

Evidence Against

- Do not routinely use Holter monitoring to evaluate stroke. [3,69-71] – Weak recommendation, moderate quality evidence
- BP treatment in the patient with acute ischemic stroke unless the hypertension is extreme or the patient has active ischemic coronary disease, heart failure, aortic dissection, hypertensive encephalopathy, or acute renal failure. [3,75,85-97] – Strong recommendation, moderate quality evidence
- Use of CT scan alone for the identification of acute ischemic stroke. [7,44-68] – Strong recommendation, moderate quality evidence

Evidence Lacking/Inconclusive

- Altering BP in the acute phase of stroke influences outcome. [3,75,85-97] – Strong recommendation, moderate quality evidence
- Anticoagulation therapy during initial stroke management reduces stroke progression [4,6,114]
- Safety and effectiveness of surgical procedures in improving patient outcomes. [121-123] – Weak recommendation, very low quality evidence
- Prophylactic treatment with antiepileptic drug in absence of clinical seizures. [3]

*NOTE: The references cited represent the entire body of evidence reviewed to make each recommendation.

Condition-Specific Elements of Clinical Management

Emergency Management: Suspected Stroke (1,3,15,17,20,42-60)

Children presenting with symptoms of stroke require immediate medical attention and rapid assessment. Notify the neurologist on call immediately. Key components of emergency management:

- Maintain airway, breathing, and circulation
- Monitor vital signs including pulse oximetry, continuous cardiac monitoring, and neurologic checks every 15 minutes until stable, then every 1 h
- Monitor oxygen saturation, administer humidified oxygen if room air $O_2 \leq 95\%$ or mental status is depressed
- Establish IV access and draw laboratory studies
- Initial laboratory studies:
- CBC with differential and platelets
- PT, PTT, Fibrinogen, INR
- Chem 10 (Electrolytes, glucose, BUN, creatinine, Calcium, Magnesium, Phosphorus)
- Blood Glucose check by Accu-Chek® at time of blood draw
- Type and Screen
- Hemoglobin profile (if indicated)
- Initial diagnostic studies:
- For infants <1 year, begin IV fluids with D_5NS at 1600 mL/m^2/24 h; avoid overhydration but correct for dehydration; monitor electrolytes
- Obtain blood glucose check (Accu-Chek®) STAT every 2 h; if initial glucose is <80, correct hypoglycemia and add dextrose to IV fluids. Otherwise, avoid the addition of dextrose.
- Maintain normothermia - administer acetaminophen for temperature >100ºF (38.3ºC).
- If seizures occur, administer nonsedating anticonvulsant such as IV fosphenytoin or leveTIRAcetam at standard loading doses.
- Adhere to strict bedrest with head of bed (HOB) flat and neck midline.
- Maintain NPO status.

Initial Management for Confirmed Stroke (1,3,15,17,20,72-97)

Continue with emergency interventions discussed above. Supportive measures for AIS include airway maintenance and breathing, control of fever, monitoring of blood pressure, and normalization of serum glucose levels (Table 3, p. 3).

- Noncontrast Brain CT
- Diffusion-weighted imaging (DWI) sequence (when feasible): (TCH policy DI-405 Safety for Magnetic Resonance Imaging)
  - Contraindications include electrically, magnetically or mechanically activated implants (e.g., cardiac pacemaker or defibrillator; implanted neural stimulator, cochlear implant), insulin pump, metal shrapnel or bullet)
  - Suspected foreign body metal in eyes or other body parts needs plain x-rays or CT imaging for confirmation.
  - Case by case determination for patients with metallic implants (e.g., aneurysm clips, surgical clips, sutures, pins, screws, dental braces), pregnant, unconscious or morbidly ill
  - MRI limited by artifact when metallic dental implants present
- 12 Lead EKG
- For children ≥1 year, begin IV fluids with 0.9% normal saline at 1600 mL/m^2/24 h; avoid overhydration but correct for dehydration; monitor electrolytes

Consults/Referrals

- Neurology
- Consider early Neurosurgical consultation for management of increased intracranial pressure in:
  - Children with depressed/ or deteriorating level of consciousness
  - Other signs of increased intracranial pressure.
- Cardiology
- Physical (PT), Occupation (OT), PM&R, and Speech therapy should be consulted within the first 24-48 h of stroke diagnosis.
- Psychology service
  - Should be consulted within 72 h of stroke diagnosis
  - Neurocognitive evaluation and follow-up after discharge should be coordinated with Psychology service
- Social Work, Child Life and Care Management should be consulted within 72 h of stroke diagnosis

Table 3. Intravenous tissue Plasminogen Activator (IV tPA) Indications and Contraindications[1,3,64,98-106]	
Indications	**Contraindications**
• 2 to 17 years of age • MRI free of hemorrhage & early infarct present w/ evidence of vascular occlusion • pediatric stroke severity score ≥4 and ≤24, • present to the EC within 4.5 h of last seen well and whom IV treatment can be administered within 4.5 hours from known symptom onset • No tPA contraindication	**HISTORY** • 4.5 hrs from last seen well • Patients in whom time of symptom onset is unknown • Stroke, major head trauma or intracranial surgery in the last 3 months • History of prior intracranial hemorrhage, known AVM or aneurysm • Major surgery or parenchymal biopsy within 10 days • GI or GU bleeding within 21 days • Patient with neoplasm/malignancy or within one month of completion of treatment for cancer. • Patients with underlying significant bleeding disorder. Patients with mild platelet dysfunction, mild von Willebrand disease or other mild bleeding disorders are not excluded. • Previously dx d primary angiitis of the central nervous system or secondary arteritis. **PATIENT FACTORS** • Patient who would decline a blood transfusion if indicated. • Clinical presentation c/w acute myocardial infarction or post MI pericarditis that requires evaluation by cardiology before treatment • Arterial puncture at noncompressible site or lumbar puncture w/in last 7 days. Patients who have had cardiac cath via a compressible artery are NOT excluded. **ETIOLOGY** • Stroke due to SBE, sickle cell disease, meningitis, embolism (bone marrow, air or fat), or moyamoya disease. **EXAM** • Persistent systolic blood pressure >15% above the 95th percentile for age while sitting or supine • Mild deficit (PedNIHSS <6) at start of tPA infusion • Severe deficit suggesting very large territory stroke pre-tPA • PedNIHSS >25, regardless of infarct volume seen on neuroimaging **IMAGING** • Symptoms suggestive of SAH even if CT or MRI of head are normal • CT with hypodensity/sulcal effacement >33% of MCA territory or ASPECTS ≤7 • Intracranial cervicocephalic arterial dissection. **LAB DATA** • Glucose <50 mg/dL (2.78 mmol/L) or >400 mg/dL (22 mmol/L) • Bleeding diathesis including Platelets <100,000, PT >15 sec (INR >1.4) or elevated PTT > upper limits of the normal range.

Table 4. First 72 Hours: Management and Interventions for Confirmed Stroke

Initial Management	Interventions
Airway and Breathing [3,4] Children may present with decreased respirations or neuro-muscular airway obstruction. Hypoventilation, with a resulting increase in carbon dioxide, may lead to cerebral vasodilation, elevating intracranial pressure.	-Pulse oximetry and capnography (if intubated) should be monitored. -Patients should receive supplemental oxygen for SpO_2 ≤95 or depressed mental status -Supplemental oxygen does not routinely need to be given to nonhypoxic stroke victims -Intubation may be necessary to restore ventilation and to protect the airway from aspiration; prevent hypo- or hyperventilation
Hyperglycemia [4,78-84] The adult American Heart Association/American Stroke Association guidelines recommend treatment with insulin for patients who have serum glucose concentrations >140 mg/dL.	- For infants <1 year, begin IV fluids with D_5NS at 1600 mL/m^2/24 h; avoid overhydration but correct for dehydration; maintain normoglycemia -For children ≥1 year: -Begin IV fluids with 0.9% normal saline at 1600 mL/m^2/24 h; avoid overhydration but correct for dehydration -Obtain blood glucose check (Accu-Chek®) STAT and every 4 h, notify MD if glucose <80 or >140 mg/dL -glucose <80: correct hypoglycemia and add Dextrose to IV fluids -glucose >140: first make sure no Dextrose is in IV fluids before considering insulin; consider Endocrine consult if needed
Hypertension [3,4,75,85-97] Most consensus guidelines recommend that blood pressure **NOT** be treated acutely in the patient with ischemic stroke unless the hypertension is extreme, or the patient has active ischemic coronary disease, heart failure, aortic dissection, hypertensive encephalopathy, or acute renal failure. Intravenous labetalol is generally the first drug of choice if pharmacologic therapy is necessary in the acute phase and if the patient is not bradycardic or asthmatic, since it allows rapid and safe titration to the goal blood pressure.	-If the Systolic/Diastolic BP is >120% for patient's age (Table 4), first look for underlying cause; if antihypertensives are needed because of high blood pressure values or hypertensive symptoms, use extreme caution when lowering blood pressure with moderate reductions of no more than **10%** of the child's presentation BP; avoid sudden decreases in BP -Administer niCARdipine or labetalol if needed for hypertension or hypertensive symptoms
Hypotension [3,4,75,85-97] Though hypotension is rare (in adults), it is associated with worse neurologic outcomes and corrective measures are important. Potential causes include: sedation, infection, sepsis, dehydration, blood volume depletion, decreased cardiac output secondary to cardiac arrhythmias. Vasopressor agents should be considered when corrective measures are ineffective.	-If the systolic/diastolic BP is <50% for patient's age (Table 5), assess for precipitating causes (e.g., sedation, infection, sepsis, dehydration) -Initiate IV fluids: For children ≥1 year, begin IV fluids with 0.9% normal saline at 1600 mL/m^2/24 h; may titrate upward or bolus fluids as tolerated avoiding overhydration but correcting for dehydration. For infants <1 year, begin IV fluids with D_5NS at 1600 mL/m^2/24 h; avoid overhydration but correct for dehydration; monitor electrolytes and supplement as needed -Correct cardiac arrhythmias if present -Administer appropriate antibiotics if s/sx infection -If clinically indicated for severe or symptomatic hypotension, consider vasopressor agent such as dopamine if hypotension is not corrected by other measures, such as IV fluid boluses and correction of fluid deficits -Avoid sedative agents unless clinically indicated

Table 5. 120th Percentile for Systolic/Diastolic BP by Age Group

Age	1-3y	4-6y	7-9y	10-12y	13-15y	>16y
Girls	135/84	140/95	146/100	154/104	160/108	163/109
Boys	136/82	144/96	148/103	155/106	163/108	170/112

Table 6. 50th Percentile for Systolic/Diastolic BP by Age Group

Age	1-3y	4-6y	7-9y	10-12y	13-15y	>16y
Girls	88/45	93/54	98/58	103/61	109/64	111/66
Boys	88/42	95/53	99/59	104/61	111/63	117/66

Initial Management	Interventions
Seizures [3,136,137] Seizures are common and may cause temporary worsening of ischemic infarcts. Most agree to treat epileptic seizures when there is documented clinical seizure and other causes (e.g., hypoglycemia, hypoxia, hypocalcemia) have been excluded. Prophylactic antiepileptic drugs not recommended.	-In the presence of clinical seizures, administer nonsedating anticonvulsant such as fosphenytoin or leveTIRAcetam at standard loading dose -Obtain fosphenytoin level 2 h after loading dose administered -Continue maintenance of antiepileptic such as fosphenytoin at 3-5 mg PE/kg/DAY q 8 h IV or leveTIRAcetam 10 mg q 12 h IV -In the presence of status epilepticus, refer to Status Epilepticus EB guideline; if not in status, avoid oversedation agents that impair LOC
Fever [72-77] Fever is associated with unfavorable outcomes and may contribute to brain injury following an acute stroke. The source of fever should be investigated and treated. Normothermia should be maintained for at least the first several days after an acute stroke.	-Maintain normothermia -Administer acetaminophen for temperature >100ºF (38.4ºC); consider cooling blanket only if unable to control temperature
Nursing Care [1,72] Nursing care is focused on preventing complications and limiting extent of ischemic brain damage. Care is focused on maintaining body systems by preventing hyperthermia, hypotension/hypertension and hypoglycemia/hyperglycemia using interventions discussed on p. 3. Neuro-checks and vital signs are closely monitored and include sensory-motor function evaluation. Assess for changes in level of consciousness, orientation, language and articulation, response to commands, gazes and visual fields, facial paresis, sensory-motor function loss. Prevent risk for pressure ulcers, impaired venous return, and falls.	-Strict bedrest with HOB flat -Use bed algorithm to determine appropriate bed surface -Use log roll to change positioning and initiate range of motion exercises -Maintain proper support of flaccid extremity with pillow or towel roll -Maintain NPO status until medically stable and swallowing ability has been evaluated -Continue neuro-checks and vital signs and include sensory-motor function in each assessment -Monitor strict intake and output -Monitor glucose -Place antiembolism (compression) stockings or sequential compression devices while on bedrest (>40 kg) -Assess risk for pressure ulcers -Use fall precautions
Physical, Occupational and Speech Therapy/PM&R [1,124-133] Physical (PT), Occupation (OT), PM&R, and Speech Therapy should be consulted within the first 24-48 h of stroke diagnosis. AIS in children often results in cognitive and physical impairments (i.e., hemiplegia, hemiparesis, impaired speech). Interventions used by PT, OT, and speech therapy can improve functional deficits experienced by survivors of childhood stroke.	-Patient NPO until evaluated by OT -Swallowing screen should be performed by OT at bedside once patient is medically stable or cleared by neurologist -Refer to speech therapy if further evaluation (swallow function study) is needed -Other interventions will be individualized depending on patient needs
Anticoagulation/Antiplatelet Therapy [1,6,114-117] Initial therapy is a consideration to limit progression of thrombosis and reduce risk of early recurrent stroke. Adult stroke guidelines recommend against the use of early anticoagulation. Early anticoagulation with heparin or low molecular weight heparins (LMWH) are associated with increased risk of bleeding complications, including an increased risk of symptomatic hemorrhagic transformation of the infarct in adult studies. Early anticoagulation is not associated with lessening the risk of early neurological worsening after adult stroke. Data are insufficient to indicate whether early anticoagulation might have efficacy among some high-risk groups, such as persons with intracardiac or intra-arterial thrombi. The efficacy of urgent anticoagulation is not established for treatment of patients with vertebrobasilar disease or an arterial dissection. The decision to treat must be balanced with estimated benefit against risk of hemorrhage. It is reasonable to use alternative antiplatelet agents other than aspirin in patients suspected of having an influenza or varicella infection.	-Antiplatelet therapy, aspirin can be given as first therapy while stroke etiology is determined if no ICH is present and patient is not already on anticoagulants -Early anticoagulation within the first 48 h carries a potentially increased risk of hemorrhage -If patient already on anticoagulation because of comorbid conditions (e.g., artificial heart valve, ventricular assist device) or if stroke is due to a very high risk lesion (e.g., intracardiac thrombus, catastrophic antiphospholipid syndrome), anticoagulation is recommended -If anticoagulation is necessary during the first 48 h from stroke onset, particularly with large size infarcts, unfractionated heparin (UFH) is recommended -Use of anticoagulation within the first 48 h requires close neurological monitoring must be maintained. Consider obtaining a CT Head and/or MRI at 24-48 h or sooner, especially if the stroke is large territory or signs of neurological worsening -See further discussion of anticoagulation/antiplatelet therapy. See p. 6 of this guideline.

Initial Management	Interventions
Surgical Interventions [1,3,4,5,6,98-123] Procedures/Surgical Intervention 1) Decompressive Surgical intervention • Hemicraniectomy in adults: usually done within the first 48 h (sometimes 72 h) for impending large size, life-threatening stroke. • Risk especially in: large artery occlusions (proximal MCA, ICA), cerebellar infarcts, and early mass effect/midline shift 2) Acute Intra-arterial Intervention for recanalization • Performed in clinically severe adult stroke because of increased morbidity/mortality • Used in adults by neurointerventionalist with: 1) Moderate/Severe strokes (NIHSS scores ≥8 included for device trials) 2) Persistent large vessel occlusions, such as proximal MCA, ICA, vertebral, or basilar thrombus • not definitively been proven in adults to improve patient outcomes • Time for Treatment in eligible adults: typically within 6 hours for all therapies (device trials permitted 8 hours); sometimes extended with life-threatening posterior circulation stroke. • Mechanical thrombectomy: symptomatic ICH in 9.8-11.2%	1) Decompressive Surgical Intervention: • Consider early Neurosurgical consultation for management of increased intracranial pressure in: 1) children with depressed or deteriorating level of consciousness 2) other signs of increased intracranial pressure. 2) Acute Intra-arterial intervention: • There are case reports and small case series of this use in acute stroke in childhood. There are no trials in children. • A physician may consider consultation to the St. Luke's neurointerventionalist, for selected patients based on significant stroke severity or life-threatening stroke, particularly if there is evidence of a persistent large vessel occlusion.
Psychology Service [1,138] Psychology service should be consulted within 72 h of stroke diagnosis. Children with stroke are at risk for developing cognitive difficulties. The developing brain can adapt, within limits, to the effects of the injury associated with AIS. Evaluation of children with stroke provides an opportunity to examine questions concerning cognitive sequelae of early stroke as well as extent and limits of neural plasticity in humans.	-Psychology Service consult -Neurocognitive evaluation and follow-up after discharge should be coordinated with Psychology service
Consultations Numerous other specialties are involved in the care of the child with AIS and should be consulted during the first 72 h.	Social Work Child Life Care Management

Principles of Anticoagulation Therapy are outlined in Table 8 on pp. 7-9 of this guideline and in the DVT guideline with the following considerations for initial anticoagulation management and short-term follow-up:

- Laboratory assessment
- Dosing
- Nursing considerations
- Therapeutic range and monitoring
- Administration
- Additional monitoring
- Bleeding complications/antidote
- Invasive procedures
- Alternate anticoagulant conversion

General Precautions (Clinical indications may outweigh risks)

- Avoid use of aspirin and NSAIDs for pain/fever (exceptions: SLE, APS, and arterial thrombosis patients)
- No rectal temperatures
- Use soft toothbrush or water-irrigating device
- Avoid arterial punctures if possible
- Apply direct pressure to cuts for 10 minutes

Contraindications to Anticoagulation Therapy

In some patients, the need for anticoagulation therapy necessitates treatment despite contraindications. Consultation with a hematologist is recommended. Contraindications for UFH, LMWH and warfarin include known allergy and history of heparin-induced thrombocytopenia. Existence of coagulopathy, thrombocytopenia, recent/active bleeding or invasive procedures within the past 24 hours should be carefully evaluated prior to initiation of treatment with UFH or LMWH. Contraindications to antiplatelet therapy, aspirin, include presence of intracranial hemorrhage. May consider alternate therapies in the presence of suspected influenza and varicella infections. [139,140]

Additional Laboratory Studies: [141,142]

In most cases, additional laboratory studies can be obtained after the diagnosis of AIS is established and the cause of the stroke is being investigated.

Studies to consider based on patient/family history and/or presenting signs/symptoms include:

ESR, CRP, cardiac enzymes & troponin, liver function tests, toxicology screen, blood alcohol level, lumbar puncture, pregnancy test.

Thrombophilia evaluation studies are ordered as a DVT panel. A Hematology consult may be considered for assistance. Specific studies included in the DVT panel are found in Table 7. [143-145] If unable to draw enough blood to perform the entire DVT panel at one time, the evaluation can occur in three steps, allowing for minimal patient blood loss (Table 7).

Table 7. DVT panel

DVT Panel	Antithrombin, Protein C, Protein S, Factor 8, Anticardiolipin IgG & IgM, Lupus anticoagulant, Anti β2-GP1- IgG & IgM, Factor V Leiden, Prothrombin G20210A gene mutation, Lipoprotein (a), Homocysteine
Blood Volume/Tubes Required	1 blue top, 2.7 mL 1 red top, 3 mL 1 purple top, 1 mL These represent the minimum blood requirements for this panel.

Table 8. Three-step DVT panel

DVT Step 1	DVT Step 2	DVT Step 3
Protein C Protein S Antithrombin Factor 8 Lupus anticoagulant	Anticardiolipin antibody Anti-β2-GP1 Lipoprotein (a) Homocysteine	FV Leiden Prothrombin gene mutation
1 blue top, 2.7 mL	1 red top, 3 mL	1 purple top, 1 mL

For a general overview of stroke etiologies, evaluation, and management strategies, refer to Table 9.

Outcome Measures

- Stable blood pressure and glucose during first 72 h after presentation (BP between 50-120%)
- Use of nicardipine, labetalol, or insulin in the first 72 h
- Normothermia maintained during first 72 h
- Time from presentation to Neurology examination
- Time from presentation to Initial Scan (DWI, CT) completion to confirm diagnosis
- Time from "last seen normal" to confirmed stroke
- Stroke protocol followed (i.e. scans ordered, document % of confirmed stroke and non-stroke patients)
- Mortality
- Intracranial hemorrhage
- Recurrent ischemic event within first 72 h

Table 9. Antiplatelet/Anticoagulation Therapy Management [4]			
	Aspirin	**LMWH (Enoxaparin)**	**UFH (Heparin)**
Initial Laboratory Assessment		Initial studies prior to initiation of therapy: ▪ CBC & DIC Panel (includes PT, PTT, thrombin time, fibrinogen, D-dimer, hepzyme PTT as needed, platelet count) [**LMWH or UFH**] ▪ Antithrombin (AT) for use in patients <6 months of age **(LMWH or UFH)** Additional laboratory studies to consider: DVT Panel (may be separated into "Three-step DVT Panel")	
Dosing	▪ 3-5 mg/kg once orally or rectally, enteric coated when possible (round to convenient amount [e.g., ½ of 81 mg tablet]); **MAX:** 325 mg/dose ▪ Do not give within 24 h of alteplase therapy Patients already on aspirin - evaluate dose of aspirin, increase to range of 3-5 mg/kg/DAY if previous dose below this range If previous dose of aspirin is higher than this range and compliance affirmed, consider alternative medications (e.g., clopidogrel, dipiramidole, or anticoagulation).	Correct underlying coagulopathy using FFP or cryoprecipitate as needed, platelets must be corrected to ≥50,000/mm³. ***Initiation of therapy:*** ▪ <2 months of age: 1.7 mg/kg/dose subcutaneous every 12 h ▪ ≥2 months of age: 1 mg/kg/dose subcutaneous every 12 h Obese patients: base dosage on actual body weight Patients with impaired renal function may require modified doses. -Consult H.A.T. team if CrCl <30 mL/minute Obtain Lovenox level 4 h after 2nd dose from initiation of therapy and 4 h after each dosage change.	Correct underlying coagulopathy using FFP or cryoprecipitate as needed, platelets must be corrected to ≥50,000/mm³. Initiation of therapy: (do not bolus) ▪ Continuous infusion: <1 year of age: 28 units/kg/h IV ≥1 year of age: 20 units/kg/h IV **MAX** initial infusion: 1,000 units/h Obtain heparin level 4 h after initiation of infusion and 4 h after each dosage change.
Nursing Considerations	Vaccinate for varicella & administer annual influenza vaccine.	Ideally, Lovenox level should be drawn by venipuncture. If venipuncture is not practical, obtain specimen from a central line. Ensure line is adequately flushed before drawing sample (Nursing Policy LT 416).	Ideally, heparin levels should be drawn by venipuncture. If venipuncture is not practical, heparin level should NOT be drawn from the same line or another line in same limb as therapeutic heparin infusion. Ensure line is adequately flushed before drawing sample (Nursing Policy LT 416).
Therapeutic Range and Monitoring	Reduce dose to 1-3 mg/kg/DAY if gastric distress or prolonged epistaxis. Hold during influenza and varicella infections. Consider holding ASA during febrile illness.	Lovenox level ▪ Treatment*: 0.5-1 units/mL ▪ Prophylaxis**: 0.2-0.4 units/mL *Under certain circumstances, alternate target ranges may be recommended. Lovenox levels may be underestimated in patients with elevated bilirubin or hemolysis. Follow TCH "Dosage Titration/Continuation Table" for therapeutic dose adjustments (see DVT guideline or enoxaparin order set).	Heparin level* ▪ 0.35-0.7 units/mL *Under certain circumstances, alternate target ranges may be recommended. Heparin levels may be underestimated in patients with elevated bilirubin or hemolysis. **Heparin levels are the primary recommended measure of heparinization.** Use of PTT to monitor UFH therapy in infants and children is problematic due to wide interindividual and age-related variation (continued on next page).

<table>
<tr><th></th><th>Aspirin</th><th>LMWH (Enoxaparin)</th><th>UFH (Heparin)</th></tr>
<tr><td>Therapeutic Range and Monitoring (cont.)</td><td></td><td></td><td>PTT may be used as a monitoring strategy in clinical scenarios when the heparin assay is considered unreliable (e.g., elevated bilirubin or increased plasma free hemoglobin) or after it has been corroborated with anti-Xa activity as measured by heparin levels.

Follow TCH “Dosage Titration for IV Infusion” Table for therapeutic dose adjustments and “Heparin Level/PTT Management Algorithm”
(see DVT guideline or heparin order set)</td></tr>
<tr><td>Administration</td><td>Administer daily at consistent time</td><td>Deep subcutaneous injection to anterolateral abdominal wall, upper arm, or thigh

Do NOT administer IM or IV.

Insuflon™ catheters may be used in patients ≥5 kg after therapeutic level achieved.</td><td>Dedicated IV line for heparin infusion

Do not stop or interrupt infusion for other medications.</td></tr>
<tr><td>Additional Monitoring</td><td></td><td>Platelet count every 3 days for 14 days until discharge. Rheumatology service patients may obtain platelet count more frequently.

-If abrupt decrease in platelet count (≥50%), consider Heparin Induced Thrombocytopenia (HIT), and consult H.A.T. team (may not be necessary if patient with SLE or APS and on rheumatology service).</td><td>Platelet count every 3 days for 14 days while on continuous infusion.

-If abrupt decrease in platelet count (≥50%), consider Heparin Induced Thrombocytopenia (HIT), and consult H.A.T. team (may not be necessary if patient with SLE or APS and on rheumatology service).</td></tr>
<tr><td>Bleeding Complications/ Antidote</td><td></td><td>Bleeding: Stop enoxaparin, consider enoxaparin antidote and/or H.A.T. team consult

Protamine sulfate (IV):
Dose based on amount of enoxaparin received
▪ Last enoxaparin injection <8 h:
1 mg per 1 mg enoxaparin
▪ Last enoxaparin injection 8-12 h:
0.5 mg per 1 mg enoxaparin
▪ Last enoxaparin injection >12 h:
Protamine may not be required

Obtain Lovenox level 15 minutes after infusion

If Lovenox level measured 2-4 h after 1st protamine dose is prolonged, administer 2nd dose
▪ 0.5 mg per 1 mg enoxaparin

Note: Anti-Xa activity never completely neutralized, maximum of 60-75%

MAX dose: 50 mg
Administer IV at a concentration of 10 mg/mL; rate not to exceed 5 mg/minute</td><td>Bleeding: Stop heparin infusion, consider heparin antidote and/or H.A.T. team consult

If anticoagulation needs to be discontinued for clinical reasons, termination of infusion usually sufficient.

Protamine sulfate (IV) for immediate effect:
Dose based on amount of heparin received in previous 2 h

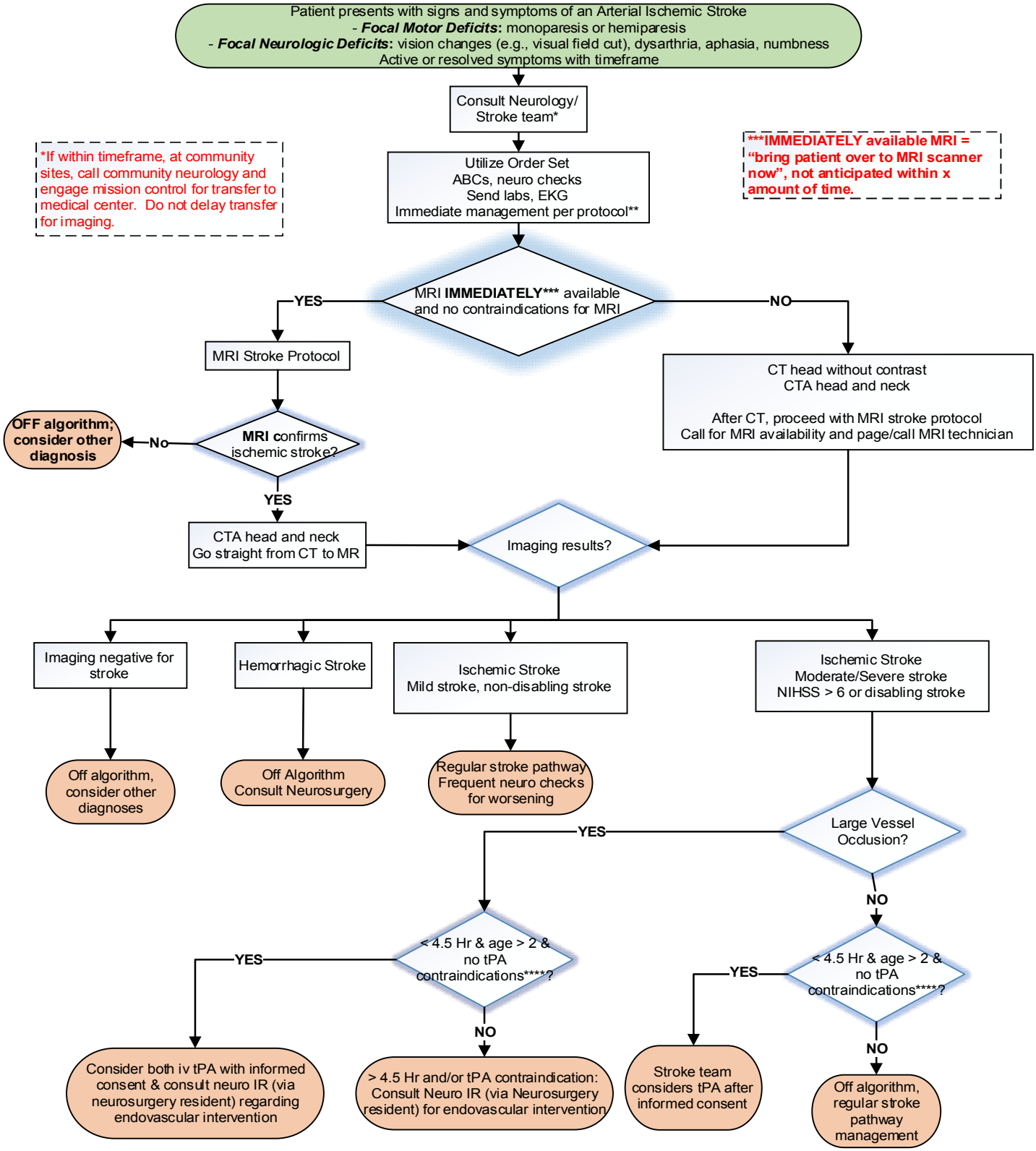
<table><tr><th>Time elapsed</th><th>Protamine (mg) per 100 units heparin received</th></tr><tr><td>Immediate</td><td>1-1.5</td></tr><tr><td>30-60 min</td><td>0.5-0.75</td></tr><tr><td>60-120 min</td><td>0.375-0.5</td></tr><tr><td>> 2 h</td><td>0.25-0.375</td></tr></table>
Obtain PTT 15 minutes after infusion

MAX dose: 50 mg

Administer IV at a concentration of 10 mg/mL; rate not to exceed 5 mg/minute</td></tr>
</table>

	Aspirin	LMWH (Enoxaparin)	UFH (Heparin)
Invasive Procedures		Major surgery: ▪ Hold 2 enoxaparin doses (minimum 24 h between last dose and procedure) -If possible, obtain Lovenox level prior to procedure; level should be < 0.1 units/mL Lumbar puncture: ▪ Hold enoxaparin dose the evening before and morning of procedure. Resume with evening dose (except with bloody taps- wait 24 h).	Invasive procedures: ▪ Hold heparin 2-4 h prior to procedure Obtain PTT prior to procedure to ensure not elevated.
Alternate Anticoagulant Conversion		<u>Enoxaparin to Heparin:</u> ▪ Begin heparin no earlier than 8 h after last enoxaparin dose ▪ If started within 8-12 h, do NOT bolus heparin and start usual maintenance dose ▪ If started after 12 h, consider heparin bolus followed by maintenance dose	<u>Heparin to Enoxaparin:</u> ▪ Administer enoxaparin immediately (within 1 h) after heparin infusion is discontinued

TEXAS CHILDREN'S HOSPITAL
EVIDENCE BASED OUTCOMES CENTER
Clinical Algorithm for Diagnosis & Management of Suspected Acute Arterial Ischemic Stroke
1st 24 hours after Onset Algorithm



Clinical standards are developed for 80% of the patient population with a particular disease. Each practitioner must use his/her clinical judgment in the management of any specific patient

++ Immediate management:

- Assess/maintain A,B,C's; frequent VS & neuro check
- Initial Labs: bedside blood glucose; CBC with platelets, PT/PTT, INR, fibrinogen, Chem 10; type and screen; Hgb profile (if SCD status unkown)
- Treat B/P < 50th % or > 120th % for age or hypertensive symptoms; avoid > 10% reduction in BP
- Obtain15 Lead EKG
- Continuous cardiac monitoring & pulse oximetry
- Maintain oxygen sat ≥ 95%-Place PIV & obtain initial labs, bedside blood glucose
- Keep glucose > 80 & < 140
- Administer IV fluids (e.g., <1y, D_5NS; ≥ 1y, 0.9%NS); consider renal status
- Administer acetaminphen T >100.4°F
- Administer nonsedating anticonvulsant IV if seizure(s) occurred
- NPO, strict bedrest with HOB flat & neck midline
- S/Sx ICP or depressed or deteriorating level of consciousness: consult neurosurgery

+++Initial aspirin therapy:

- Patients not on antiplatelet or anticoagulant should receive aspirin 3 - 5 mg/kg orally or rectally once when stroke confirmed (**MAX**: 325mg/dose)
- Patients already on aspirin, evaluate dose and increase to range of 3-5 mg/kg if previous dose below this range
- If previous dose of aspirin is therapeutic and compliance is confirmed, consider alternative medications (e.g. dipyRIDamole, clopidogrel or anticoagulation)

Anticoagulation therapy:

- Early anticoagulation within first 48 h carries a potentially increased risk of hemorrhage
- If patient already on anticoagulation because of comorbid conditions or if stroke is due to a very high risk lesion (e.g. craniocervical [intracranial or extracranial] arterial dissection, intracardiac thrombus, catastrophic antiphospholipid syndrome), anticoagulation is recommended.
- If anticoagulation is indicated, unfractionated heparin during the first 48 h is recommended
- Use of anticoagulation in first 48 h requires close neurological monitoring. Consider a CT head and/or MRI at 24 -48 h or sooner, especially if the stroke is large territory or there are signs of neurological worsening

******tPA contraindications:**

HISTORY
- > 4.5 hrs from last seen well
- Patients in whom time of symptom onset is unknown
- Stroke, major head trauma or intracranial surgery in the last 3 months
- History of prior intracranial hemorrhage, known AVM or aneurysm
- Major surgery or parenchymal biopsy within 10 days
- GI or GU bleeding within 21 days
- Patient with neoplasm/malignancy or within one month of completion of treatment for cancer.
- Patients with underlying significant bleeding disorder. Patients with mild platelet dysfunction , mild von Willebrand disease or other mild bleeding disorders are not excluded.
- Previously dx d primary angiitis of the central nervous system or secondary arteritis.

PATIENT FACTORS
- Patient who would decline a blood transfusion if indicated.
- Clinical presentation c/w acute myocardial infarction or post MI pericarditis that requires evaluation by cardiology before treatment
- Arterial puncture at noncompressible site or lumbar puncture w/in last 7 days. Patients who have had cardiac cath via a compressible artery are NOT excluded.

ETIOLOGY
- Stroke due to SBE, sickle cell disease, meningitis, embolism (bone marrow, air or fat), or moyamoya disease.

EXAM
- Persistent systolic blood pressure > 15% above the 95th percentile for age while sitting or supine
- Mild deficit (PedNIHSS <6) at start of tPA infusion
- Severe deficit suggesting very large territory stroke pre-tPA
- PedNIHSS >25, regardless of infarct volume seen on neuroimaging

IMAGING
- Symptoms suggestive of SAH even if CT or MRI of head are normal
- CT with hypodensity/sulcal effacement >33% of MCA territory or ASPECTS ≤7
- Intracranial cervicocephalic arterial dissection.

LAB DATA
- Glucose <50 mg/dL (2.78 mmol/L) or >400 mg/dL (22 mmol/L)
- Bleeding diathesis including Platelets <100,000, PT >15 sec (INR >1.4) or elevated PTT > upper limits of the normal range.

Systolic BP should be maintained between 50th %ile for age and 15% above 95th %ile for age
Treat to lower BP if > 15% above 95th %ile for age for more than 1 hr.
OR
If > 20% above 95th %ile for age at any time
SEE CHART BELOW

50th Percentile for Systolic/Diastolic BP by age group

Age	1-3y	4-6y	7-9y	10-12y	13-15y	> 16y
Girls	88/45	93/54	98/58	103/61	109/64	111/66
Boys	88/42	95/53	99/59	104/61	111/63	117/66

120th Percentile for Systolic/Diastolic BP by age group

Age	1-3y	4-6y	7-9y	10-12y	13-15y	> 16y
Girls	135/84	140/95	146/100	154/104	160/108	163/109
Boys	136/82	144/96	148/103	155/106	163/108	170/112

tPA dosing recommendations:
Total dose: 0.9 mg/kg IV
Max dose: 90 mg
Bolus dose: 10% of total dose IV over 5 min
Infusion dose: remaining 90% IV over 1 hour
Nurse/MD double checks dose with pharmacy
SEE CHART BELOW for age-based tPA acceptable BP parameters

Systolic Blood Pressure Parameters - Females

Age	50%	95%	>15% above 98%	>20% above 95%
1-4 years	90	111	128	133
5 years	94	113	130	136
6-10 years	96	121	139	145
11- 18 years	105	131	151	157
>18 years	110	140	161	168

Systolic Blood Pressure Parameters - Males

Age	50%	95%	>15% above 98%	>20% above 95%
1-4 years	90	112	129	134
5 years	95	113	130	136
6-10 years	96	121	139	145
11- 18 years	105	140	161	168
>18 years	110	140	161	168

Appendix 1. Risk Categories and Associated Conditions for Childhood Acute Ischemic Stroke

Congenital heart disease
- Aortic stenosis
- Atrial septal defect
- Cardiac rhabdomyoma
- Coarctation of aorta
- Complex congenital heart defects
- Mitral stenosis
- Mitral valve prolapse
- Ventricular septal defect

Acquired heart disease
- Arrhythmia
- Atrial myxoma
- Bacterial endocarditis
- Cardiomyopathy
- Libman-Sachs endocarditis
- Myocardial infarction
- Myocarditis
- Prosthetic heart valve
- Rheumatic heart disease

Systemic vascular disease
- Atherosclerosis
- Diabetes
- Familial hypercholesterolemia
- Hypernatremia
- Progeria
- Superior vena cava syndrome
- Systemic hypertension
- Volume depletion or systemic hypotension

Vasculitis
- Acquired immunodeficiency syndrome
- Behcet's syndrome
- Dermatomyositis
- Drug abuse (cocaine, amphetamines)
- Inflammatory bowel disease
- Kawasaki syndrome
- Meningitis
- Mixed connective tissue disease
- Mucor mycosis
- Polyarteritis nodosa
- CNS Vasculitis
- Rheumatoid arthritis
- Sarcoidosis
- Sneddon's syndrome
- Systemic lupus erythematosus
- Takayasu's arteritis
- Varicella

Vasculopathies
- Down's syndrome
- Ehlers-Danlos type IV
- Fabry's disease
- Lupus Erythematosis
- Malignant atrophic papulosis
- Moyamoya syndrome
- Neurofibromatosis
- Pseudoxanthoma elasticum
- Spontaneous arterial dissection
- Williams syndrome

Metabolic disorders
- Homocystinuria
- Isovaleric acidemia
- MELAS
- Methylmalonic and propionic academia
- NADH-CoQ reductase deficiency
- Ornithine transcarbamylase deficiency

Vasospastic disorders
- Alternating hemiplegia
- Primary cerebral/retinal vasospasm
- Vasospasm due to subarachnoid hemorrhage

Hematologic disorders and coagulopathies
- Antithrombin III deficiency
- Antiphospholipid Antibody Syndrome
- Disseminated intravascular coagulation (DIC)
- Fanconi anemia
- Hemoglobinopathies (sickle cell anemia, hemoglobin SC disease)
- Hemolytic-uremic syndrome
- Leukemia or other neoplasm
- Liver dysfunction with coagulation defect
- Nephrotic syndrome
- Oral contraceptives
- Paroxysmal nocturnal hemoglobinuria
- Polycythemia
- Protein C deficiency
- Protein S deficiency
- Systemic infection
- Thrombocytosis
- Thrombotic thrombocytopenic purpura

Congenital cerebrovascular anomalies
- Arterial fibromuscular dysplasia
- Agenesis/hypoplasia of vascular channels
- Sturge-Weber syndrome

Trauma
- Blunt cervical arterial trauma
- Child abuse
- Coagulation defect with minor trauma
- Dissection with minor trauma
- Fat or air embolism
- Fibrocartilaginous embolism
- Foreign body embolism
- Intraoral trauma
- Penetrating intracranial trauma
- Post-traumatic arterial dissection
- Post-traumatic carotid cavernous fistula

Iatrogenic
- Arteriography
- Balloon angioplasty
- Bone marrow transplant
- Cardiac surgery
- Carotid ligation (eg, ECMO)
- Chemotherapy
- Chiropractic manipulation
- L-asparaginase therapy
- Post-irradiation
- Temporal artery catheterization

Table 9. General Overview of Stroke Etiologies, Evaluation and Management Strategies [1,3,6,146-147]		
Etiology	**Evaluation/Studies**	**Management Discussion**
Cardioembolic **Congenital** **Acquired** • Recent cardiac surgery or invasive cardiac procedure (e.g., cardiac catheterization or electrophysiology study) • Congenital heart disease, especially with intracardiac shunting • Mechanical circulatory support (ECMO, or ventricular assist device) • Cardiomyopathy, especially in the setting of depressed ventricular function and/or arrhythmias • Chronic arrhythmias (e.g., atrial fibrillation) • Valvular heart disease, especially with prosthetic valves • Endocarditis • Cardiac tumors • Suspect especially with wedge infarct or large artery occlusion/ thrombus	**Basic stroke evaluation includes:** - Transthoracic echogradiogram with bubble contrast • Evaluates left atrial & ventricular size & function Guide to morphology & function of mitral & aortic valve - Continuous cardiac monitoring • Assess for atrial or ventricular arrhythmia **Further studies to consider:** Transesophageal echocardiogram with Cardiology consultation • Modality of choice for aortic root, atria, & interatrial septum • Atrial septal aneurysms, patent foramen ovale, left atrial appendage thrombi, & valvular vegetations more clearly visualized • Beneficial in patients with large body habitus, or patients which are not able to have adequate visualization of chambers, valves, & wall function Consider TEE if the basic cardiac workup is normal, but a high suspicion remains of a cardioembolic source based on history, infarct appearance, or otherwise negative vascular imaging.	• Cardiac embolism (unrelated to a PFO) with a high risk of recurrent embolism ○ UFH while warfarin therapy is initiated & adjusted. LMWH may be used instead of warfarin ○ Continue either LMWH or warfarin for at least 1 year ○ If the risk of recurrent embolism is high, continue anticoagulation indefinitely as long as it is well tolerated • Suspected cardiac embolism (unrelated to a PFO) with a lower or unknown risk of stroke ○ Begin/Continue aspirin for at least 1 year • PFO, in the setting of no other cardiac source: aspirin • Surgical repair/Transcatheter closure ○ Can be used with ASD to reduce stroke risk and prevent long-term cardiac complications ○ Recommendation does not apply to PFO • Prosthetic valve endocarditis: little data available, consider continuing maintenance anticoagulation in those already taking it • Native valve endocarditis: anticoagulation not recommended
Vasculopathy **Acquired** **Traumatic** **Structural** **Dissection** - **Traumatic:** "major" (ex. MVA, direct head injury) & "minor" (minor whiplash injuries, cervical manipulation, trampoline use, activities inducing hyperextension of the neck) trauma - **Spontaneous:** recurrence rate of cervical carotid dissection ~1% per year - **Increased risk of dissections with:** • Trauma • Family history of arterial dissections • Fibromuscular dysplasia • Ehlers-Danlos Syndrome type IV • Marfan Syndrome • Coarctation of the aorta	**Basic Stroke Imaging Evaluation includes:** • Imaging of cerebral vasculature from the heart to the brain • MRI brain with contrast, MRA head without contrast, MRA neck with contrast, with T1 and T2 fat suppression: fat suppression aids in visualization of dissection. • Alternative: CT Angiogram Head & Neck: Useful for patients that are unable to obtain MRI due to contraindication or medical instability **Further Studies to consider:** Conventional Angiogram, 4 vessel Useful if non-invasive imaging yields unclear or negative findings, to better evaluate the vasculature. Consider consultation with neuroradiology. Must consider use of iodine contrast & invasiveness (~1% risk of complications: stroke, hemorrhage, thrombosis). Some conditions, including extracranial arterial dissections, particularly	• Extracranial cervicocephalic arterial dissection (CCAD): ○ Either UFH or LMWH as a bridge to oral anticoagulation Subcutaneous LMWH or warfarin for 3 to 6 months ○ Antiplatelet agent may be substituted for LMWH or warfarin ○ Extending anticoagulant therapy beyond 6 months is an option with recurrent symptoms ○ Antiplatelet agents can be given beyond 6 months, especially with radiographic evidence of residual abnormality of dissected artery ○ With recurrent symptoms from a CCAD despite medical therapy, surgical procedures may be considered • Intracranial dissection or those with SAH resulting from CCAD: ○ Anticoagulation is not routinely recommended because of the potential increased risk of SAH • Spontaneous dissection/Dissection with only minor trauma: ○ Assess for connective tissue diseases if clinically indicated ○ Assess aortic root size on TTE at initial evaluation, after 1-2 years of follow-up, and as indicated. ○ Consider follow-up imaging of vessels in 1-2 years and as indicated because of recurrence risk.

• Cystic medial necrosis • Autosomal-dominant polycystic kidney disease • Osteogenesis imperfecta • Atherosclerosis • Extreme arterial tortuosity • Moyamoya syndrome • Pharyngeal infections • Alpha-1 antitrypsin deficiency **Moyamoya Vasculopathy** **Fibromuscular Dysplasia**	involving the posterior circulation, and small-vessel vasculitis, are difficult to exclude on MRA. Moyamoya: Needs 6 vessel angiographic study to assess the external carotid circulation	○ Consider genetic/metabolic testing of conditions that predispose to spontaneous dissections • Indirect revascularization techniques are preferable and should be used in younger children whose small-caliber vessels make direct anastomosis difficult, whereas direct bypass techniques are preferable in older individuals • Revascularization surgery is useful for moyamoya. Indications include progressive ischemic symptoms or evidence of inadequate blood flow or cerebral perfusion reserve, without a contraindication to surgery • Management of hypotension, hypovolemia, hyperthermia, & hypercarbia during the intra-/perioperative periods may reduce the risk of perioperative stroke • Aspirin is considered in individuals with moyamoya after revascularization surgery or in asymptomatic individuals for whom surgery is not anticipated • Except in selected individuals with frequent TIAs or multiple infarctions despite antiplatelet therapy and surgery, anticoagulants are not recommended
Hemoglobinopathy • Sickle Cell Disease (Hb SS, S beta thalassemia; some increased risk in other subtypes as well, such as HbSC)	○ MRI brain without contrast, MRA head without contrast ○ Consider MRA neck ○ Diagnostic angiography for suspicion of moyamoya syndrome • Cardiac evaluation continues to be important, as SCD can lead to cardiomyopathy and pulmonary hypertension.	• IV hydration and exchange transfusion to reduce sickle Hb to ≤30% total Hb, consult renal service for exchange transfusion • After exchange transfusion, recommend long-term transfusion program • Hydroxyurea may be used in children & young adults with SCD and stroke who cannot continue on long-term transfusion • Bone marrow transplantation is an option for children with SCD and stroke • Surgical revascularization procedures are a last resort in children with SCD who continue to have cerebrovascular dysfunction despite medical management
Prothrombotic Conditions • Primary (hereditary) hypercoagulable states • Systemic inflammatory conditions (SLE, Crohn's disease, Behçet's) • Antithrombin deficiency • Activated protein C resistance with or without factor V Leiden mutation • Prothrombin gene mutation G20210A • Thermolabile variant of MTHFR • Disorders of fibrinogen • Disorders of plasminogen activator inhibitor • Antiphospholipid antibody syndrome, APS (positive aPL antibodies or lupus anticoagulant) • Elevation in Factors VII or VIII • Deficiencies in: Factor XII, Protein C, Antithrombin, or Protein S • Lipoprotein a	See DVT guideline for work-up	• It is reasonable to : ○ Discontinue oral contraceptives in adolescents with AIS or CVST ○ Measure the serum homocysteine level of children with CVST or AIS and institute measures to lower the homocysteine level when it is higher than normal • Measures to lower the homocysteine level might include diet or supplementation of folate, vitamin B6, or vitamin B12 • Anticoagulation regimen to be dictated by consultant services, in case of hypercoagulable state or APS. • Consider using agents to lower lipoprotein a, including aspirin and niacin

Vasculitis • **Infectious** • **Multisystem noninfectious inflammatory vasculitis** • **Primary CNS vasculitis** Consider vasculitis in recurrent stroke, with ischemic or hemorrhagic stroke associated with encephalopathic changes, & stroke accompanied by fever, multifocal neurological events, unexplained skin lesions (petechiae, purpura or ulcers), renal dysfunction, arthritis, respiratory involvement or lab anomalies suggestive of inflammation (elevated ESR & CRP, elevated WBC or platelets, anemia) **Infectious:** reported etiologies include tuberculosis, varicella, aspergillosis, Mycoplasma pneumoniae, Coxsackie-9 virus, California encephalitis virus, mumps, paramyxovirus, Borrelia burgdorferi, cat-scratch disease, brucellosis, & neurocystercercosis. Lyme neuroborreliosis, HIV, syphilis, multiple forms of bacterial meningitis **Systemic Inflammatory:** Among those with increased risk of CNS involvement include: • Systemic lupus erythematosus (SLE) • Sjogren's syndrome • Behcet's disease • Polyarteritis nodosa • Wegener's granulomatosus	**Evaluation of CNS or systemic inflammation may include:** ESR, CRP & CBC (ESR & CRP are nonspecific markers of inflammation & may be normal in children with isolated CNS vasculitis) Consultation with the rheumatology service should be considered in a timely fashion. LP with opening pressure and studies specific to the suspected or known disease. If suspicion of infection, obtain bacterial/fungal/viral studies including VZV PCR, EBV PCR, and mycoplasma PCR on the CSF as well as serum. Primary/secondary vasculitic disorders may involve large, medium-sized, or small arteries. Classic angiographic findings of arteritis are nonspecific and may not be visualized in cases of small vessel arterial disease. Consider tissue histopathology via brain biopsy when isolated CNS vasculitis is suspected.	• Treatment of underlying infectious or inflammatory process dictated by primary service or consultant • Treatment of underlying systemic inflammatory condition may include corticosteroids and other immunosuppressive regimens once infectious etiology has been ruled out) • Anticoagulation regimen to be dictated by rheumatology service in cases of children with systemic inflammatory disorders. Regimens may include UFH, LMWH or Coumadin
Metabolic Consider metabolic causes of stroke with: • Dysmorphic features • Multisystem disease (renal/cardiology) • Ophthalmologic disease (cataracts, lens dislocations) • Other premorbid or comorbid neurological diseases/findings such as seizures, microcephaly, global developmental delay or mental retardation, myopathy, ptosis and ophthalmoplegia Increased risk of stroke with: [146] • Sphingolipidoses: Fabry Disease • Mitochondrial Disease: MELAS • Hereditary connective tissue disorders: Homocystinuria • Organic acidurias: branched-chain organic acidurias (isovaleric aciduria, methylmalonic aciduria, proprionic aciduria); Glutaric aciduria (type 1 & 2) Urea cycle disorders: carbomoyl phosphate synthetase 1 deficiency, ornithine transcarbamylase deficiency, citrullinemia	• Recommend basic cardiac evaluation. • Recommend basic imaging evaluation as some metabolic diseases are associated with vessel abnormalities. • Recommend serum, urine, or CSF investigations aimed at the suspected disorder, with may include analysis of serum amino acids, urine organic acids, acylcarnitine profile analysis, measurement of lactate, measurement of ammonia, assessment of liver function, serum homocysteine, and urine homocysteine. • Recommend ophthalmologic assessment as indicated in suspected disorder. Recommend specific genetic screening as indicated in the suspected disorder.	• Individuals with Fabry disease should receive alpha-galactosidase replacement therapy • Specific testing as indicated for the suspected disorder Formal consultation with the genetics/metabolic division in cases with clinical suspicion of stroke related to metabolic disease.

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Clinical Standards Preparation

This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children's Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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No relevant financial or intellectual conflicts to report.

Development Process

This guideline was developed using the process outlined in the EBOC Manual. The review summary documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts
2. Review of Existing External Guidelines
   - TCH Guideline for Childhood Cerebral Arterial Ischemic Stroke (AIS) and Thrombosis, Stroke in Childhood: Clinical guidelines for diagnosis, management and rehabilitation, Antithrombotic Therapy in Neonates and Children: American College of Chest Physicians Evidence-Based Clinical Practice Guideline (8th Edition), Management of Stroke in Infants and Children: A Scientific Statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young, Antithrombotic and Thrombolytic Therapy for Ischemic Stroke, Guidelines for the Early Management of Adults with Ischemic Stroke: A Guideline from the American Heart Association/American Stroke Association Stroke Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups, Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest physicians evidence-based clinical practice guidelines (8th Edition). Expansion of the Time Window for Treatment of Acute Ischemic Stroke with Intravenous Tissue Plasminogen Activator: A Science Advisory from the American Heart Association/American Stroke Association
3. Literature Review of Relevant Evidence
   - Searched: PubMed, Cochrane Database
4. Critically Analyze the Evidence
   - 5 Meta-analyses/Systematic reviews, 5 randomized controlled trials, and 61 non-randomized studies
5. Summarize the Evidence
   - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in an Acute Ischemic Stroke in Children evidence-based review manual within EBOC.

Evaluating the Quality of the Evidence

Published clinical guidelines were evaluated for this review using the **AGREE II** criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.
This clinical standard specifically summarizes the evidence *in support of* or *against* specific interventions and identifies where evidence is *lacking/inconclusive*. The following categories describe how research findings provide support for treatment interventions.
"Evidence Supports" provides evidence to support an intervention
"Evidence Against" provides evidence against an intervention.
"Evidence Lacking/Inconclusive" indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn *from the evidence*.
The **GRADE** criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	**Type of Evidence**
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
Low	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

Recommendations

Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the diagnosis/management of acute arterial ischemic stroke in children.

When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process

Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children's Hospital. Content Expert Teams are involved with every review and update.

Disclaimer

Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient's family, to make the ultimate judgment regarding care.

Version History

Date	Comments
Jan 2019	Updated