Protocol for IV rtPA Treatment of Acute Ischemic Stroke

Acute stroke management is progressing very rapidly. Our team offers several options for acute stroke therapy, including endovascular therapy and clinical trials, and is available for immediate consultation 24 hours per day and 7 days per week.

1. When should the stroke team be called?

- Contact the Stroke Team at **(513) 844-7686** as soon a **potential** candidate for treatment is identified (preferably **before** the CT scan is completed).
- Potential treatment candidates are:
  - Patients of any age with a suspected ischemic stroke or TIA who were "Last Seen Normal" **within 12 hours** of symptom onset

2. Sequence of events by ED (FASTER TREATMENT = BETTER CLINICAL OUTCOMES)

- Determine "Last Seen Normal" time. **WITHIN 5 MINUTES OF ED ARRIVAL**
  - Patients are eligible for IV rtPA ***up to 4.5 hours*** from onset.
  - Select stroke patients are eligible for intra-arterial therapies ***up to 6 hours*** from onset.
  - TIA/minor stroke patients may be eligible for trials ***up to 12 hours*** from onset.

- For Patients that are possible candidates for tPA treatment or intervention:
  - Perform brief neurological exam and activate Stroke Team (513-844-7686). **WITHIN 10 MINUTES OF ED ARRIVAL**
  - Perform non-contrast CT scan rapidly to rule out intracranial hemorrhage. **WITHIN 20 MINUTES OF ED ARRIVAL**
  - Draw bloods for lab tests (CBC, Renal, Coags, Pregnancy, fingerstick glucose).
    - NOTE: Fingerstick glucose should be obtained promptly to determine IV rtPA eligibility. IV rtPA should not be delayed to wait for other lab results unless there is clinical suspicion for potential abnormalities.
  - Establish two IV lines.
  - Perform EKG.
  - Review eligibility criteria for IV rtPA (details below)
  - Interpret CT scan to rule out ICH or significant ischemic changes. **WITHIN 35 MINUTES OF ARRIVAL**
  - Store IV rtPA in Emergency Dept pyxis for ready accessibility.
  - Start IV rt-PA bolus if eligible. **WITHIN 45 MINUTES OF ARRIVAL**

3. Treatment

- Mix IV rtPA - 0.9 mg/kg dose (maximum 90 mg). Administer 10% as bolus over 1-2 minutes and remainder as infusion over 60 minutes.
  - Do not use the cardiac dose.
  - Do not exceed the 90 mg maximum dose.
  - Use rtPA=Activase=Alteplase. Do not use other thrombolytic agents.
  - Do not give aspirin, clopidogrel, heparin, warfarin or other oral anticoagulants for the first 24 hours after IV rt-PA.

- Monitor the patient carefully, especially blood pressure.
  - Treat BP>180/105 (details below)
  - Repeat head CT stat if increased BP, headache, nausea, vomiting, or decline in neurological status
  - Call stroke team MD with any questions or concerns – 513-844-7686

4. Adjunctive / Additional Therapy

- Potential IV rtPA treatment candidates **should not** receive antiplatelet (aspirin, clopidogrel) or anticoagulant (heparin, warfarin, or other novel oral agents such as dabigatran) medications upon arrival to the Emergency Department if potential reperfusion treatment candidate.
- However, patients who have taken antiplatelet medications prior to arrival in the Emergency Department **are** still considered candidates and those taking anticoagulant medications **may** still be considered candidates for thrombolytic therapy.
- No concomitant antiplatelet or anticoagulant medications should be administered during the first 24 hours after symptom onset. At 24 +/- 6 hours, a non-contrast CT scan or MRI must be performed (to rule out any intracranial hemorrhage) before starting an antiplatelet or anticoagulant medication.
- Endovascular reperfusion therapies (as primary treatment of IV rtPA-ineligible patients or adjunctive therapy among IV rtPA patients with severe strokes) will be considered in select patients as per the stroke team's clinical judgment and rapidly evolving evidence.

5. Criteria for IV rtPA Eligibility are pasted below. (American Heart/Stroke Association 2013 Acute Ischemic Stroke Guideline).

Table 10: Eligibility Criteria for Patients Treated with IV rtPA Within 3 Hours

Table 11: Eligibility Criteria for Patients Treated with IV rtPA Between 3 to 4.5 Hours

NOTE: Clinical judgment is needed to interpret these eligibility criteria in individual patient circumstances.

Table 10. Inclusion and Exclusion Characteristics of Patients With Ischemic Stroke Who Could Be Treated With IV rtPA Within 3 Hours From Symptom Onset

Inclusion criteria
Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms <3 hours before beginning treatment
Aged ≥18 years
Exclusion criteria
Significant head trauma or prior stroke in previous 3 months
Symptoms suggest subarachnoid hemorrhage
Arterial puncture at noncompressible site in previous 7 days
History of previous intracranial hemorrhage
Intracranial neoplasm, arteriovenous malformation, or aneurysm
Recent intracranial or intraspinal surgery
Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)
Active internal bleeding
Acute bleeding diathesis, including but not limited to
Platelet count <100 000/mm^3
Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
Current use of anticoagulant with INR >1.7 or PT >15 seconds
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
Blood glucose concentration <50 mg/dL (2.7 mmol/L)
CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)
Relative exclusion criteria
Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV rtPA administration carefully if any of these relative contraindications are present:
Only minor or rapidly improving stroke symptoms (clearing spontaneously)
Pregnancy
Seizure at onset with postictal residual neurological impairments
Major surgery or serious trauma within previous 14 days
Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
Recent acute myocardial infarction (within previous 3 months)

The checklist includes some FDA-approved indications and contraindications for administration of IV rtPA for acute ischemic stroke. Recent guideline revisions have modified the original FDA-approved indications. A physician with expertise in acute stroke care may modify this list.

Onset time is defined as either the witnessed onset of symptoms or the time last known normal if symptom onset was not witnessed.

In patients without recent use of oral anticoagulants or heparin, treatment with IV rtPA can be initiated before availability of coagulation test results but should be discontinued if INR is >1.7 or PT is abnormally elevated by local laboratory standards.

In patients without history of thrombocytopenia, treatment with IV rtPA can be initiated before availability of platelet count but should be discontinued if platelet count is <100 000/mm^3.

aPTT indicates activated partial thromboplastin time; CT, computed tomography; ECT, ecarin clotting time;FDA, Food and Drug Administration; INR, international normalized ratio; IV, intravenous; PT, partial thromboplastin time; rtPA, recombinant tissue plasminogen activator; and TT, thrombin time.

Table 11. Additional Inclusion and Exclusion Characteristics of Patients With Acute Ischemic Stroke Who Could Be Treated With IV rtPA Within 3 to 4.5 Hours From Symptom Onset

Inclusion criteria
Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms within 3 to 4.5 hours before beginning treatment
Relative exclusion criteria
Aged >80 years
Severe stroke (NIHSS>25)
Taking an oral anticoagulant regardless of INR
History of both diabetes and prior ischemic stroke

INR indicates international normalized ratio; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; and rtPA, recombinant tissue plasminogen activator.

6. Blood Pressure Control

- **PRETREATMENT**
  - **For IV rtPA candidates**: BP should be brought to **<185/110 mmHg** if possible. Gently treat (usually labetolol 10 mg to start, assuming no clinical contraindications, details in box below) if >185/110 after patient has completed CT scan. This must be done without aggressive antihypertensive treatment for the patient to remain eligible for IV rtPA. If blood pressure remains >185/110 with nonaggressive measures, then the patient is not eligible for IV rtPA.

BLOOD PRESSURE MANAGEMENT PRIOR TO IV rtPA ADMINISTRATION

- Up to two of the following agents may be used for nonaggressive treatment:
  - Labetalol 10 to 20 mg IV over 1 to 2 minutes, may repeat X 1 (up to max total dose of 40 mg)
  - Nicardipine infusion, 5 mg/h, titrate up by 2.5 mg/h at 5-15-minute intervals (up to max dose 15 mg/h; when desired blood pressure attained, reduce to 3 mg/h)
  - Enalaprilat 0.625 to 1.25 mg IV (up to max dose of 1.25 mg)
  - Hydralazine 10 mg IV over 1 to 2 minutes, may repeat X1 (up to max dose of 20 mg)
  - Nitropaste 1 to 2 inches (up to max dose of 2 inches)

  - **If not IV rtPA not planned**, then permissive HTN up to 220/120 may be reasonable.

- **POST tPA TREATMENT:**
  - **During/after treatment with rtPA or other acute reperfusion intervention, BP must be aggressively maintained at <180/105**
    - Monitor BP every 15 minutes for first 2 hours, then every 30 minutes for next 6 hours, then every hour for the next 16 hours.
    - Monitor blood pressure every 15 minutes during the antihypertensive therapy. Observe for hypotension.

BLOOD PRESSURE MANAGEMENT DURING/AFTER ADMINISTERING IV rtPA

If systolic BP >180–230 mm Hg or diastolic BP >105–120 mm Hg:

- Labetalol 10 mg IV followed by continuous IV infusion 2–8 mg/min; or
- Nicardipine 5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5–15 minutes, maximum 15 mg/h

If BP not controlled or diastolic BP >140 mm Hg:

- Consider IV sodium nitroprusside

7. Risk and Management of intracranial hemorrhage after thrombolysis

In the original NINDS rtPA trials, **6.4% of the 312 patients** treated with rtPA developed symptomatic intracranial hemorrhage compared with 0.6% of 312 patients treated with placebo ((N Engl J Med 1995;333:1581-7). The overall benefit of IV rtPA was demonstrated despite this increased risk of intracranial hemorrhage. Over a 10-year period from 2003-2012, **4.9% of 58,353** patients treated with rtPA developed symptomatic intracranial hemorrhage in the AHA Get With the Guidelines (GWTG) registry of 1,395 US hospitals treated (JAMA. 2013;309:2480-8.).

- Suspect intracranial hemorrhage if there is any acute neurological deterioration, new headache, acute hypertension, seizure, nausea and vomiting, or acute increase in BP.

- **If any hemorrhage is suspected, then do the following:**
  - Call treating stroke team MD (513-844-7686) immediately.
  - Discontinue rt-PA infusion until ICH is ruled out.
  - Immediately perform CT scan
  - Draw blood for INR, PT, aPTT, platelet count, fibrinogen and type and screen
  - Prepare for administration of 6 to 8 units of cryoprecipitate.
  - Prepare for administration of 6 to 8 units of platelets.

- **If intracranial hemorrhage present:**
  - Consider administering 6-8 units cryoprecipitate followed by 6-8 units platelets
  - Consider emergent neurosurgical consultation
  - Notify patient's family or next-of-kin.

8. Management of Angioedema after Thrombolysis

MEDICAL MANAGEMENT OF ANGIOEDEMA

EARLY DIAGNOSIS IS KEY

Incidence: **Estimated 1-2% of all rt-PA treated stroke.**
Common in patients taking ACE inhibitors.
Usually starts near end of rt-PA infusion.

1. **Begin examining tongue 20 minutes** before intravenous rt-PA infusion complete, and repeat several times until 20 minutes after rt-PA infusion. Look for any signs of unilateral or bilateral tongue enlargement.

2. **If angioedema is suspected immediately:**

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   a. Consider early discontinuation of rt-PA infusion
   b. Benedryl 50 mg IV
   c. Ranitidine 50 mg IV or Famotidine 20 mg IV

3. **If tongue continues to enlarge after steps a-c:**

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   a. Give Solumedrol 80-100 mg IV

4. **If any further increase in angioedema:**

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   a. Epinephrine 0.1% 0.3 mL SQ. or by nebulizer 0.5 mL
   b. Call ENT / Anesthesiology / or appropriate in house service STAT for possible emergent cricotomy / tracheostomy or fiberoptic nasotracheal intubation if oral intubation unsuccessful.

↙	↓	↘
Tongue large but oral intubation possible	Tongue too large for orotracheal intubation	Severe stridor impending airway obstruction
↓	↓	↓
Perform orotracheal intubation STAT	Perform fiberoptic nasotracheal intubation	Perform tracheostomy

9. Post IV rtPA Stroke Monitoring

- Admit patient to ICU and **follow post-tPA order set**, including:
  - Frequent monitoring of BP and neuro status
    - Q15 min X 2 hours, q30 min X 6 hours, then q1 hour X 16 hours
    - For transfer patients arriving from outside hospitals > 2 hours after tPA administration, vital sign frequency will be determined by time of tPA administration (e.g. patients arriving 3 hours after initiation of tPA should have q30 minute vital signs)
  - Call stroke MD if BP>180/105, decline in neuro status, or new headache, nausea, or vomiting
  - NPO until swallowing assessed
  - DVT prophylaxis with intermittent stocking compression devices (SCDs)

- Consider transfer to a Neuroscience Intensive Care Unit for patients needing specialized monitoring and management including:
  - Severe (NIHSS ≥10) stroke with risk of malignant MCA syndrome requiring anticipation and consideration of decompressive hemicraniectomy by neurosurgery
  - Cerebellar stroke with risk of malignant edema requiring anticipation and consideration of posterior decompression by neurosurgery,
  - Fluctuating neurological symptoms requiring specialized blood pressure management
  - Posterior circulation syndrome or large artery occlusion that may require more aggressive endovascular measures.