Protocol for IV Alteplase Treatment of Acute Ischemic Stroke
Adapted from 2018 AHA/ASA Guidelines for Acute Ischemic Stroke

1. Potential IV alteplase candidates
   - Patients of any age with suspected ischemic stroke **within 4.5 hours** of last known well.
   - Selected patients **beyond 4.5 hours** from last known well, with unwitnessed time of onset.
   - See more details regarding eligibility criteria below (#5).

2. Sequence of events by ED (FASTER TREATMENT = BETTER CLINICAL OUTCOMES)
   - Determine “Last Known Well” time. **WITHIN 5 MIN OF ED ARRIVAL**
   - Activate Stroke Team (513-844-7686). **WITHIN 10 MIN OF ED ARRIVAL**
   - Perform non-contrast CT scan and CTA (head/neck). **WITHIN 20 MIN OF ED ARRIVAL**
   - Draw bloods for lab tests (CBC, renal, coags, pregnancy, fingerstick glucose).
     - Obtain fingerstick glucose promptly to determine IV alteplase eligibility.
     - Do not delay alteplase for other lab results unless clinical suspicion of abnormality.
   - Establish two IV lines.
   - Record blood pressure.
     - Gently treat (usually labetolol 10 mg to start, assuming no clinical contraindications) if >185/110 if potential IV alteplase candidate (details below).
   - Review eligibility criteria for IV alteplase (details below)
   - Interpret CT scan -- rule out bleed or subacute ischemia. **WITHIN 35 MIN OF ARRIVAL**
   - Start IV alteplase bolus if eligible. **WITHIN 45 MIN OF ARRIVAL**

3. Treatment
   - Mix IV alteplase - 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.

4. Adjunctive / Additional therapies
   - Potential alteplase candidates **should not** receive antiplatelets (aspirin, clopidogrel) or anticoagulants (heparin, warfarin, or DOACs) upon arrival to Emergency Dept.
   - However, patients who have taken antiplatelets prior to arrival in the Emergency Department **are** still considered alteplase candidates and those taking anticoagulant medications **may** still be candidates as well.
   - At 24 +/- 6 hours, a non-contrast CT scan or MRI should be performed (to rule out any intracranial hemorrhage) before starting an antiplatelet/anticoagulant medication.
5. Key criteria for IV alteplase eligibility (from 2018 AHA/ASA Guidelines)

- Within 4.5 hours
  - No upper age limits
  - BP <185/110 (see pretreatment recommendations below)
  - Exclusions
    - CT brain imaging exhibits extensive regions of clear hypoattenuation
    - Ischemic stroke within 3 months
    - Severe head trauma within 3 months
    - Intracranial/intraspinal surgery within 3 months
    - History of intracranial hemorrhage
    - Suspected subarachnoid hemorrhage
    - GI malignancy or recent GI bleed
    - Platelets <100 000/mm3, INR >1.7, aPTT >40 s, or PT >15 s
    - LMWH within 24 hours
    - DOAC within 48 hours
    - High suspicion of infectious endocarditis
    - Suspected aortic dissection
    - Suspected intra-axial intracranial neoplasm

- Beyond 4.5 hours from last known well (newly emerging therapy based on recently published WAKE UP trial: https://www.nejm.org/doi/full/10.1056/NEJMoa1804355)
  - Unwitnessed event (recognized symptoms upon awakening or unable to report timing of onset due to, for example, confusion or aphasia)
  - MRI suggestive of more recent onset of event
    - Based on MRI-DWI positivity and FLAIR negativity
  - Note that acute MRI may be challenging to obtain in some practice environments and this may limit eligibility by this criterion at this time.
  - Age up to 80 years and functionally independent
  - No large vessel occlusion (LVO); LVO patients are prioritized for EVT
  - Not severe stroke (NIHSS <=25)
  - Meets other standard alteplase eligibility other than time from last known well

6. Post IV alteplase stroke monitoring

- Admit patient to ICU and follow post-alteplase order set, including:
  - Monitor BP and neuro status
    - Q15 min X 2 hours, q30 min X 6 hours, then q1 hour X 16 hours
  - Treat BP>180/105 (details below)
  - Call stroke physician at 513-855-7686 if BP>180/105, decline in neuro status, or new headache, nausea, or vomiting
    - Hold infusion and repeat head CT stat
  - NPO until swallowing assessed
  - DVT prophylaxis with intermittent stocking compression devices (SCDs) but no anticoagulants
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
- Large vessel occlusion that may require endovascular measures in upcoming hours, given the higher risk of neurological deterioration.

7. Blood pressure management considerations

- **PRETREATMENT**
  - **For IV alteplase candidates:** BP should be brought to <185/110 mmHg if possible. This must be done without aggressive antihypertensive treatment for the patient to remain eligible for IV alteplase. If blood pressure remains >185/110 with nonaggressive measures (rarely), then the patient is not eligible for IV alteplase.

  **BLOOD PRESSURE MANAGEMENT PRIOR TO IV ALTEPLASE ADMINISTRATION**
  *Up to two of the following agents may be used for nonaggressive treatment:*
  - Labetalol 10 to 20 mg IV over 1-2 minutes, may repeat X 1 (max dose 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 BP 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 1-2 minutes, may repeat X1 (max dose 20 mg)
  - Nitropaste 1 to 2 inches (up to max dose of 2 inches)

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

- **POST TREATMENT:**
  - **During/after treatment with alteplase or another 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 alteplase**
  *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
8. Management of intracranial hemorrhage after thrombolysis

- If an intracranial hemorrhage is suspected, the treating stroke physician (513-844-7686) should be contacted IMMEDIATELY.
- Suspect intracranial hemorrhage if there is any acute neurological deterioration (new headache, acute hypertension, seizure, or nausea and vomiting) or acute increase in BP.
- If hemorrhage is suspected, then do the following:

<table>
<thead>
<tr>
<th>Class Iib, LOE C-E0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop alteplase infusion</td>
</tr>
<tr>
<td>CBC, PT (INR), aPTT, fibrinogen level, and type and cross-match</td>
</tr>
<tr>
<td>Emergent nonenhanced head CT</td>
</tr>
<tr>
<td>Cryoprecipitate (includes factor VIII): 10 U infused over 10–30 min (onset in 1 h, peaks in 12 h); administer additional dose for fibrinogen level of &lt;200 mg/dL</td>
</tr>
<tr>
<td>Tranexamic acid 1000 mg IV infused over 10 min OR e-aminocaproic acid 4–5 g over 1 h, followed by 1 g IV until bleeding is controlled (peak onset in 3 h)</td>
</tr>
<tr>
<td>Hematology and neurosurgery consultations</td>
</tr>
<tr>
<td>Supportive therapy, including BP management, ICP, CPP, MAP, temperature, and glucose control</td>
</tr>
</tbody>
</table>

9. Management of angioedema after thrombolysis

<table>
<thead>
<tr>
<th>Class Iib, LOE C-E0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintain airway</td>
</tr>
<tr>
<td>Endotracheal intubation may not be necessary if edema is limited to anterior tongue and lips.</td>
</tr>
<tr>
<td>Edema involving larynx, palate, floor of mouth, or oropharynx with rapid progression (within 30 min) poses higher risk of requiring intubation.</td>
</tr>
<tr>
<td>Awake therapeutic intubation is optimal. Nasal-tracheal intubation may be required but poses risk of epistaxis post IV alteplase. Cricothyroidotomy is rarely needed and also problematic after IV alteplase.</td>
</tr>
<tr>
<td>Discontinue IV alteplase infusion and hold ACEIs</td>
</tr>
<tr>
<td>Administer IV methylprednisolone 125 mg</td>
</tr>
<tr>
<td>Administer IV diphenhydramine 50 mg</td>
</tr>
<tr>
<td>Administer ranitidine 50 mg IV or famotidine 20 mg IV</td>
</tr>
<tr>
<td>If there is further increase in angioedema, administer epinephrine (0.1%) 0.3 mL subcutaneously or by nebulizer 0.5 mL</td>
</tr>
<tr>
<td>icatibant, a selective bradykinin B₂ receptor antagonist, 3 mL (30 mg) subcutaneously in abdominal area; additional injection of 30 mg may be administered at intervals of 6 h not to exceed total of 3 injections in 24 h; and plasma-derived C1 esterase inhibitor (20 IU/kg) has been successfully used in hereditary angioedema and ACEI-related angioedema</td>
</tr>
<tr>
<td>Supportive care</td>
</tr>
</tbody>
</table>