SUSPECTED ACUTE STROKE PATHWAY

EXECUTIVE SUMMARY

Physician Owner(s): Dr. Geetanjali Rathore

Primary Objective

Early identification of acute focal neurological deficits and/or altered mental status followed by immediate rapid MRI brain imaging and radiologist interpretation for timely intervention in confirmed stroke cases.

Recommendations

Stroke versus Transient Ischemic Attack (TIA)

- Children who present with focal neuroglial deficits and/or a sudden unexplained change in mental status who were last seen normal < 24 hours ago AND whose symptoms have not completely resolved should be started on the suspected acute stroke pathway.
- Children with focal neurological deficits and/or a sudden unexplained change in mental status who were last seen normal > 24 hours ago should be managed off pathway as having subacute stroke.
- Additionally, children with focal neurological deficits and/or a sudden unexplained change in mental status who were last seen normal < 24 hours ago, but whose symptoms have completely resolved should be managed off pathway as having a transient ischemic attack (TIA).
- Risk factors for pediatric stroke include:
  - Sickle cell disease
  - Congenital or acquired heart disease
  - Head and neck infections
  - Systemic conditions, such as inflammatory bowel disease and autoimmune disorders
  - Head trauma

Tissue Plasminogen Activator (tPA)

- Alteplase (tissue plasminogen activator or tPA) acts by binding to fibrin in a thrombus where it converts plasminogen that has been trapped within that thrombus to plasmin, ultimately resulting in the initiation of local fibrinolysis. [1]
- Published literature describing the appropriate dosage of tPA in pediatric for acute ischemic stroke is limited. Due to the paucity of evidence, current practice is to follow adult dosing guidelines for treatment. Therapy should be initiated as soon as possible following onset of symptoms, ideally within 3-4.5 hours.[7]
  - Recommended total dose: 0.9mg/kg (90mg maximum total dose) divided as follows
    - 0.09mg/kg given as a bolus over 1 minute, followed by
    - 0.81mg/kg as a continuous infusion over 60 minutes. [1]
- Unintended bleeding episodes are the largest risk associated with use of tPA, particularly related to arterial or venous puncture sites (may be fatal). Intracranial hemorrhage in the hours and days following administration are greater than 10%. Hypersensitivity reactions have been reported, including anaphylaxis. [1]
- Contraindications to therapy are mainly based on risk factors for further bleeding, including recent surgeries, recent GI bleeds, a history of a prior intracranial hemorrhage, or an arterial puncture at a non-compressible site or lumbar puncture within the previous week, or hematologic lab abnormalities such as low platelets or elevate PT or INR. Glucose should fall between 100 and 400, and patients should remain normotensive.

Other exclusion criteria fall elsewhere in this pathway and should be assessed upon ordering and prior to administration.[7]

Labs Recommended labs obtained:

- CBC, Chem 14, PT, PTT, INR, ESR, CRP

- Glucose:
  - 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 as well. Ferriero, 2019. Grelli et al performed the only study examining the influence of hyperglycemia on outcomes in childhood stroke. In this retrospective multivariate analysis of 98 children with stroke examining the association among hypertension, hypotension, hyperglycemia, fever, and Pediatric Stroke Outcome Measure, hyperglycemia was independently associated with adverse outcome. Hyperglycemia was also relatively common (18%), and hypoglycemia was rare (3%).
  - The timing and goals of treatment of hyperglycemia are poorly understood, however evidence shows better outcomes when glucose <140 is maintained. For stroke patients, glucose should be maintained >80 and <140.
- Hgb, PT, PTT, INR, Platelets:
  - Populations with known increased risk for stroke include children with congenital cardiac disease, bleeding disorders, hemoglobinopathies (i.e. HbSS, Sickle Cell Disease), as well as genetic and acquired thrombophilias.
  - Obtaining the above labs will help guide treatment for patients at higher risk of pediatric stroke
  - If a bleeding disorder is known, rapid correction should be instituted.
- Serum pregnancy test
  - For post-menarchal females, a serum pregnancy test should be obtained. There is limited data on the use of tPA in pregnant women as pregnancy is a relative contra-indication to the use of tPA and pregnant women were excluded from the tPA trials on patients with acute ischemic stroke. There is concern for increased bleeding/hemorrhage, particularly uterine, in pregnant women who receive tPA for acute ischemic stroke; however, current expert consensus is that benefits of treatment for a moderate to severe stroke outweigh the risks of tPA. Furthermore, a pregnant patient deemed candidate for thrombectomy would also need additional protections taken in the fluoroscopy suite while undergoing thrombectomy.[13] A positive pregnancy test (urine or serum) is not a contraindication in a patient with a moderate to severe stroke, so could consider treatment prior to result if it would result in a delay in care.[16]

Imaging

- In general, head CT does not require patient sedation, but the sensitivity of this method to detect arterial ischemic stroke (AIS) is low, especially early.[9] A study from a large tertiary children's medical center in Australia found that ischemic stroke was not visualized on head CT in 62 of 74 (84%) of children with this condition; all of these children had their stroke confirmed by MRI of the brain.[19]

- Children's Hospital and Medical Center's "Stroke Protocol" Brain MRI (MR Stroke Brain WO + MRA Head WO) was developed in accordance with commonly reported protocols for stroke.[14, 15, 18] No IV is needed for this MRI.
- Children with implants require full implant safety review PRIOR TO ENTERING THE MRI ENVIRONMENT, *without exception*.
    - Children with a cardiac pacemaker will need special evaluation and monitoring if the pacer is MR compatible. This requires coordination with EP cardiology service and required personnel may or may not be available in a rapid timeline.
    - Some devices like vagal nerve stimulators cannot have a DWI sequence and are limited to their own unique protocol, which may affect specificity of results.
- The "Stroke Protocol" exam utilizes fast MRI techniques to produce a focused, expedient MRI exam with high specificity for infarct. This exam is preferred first line imaging for acute pediatric stroke evaluation unless the patient has a contraindication to MRI or cannot obtain MRI in less than 60 minutes from time of stroke activation.
        - The sequences acquired during the "Stroke Protocol" include:
            - Axial DWI - for seeing infarct
            - Axial SWI - for hemorrhage (or calcification)
            - Axial T2, Axial FLAIR: evaluate parenchymal signal, ventricles
            - Sagittal T1 Single Shot: evaluate midline structures, T1 hyperintense material
            - Noncontrast MRA Circle of Willis: evaluate arteries
    - Additional imaging of the brain and/or vascular anatomy (e.g. neck MRA, contrast-enhanced angiographic studies) may at times be necessary [3] and should be considered by clinicians (or interpreting radiologist) on a case-by-case basis based on findings on stroke protocol MRI and feasibility.
    - Metallic implants including some dental devices or braces can produce artifacts that impact image quality or exam interpretation. Other studies (such as CTA head or neck) could be suggested pending radiology physician review.
    - For cooperative patients, the stroke protocol brain MRI will take approximately 10 minutes of scan time (not counting transfer time or repeat imaging for motion) and is performed *without sedation*.
    - Children with a pacemaker or other devices like a vagal nerve stimulator should consider non-contrast head CT first to exclude hemorrhage and avoid delays to treatment. The required pre-MRI implant evaluation process often takes longer than 60 minutes to complete.

Supportive Care

- Head of bed flat to improve perfusion in case of occlusive vessel.
    - Acute ischemic stroke is caused by a critical reduction in blood flow to the brain. Cerebral blood flow (CBF) is almost totally arrested in the core region of the insult, which leads to neuronal death within minutes. The tissue surrounding the core is severely hypoperfused and functionally impaired but still viable. This zone, called the penumbra, is at high risk of infarction. It permits cell survival for a certain period of time; however, it is extremely vulnerable to CBF fluctuations. The simple process of positioning an acute stroke patient lying flat or head down allows gravitational

force to enhance blood flow in the collateral and leptomeningeal circulation, hence reducing the risk for extension of the ischemic zone. [2]

- Keep blood pressure within normal limits for age and avoid low blood pressure to avoid hypoperfusion
    - An acute hypertensive response can also be observed in patients with an acute ischemic stroke. It is usually self-limiting, and the BP spontaneously falls over the week after the onset of stroke. However, since the acute hypertensive response to stroke is known to be an independent predictor of poor outcome, it is necessary to maintain optimal BP during the acute stroke period. Many previous trials. A higher BP may be beneficial for the penumbra, which is viable but under-perfused, by increasing collateral flow. Lowering BP may potentially increase the risk of infarction growth. On the other hand, a higher BP may increase the risk of hemorrhagic transformation and cerebral edema. Maintaining normal BP is an important factor improving cerebral blood flow in the penumbra by improving collateral circulation.[10]
- Vital signs and neuro check every 15 minutes to detect early change in clinical status which could detect worsening or extension of stroke or hemorrhagic conversion **(citation)**
    - Compared with less frequent/intermittent monitoring, continuous monitoring significantly reduces disability due to neurological complications, length of stay, need for institutionalization and mortality. [5]
- Normal saline (DO NOT give dextrose) if considering fluids
    - The American Stroke Association Guideline states that “Hypovolemia should be corrected with intravenous normal saline” in acute stroke patients. The European Stroke Organization guideline recommends normal saline (0.9%) for fluid replacement during the first 24 h after stroke. These recommendations are based on studies demonstrating that higher serum osmolarity in acute ischemic stroke patients is associated with poor outcome A common cause of in-hospital death from acute ischemic stroke is brain edema and elevated intracranial pressure. Administration of a hypo-osmolar fluid such as 5% dextrose or half normal saline carries a theoretical risk of increasing the severity of cerebral edema. The proposed mechanism is by creating an osmotic gradient that would shift free water across the blood-brain barrier to balance out the hypo-osmolar effects of these solutions in the plasma.[20]

Pediatric National Institutes of Health Stroke Scale

- Pediatric NIH Stroke Scale (NIHSS)
- The Pediatric NIH Stroke Scale (PedsNIHSS) is a scoring tool developed by both adult and pediatric stroke experts where the NIH Stroke Scale was adapted for age-specific variations in a neurologic assessment allowing for a stroke assessment in a child as young as 2 years old. The PedsNIHSS has been validated as a reliable method to assess stroke risk when performed by skilled child neurologists[8] and retrospectively from medical records[4] ; having good inter-rater reliability in both instances. Furthermore, stroke recognition tools have been shown to improve diagnostic accuracy in prehospital and in ED settings, thus allowing for faster diagnosis and ultimately treatment. Given the importance of stroke recognition tools and the good interrater reliability of the PedsNIHSS, it has become the standard evaluation tool of acute stroke in children. [12]

High Risk Patients

- Cardiac Disease:
  - The 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.
- Cerebral sinovenous thrombosis (CVST):
  - Children with confirmed CSVT warrant a thorough evaluation for risk factors, as well as acquired and genetic thrombophilia.
  - Modifiable risk factors, including fever, infection, anemia, and dehydration, should be treated.
  - It is reasonable to consider complete blood counts, iron studies, and testing for blood, urine, respiratory, stool, and CSF pathogens as clinically indicated.
  - Up to 60% of children with CSVT have abnormalities detected on thrombophilia testing compared with 15% to 25% of adults.
  - Deficiencies of protein C, protein S, and antithrombin III are associated with increased risk of venous thrombosis. Mutations in the FVL and prothrombin 20210A genes, as well as elevated blood levels of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibody), homocysteine, and lipoprotein(a), also appear to be associated with increased risk for CSVT. Ferriero, 2019
- Hemorrhagic Stroke
  - Acute hemorrhagic stroke management includes airway and cardiovascular management, seizure control (when present), raising the head of the bed to 30° (to reduce swelling), isotonic fluids, normoglycemia, and normothermia.
- Sickle Cell Disease
  - To avoid undertreatment of stroke in this high-risk population presenting with focal neurological deficits, prompt intervention with simple blood transfusion therapy within several hours of presentation is recommended
  - This increases oxygen delivery if the hemoglobin is <10 g/dL. In general, the simple transfusion should be provided as soon as possible after focal neurological deficits and even before the MRI. With simple blood transfusion therapy, the hemoglobin should not be increased to >11 g/dL as the target.
  - If the baseline hemoglobin is >10 g/dL, (more likely with hemoglobin SCD), an initial exchange blood transfusion should be performed to decrease the hemoglobin level to <10 g/dL.
  - Regardless of the type of SCD, after a simple transfusion has been given within a 6-hour window of presentation, an exchange transfusion is recommended to lower the hemoglobin S level to approximately 15% and to increase the hemoglobin to around 10 g/dL.
  - No absolute threshold is established for when an exchange transfusion should not be completed after an acute focal neurological deficit (stroke or TIA).

Rationale

Safety: Better access to MRI and faster brain imaging sequences will decrease the need for head imaging with CT, which will decrease patient's lifetime exposure to radiation.

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EXECUTIVE SUMMARY

Physician Owner(s): Dr. Geetanjali Rathore

Quality: Shall be improved by decreasing the amount of time between acute stroke recognition and intervention.
Cost: Early identification of acute stroke will decrease both the short and long term costs associated with caring for these patients.
Delivery: Shall be improved by giving suspected stroke cases prioritization over non-acute conditions.
Engagement: Is created and supported by the involvement of a multidisciplinary team in the development and maintenance of the pathway.
Patient/Family Satisfaction: Early identification will lead to early intervention. Early intervention will decrease the impairments of patients with stroke which will improve both patient and family satisfaction.

Metrics

1. Maintain utilization of Suspected ACUTE stroke pathway order set and/or Stroke panel at 80% by May 2024. (Process Metric)
2. Increase documentation of NIH Stroke Scale by 40% by May 2024. (Process Metric)
3. Maintain time from TPA order placement to TPA administration ≤ 60 minutes by May 2024. (Outcome Metric)
4. Maintain time from stroke alert being called to time of imaging ≤ 60 minutes by May 2024. (Outcome Metric)
5. Monitor Length of stay in the ED. (Balancing Metric)

Team Members

- Champion: Geetanjali Rathore, MD
- Team Members:
    - Bridget Norton, MD, MBA (Pediatric Intensive Care; Director of Clinical Effectiveness)
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    - Rob Chaplin, MD (Pediatric Intensive Care)
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    - Krisi Kult, MSN, RN, CPEN, CPN (Emergency Medicine)
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    - Abby Vipond, MSN, APRN, FNP-C (Clinical Effectiveness Project Manager)
    - Taelyr Weekly, PhD, MPH, BSN, RN (Clinical Effectiveness Project Manager)

Evidence

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Appendix A:

Tissue Plasminogen Activator (tPA) Contraindications: [17]

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 arteriovenous malformation (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 diagnosed primary angiitis of the central nervous system or secondary arteritis.

Patient Factors

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

Etiology

- Stroke due to subacute bacterial endocarditis (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 subarachnoid hemorrhage even if CT or MRI of head are normal
- CT with hypodensity/sulcal effacement > 33% of middle cerebral artery (MCA) territory or Alberta Stroke Program Early CT Scoring (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.

Appendix B

Blood Pressure Normal Limits for Age Parameters:
Notify provider for blood pressure outside of normal range

Age	Blood Pressure (mm Hg)
0-3 mo	65-85/45-55
3-6 mo	70-90/50-65
6-12 mo	80-100/55-65
1-3 yr	90-105/55-70
3-6 yr	95-110/60-75
6-12 yr	100-120/60-75
12+ yr	110-135/65-85