

Dartmouth-Hitchcock Medical Center
Mary-Hitchcock Memorial Hospital

Practice Guidelines are intended to assist physicians and other health care providers in clinical decision-making by describing generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. These guidelines should not be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the same results. Final judgement regarding the care of an individual patient must be made by each physician. Parts of this guideline were taken with permission from the Clinical Practice Guideline "rt-PA to Treat Acute Ischemic Stroke" from Baystate Health System.

Clinical Practice Guideline

Guideline for the Use of Intravenous ALTEPLASE (t-PA) in Adult Patients with Acute Ischemic Stroke (Updated 2005)

Stroke Collaborative Practice Team Members:

Linda Arsenault, M.S., R.N.
Nancy Bagley, M.D.
Robin Clark, A.R.N.P.
Laurence Cromwell, M.D.
Donna Crowley, M.S., R.N.
Jonathan Friedman, M.D.
Donald S. Likosky, PhD
Timothy G. Lukovits, M.D.
Richard Powell, M.D.
Scott Rodi, M.D.
Jane Stephenson, M.S.W.
Cynthia Tebbets, R.N.
Connie Thompson, R.N.
Joyce Truman, R.N.
Mary S. Turner, MS, CCC-SLP

Also Endorsed By:

James AuBuchon, MD
Cliff Eskey, M.D.
Alexander Mamourian, M.D.
Pharmacy P and T Committee
Office of Clinical Affairs
Section of Emergency Medicine
Section of Neurology

Introduction

In 1996, the Food and Drug Administration (FDA) approved the use of ALTEPLASE (t-PA) for acute ischemic stroke after the report of a randomized, two-part trial sponsored by the National Institute of Neurological Disorders and Stroke (NINDS)¹. The committees of the American Heart Association (AHA)^{2,4} and the American Academy of Neurology (AAN)³ then published guidelines endorsing the use of ALTEPLASE t-PA for acute ischemic stroke under strict inclusion and exclusion criteria. The enclosed practice guideline and order set are based on the NINDS rt-PA Stroke Study and the AHA and AAN guidelines and will allow for optimal patient selection and management. This practice guideline was reviewed and minor revisions were made in 2005. The update includes the use of Nicardipine for blood pressure control.

Key Points

- The FDA has approved the use of ALTEPLASE (t-PA) for acute ischemic stroke following the report of a randomized two part clinical trial sponsored by the National Institute of Neurologic Disorders and Stroke (NINDS). The American Heart Association and the American Academy of Neurology have also endorsed the use of ALTEPLASE t-PA under strict inclusion and exclusion criteria.
- The use of ALTEPLASE (t-PA) for acute ischemic stroke resulted in a significant improvement in NIH Stoke Scale within the first 24 hours as well as neurologic and functional outcomes at three months if administered **within 3 hours** of stroke onset. Significantly more patients had complete recovery at three months who were treated with t-PA than placebo. These outcomes were at the expense of an increase in symptomatic intracerebral hemorrhages within 36 hours of the onset of stroke. However, in the patients who experienced intra-cerebral hemorrhages post ALTEPLASE (t-PA) infusion, the majority of hemorrhages occurred in patients with extremely severe strokes.
- Determination of appropriate patients for candidacy for ALTEPLASE (t-PA) is based on well researched inclusion and exclusion criteria. Assessment of each patient considered for ALTEPLASE (t-PA) administration will be done by a physician. Minimum inclusion criteria are:
 - *symptom onset less than 180 minutes*
 - *patient is ≥ 18 years of age*
 - *clinical diagnosis of ischemic stroke causing a measurable neurological deficit*
 - *patient/family are informed of possible benefits and risk of t-PA.*
- Coordination of the acute stroke response team is critical to success. Each team member is responsible for a designated component of care. The **Emergency Medical System (EMS)** and **Emergency Department Staff** will identify potential candidates and begin the determination process. **Neurologists**, who are part of an Acute Stroke Response Team, will respond immediately to consult on a potential candidate. CT scan will be done and reviewed by the **Radiologist** as soon as possible.
- Once the decision to treat is made, the ALTEPLASE (t-PA) order sets will be implemented. The order sets provide recommendations for: ALTEPLASE (t-PA) drug dosage, management of hypertension, monitoring parameters, additional diagnostics, treating a bleeding event, care of the patient receiving ALTEPLASE (t-PA) and care of the patient post ALTEPLASE (t-PA) infusion.
- Recent data now suggests initial hospitalization of patients treated with ALTEPLASE (t-PA) is shorter than patients not treated with ALTEPLASE (t-PA). Also more patients treated with ALTEPLASE (t-PA) were discharged to home and required less inpatient rehabilitation and nursing home care.

Minimum Inclusion Criteria For IV Treatment With ALTEPLASE (t-PA)

Caveat: Caution in differential diagnosis (exclude migraine, Bell's Palsy, Todd's post-ictal paralysis, TIA, giant cell arteritis/vasculitis, etc.).

- Age ≥ 18 years.
- Clinical diagnosis of acute ischemic stroke causing a measurable neurological deficit.
- Time of *symptom onset* well established to be **less than 180 minutes** before infusion would begin. Patients thus awakening with stroke are generally ineligible.
- Potential benefits and risks discussed with patient, family, and/or legal guardian before treatment begun.

Exclusion Criteria

- Only minor or rapidly improving stroke symptoms. Examples of such exclusions are: ataxia alone; sensory loss alone; dysarthria alone; minimal weakness.
- Evidence of intracranial or subarachnoid hemorrhage on pretreatment Computerized Axial Tomography (CT).
- Clinical presentation suggestive of subarachnoid hemorrhage, even with normal CT.
- Awakening with stroke and ≥ 3 hours has past since patient last seen at baseline.
- Active internal bleeding.
- History of intracranial hemorrhage.
- Known bleeding diathesis, including but not limited to:
 - *Platelet count $< 100,000/mm^3$.*
 - *Patient has received un-fractionated heparin and has an elevated aPTT (greater than upper limit of normal for laboratory).*
 - *Patient has received low molecular weight heparin in past 24 hours.*
 - *Current use of oral anticoagulants (e.g., warfarin sodium) or recent use with an elevated INR > 1.5 .*

*In patients without recent use of oral anticoagulants or heparin, treatment with ALTEPLASE (t-PA) can be initiated prior to the availability of coagulation results but should be discontinued if either the INR is greater than 1.7 or the aPTT is elevated.

- Current pregnancy.
- Within 3 months any intracranial surgery, serious head trauma, or previous stroke.
- Major surgery or truncal trauma within the preceding 14 days.
- History of gastrointestinal or urinary tract hemorrhage within 21 days.
- Recent arterial puncture at a noncompressible site.
- Recent lumbar puncture.
- On repeated measurements, systolic blood pressure greater than 185 mm Hg or diastolic blood pressure greater than 110 mm Hg at the time treatment is to begin and patient requires aggressive treatment to reduce blood pressure to within these limits.
- Abnormal blood glucose (< 50 or > 400 mg/dL).
- Post-myocardial infarction pericarditis.
- Seizure near the time of onset of stroke symptoms.
- History of severe dementia or severe pre-existing neurologic impairment.

Note: Current or recent use of aspirin, ticlopidine, or clopidogrel is not a contraindication.

Warnings/Relative Contraindications

- Age ≥ 85 years
- Severe neurologic deficit (e.g., National Institutes of Health Stroke Scale Score > 20).
- Baseline CT scan evidence of extensive ischemic changes. This includes early evidence of sulcal effacement, herniation, mass effect, or edema.
- Recent myocardial infarction (given risk of post-myocardial infarction pericarditis and LV thromboembolism), recent dysfunctional uterine bleeding, or active menstruation.

Treatment

- ALTEPLASE (tPA) 0.9 mg/kg (maximum of 90 mg) infused over 60 minutes with 10% of the total dose administered as an initial intravenous bolus over 1 minute.

Protocol for Activating a Stroke Alert and Paging the Acute Stroke Response Team

- Upon notification by EMS personnel that an incoming stroke patient meets specific criteria, as outlined in this protocol, the ED will call the operator to initiate a STROKE ALERT and the stroke team members will be paged with the text "STROKE ALERT" and the estimated time of arrival. For patients arriving to the ED by car or for patients with in-hospital stroke, the ED or treating hospital physician will determine if the patient meets specific criteria, as outlined in this protocol, and call a STROKE ALERT. Upon receipt of page, appropriate team members will promptly respond to the emergency department to evaluate the patient.

Criteria for ED to call a STROKE ALERT for patients being transported by EMS:

1. EMS is transporting a patient with a suspected acute stroke (symptoms include sudden numbness, weakness or paralysis of face, arm or leg - especially on one side of the body; sudden confusion, trouble speaking or understanding speech; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; or sudden severe headache with no known cause)
2. Symptom onset less than 5 hours [N.B. IV ALTEPLASE (t-PA) is approved only for treatment within 3 hours of symptom onset].
3. Age greater than or equal to 18 years
4. Blood glucose is 50-400 mg/dL or is not available.
5. No severe trauma or witnessed seizure
6. Positive Cincinnati Stroke Scale obtained by EMS (facial droop, arm drift or abnormal speech)

Criteria for calling a STROKE ALERT for patients who come to ED by car or for patients with in-hospital stroke

1. Suspected acute stroke (symptoms include sudden numbness, weakness or paralysis of face, arm or leg - especially on one side of the body; sudden confusion, trouble speaking or understanding speech; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; or sudden severe headache with no known cause)
2. Symptom onset less than 5 hours [N.B. IV ALTEPLASE (t-PA) is approved only for treatment within 3 hours of symptom onset].
3. Age greater than or equal to 18 years
4. Blood glucose is 50-400 mg/dL or is not available.
5. No severe trauma or witnessed seizure
6. Positive Cincinnati Stroke Scale obtained by ED or other hospital staff (facial droop, arm drift or abnormal speech).

To Respond:

1. Neurology resident covering the ED
2. Stroke Center Co-Director and Nurse Practitioner (if available in house): Timothy Lukovits, M.D., pager 2410 and Robin Clark, A.R.N.P., pager 4440.

*If team does not respond by phone or in-person within 10 minutes, have Operator repeat stroke alert page.

Sequence Of Events

- Determine whether timing allows treatment initiation with ALTEPLASE (t-PA) before the three-hour limit.
- Activate Stroke Alert if above criteria are met AND PAGE Neurology Resident on call for ED.
- Draw blood for tests while preparations are made to perform non-contrast CT scan.
- Start recording blood pressure, pulse rate, oxygen saturation, respiratory rate and temperature.
- Neurological examination (NIHSS score).
- CT scan without contrast.
- Determine if CT has evidence of hemorrhage.
- If patient has severe head or neck pain, or is somnolent or stuporous, be sure there is no evidence of subarachnoid hemorrhage.
- If there is a significant abnormal lucency suggestive of infarction, reconsider the patient's history, since the stroke may have occurred earlier.
- Review required test results:
 - *Platelet count.*
 - *Blood glucose.*
 - *PT or aPTT (in patients with recent use of oral anticoagulants or heparin).*
- Review patient inclusion and exclusion criteria.
- Infuse ALTEPLASE (t-PA): Give a total of 0.9 mg/kg over 60 minutes, starting with 10% as a bolus over one minute intravenously. Maximum total dose =90mg. See dosing sheet.
- **Do not give** aspirin, ticlopidine, clopidogrel, glycoprotein IIB/IIIA agents, heparin in any form or warfarin for 24 hours.
- Monitor the patient carefully, especially the blood pressure. Follow the blood pressure algorithm (*see below orders*).
- Monitor neurological status (*see below orders*).

Adjunctive Therapy

Bleeding Precautions

- No concomitant antithrombotic or antiplatelet therapy during the first 24 hours after symptom onset. If heparin or any other anticoagulant is indicated after 24 hours, consider performing a non-contrast CT scan or other sensitive diagnostic imaging method to rule out any hemorrhage before starting an anticoagulant.
- Restrict central venous access and arterial punctures during first 24 hours.
- Avoid inserting indwelling bladder catheter during infusion and for 30 minutes after ALTEPLASE (t-PA) infusion ends.

Blood Pressure Control (excessively high blood pressure might increase bleeding risk while extensively low blood pressure may exacerbate ischemic symptoms):

- **Pretreatment**
 - **Monitor blood pressure every 15 minutes. It should be below 185/110 mm/hg before initiating t-PA.**
- **During and after treatment:** Monitor blood pressure for the first 24 hours after starting treatment:
 - every 15 minutes for 2 hours after starting the infusion, **then**
 - every 30 minutes for 6 hours, then every hour for 18 hours, and then q 4 hours for 24 hours, then per routine.
 - If systolic BP is > or equal to 180 mm Hg or if diastolic BP is 105 to 140 mm Hg on two successive readings 5 to 10 minutes apart, give labetalol 10 mg IV over 2 minutes. The dose may be repeated or doubled every 10 to 20 minutes, up to 300 mg.

Alternatively, following the first bolus of labetalol, an IV infusion of 0.5-2 mg/min of labetalol may be initiated and continued until the desired blood pressure is reached. Monitor for hypotension.

- If systolic BP is persistently > 180 mm Hg despite labetalol, start an intravenous infusion of Nicardipine. Start at 5mg/hour and titrate to maintain SBP less than 180 and DPB less than 105 by increasing infusion rate by 2.5 mg/hour every 5 minutes to a maximum of 15 mg/hour. **Frequent BP measurements (every 15 minutes) are recommended for 1 hour after initiation of the Nicardipine infusion and after a dose change, then every 30 minutes.** Monitor for hypotension.
- If systolic BP is persistently > 180 mm Hg despite labetalol and Nicardipine or if diastolic BP > 140 mm Hg on two successive readings 5-10 minutes apart, start an intravenous infusion of sodium nitroprusside, 0.5 to 10 micrograms/kg/min. Weigh benefits/risks of indwelling A-line. Monitor for hypotension.
- Monitor for severe headache; neck pain/rigidity; decline or abrupt change in mental status; HR <50 or >120 bpm; accelerating BP; nausea/ vomiting; seizure activity; caudal progression of respirations; muscle tone; decerebrate/decorticate posturing; "blown pupil" or other deteriorating neurological signs: **report STAT to M.D.** This may indicate intracranial hemorrhage.
- If an intracranial hemorrhage is suspected, the administration of ALTEPLASE (t-PA) should be immediately discontinued and an emergency CT scan should be obtained.

Management of Intracranial Hemorrhage or Other Major Bleeding Complication:

- Suspect the occurrence of intracranial hemorrhage following the start of ALTEPLASE (t-PA) infusion if there is any subsequent neurological deterioration, change in seizure pattern, new or severe exacerbation of headache, brady- or tachycardia, acute hypertension or other sudden change in vital signs including respiratory pattern, muscle tone, decerebrate/decorticate posturing, or onset of nausea and vomiting.
- If hemorrhage is suspected:
 - Discontinue ALTEPLASE (t-PA) infusion unless other causes of neurological deterioration are apparent.
 - Immediate CT scan to check for presence of hemorrhage.
 - Draw blood for Hct/Hgb, PT, aPTT, platelet count, fibrinogen and type and cross.
 - Prepare for administration of plasma and/or cryoprecipitate if clinically significant abnormalities in coagulation screening tests are found.

Dosage should be based on extent of abnormality and blood volume. Usual (initial) dosage of plasma is 10-20 mL/kg; additional doses may be necessary depending on extent of deficiency. Cryoprecipitate is indicated for the replenishment of fibrinogen; the usual target is 200 mg/dL. If the patient is deficient in Factor VIII, virally inactivated Antihemophilic Factor is indicated; the usual target is 100% activity. The blood bank will calculate and send the appropriate volume of plasma and/or cryoprecipitate based on the patient's weight.

- Prepare for administration of platelets.

Dosage depends on extent of thrombocytopenia, content of unit(s), and size of patient. Usual (initial) dose is one unit of Platelets, Pheresis or 4-8 units of platelet concentrate. The platelet count should be raised to 50-100,000/ μ L through transfusion(s).

- Prepare for the administration of Red Blood Cells.

Transfusion of red cells is not likely to be necessary unless bleeding develops at extracranial sites or evacuation surgical of the intracranial hemorrhage is necessary. The dosage will depend on the patient's co-morbidities, symptomatology and initial hemoglobin concentration. Volume resuscitation should be attempted before deciding whether transfusion is required.

- If intracranial hemorrhage present:
 - STAT neurosurgery consult.
 - STAT hematology consult.
- Second CT to assess progression of intracranial hemorrhage when appropriate.

References

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *The New England Journal of Medicine*. 1995; 333:1581-7.
2. Adams HP Jr, Brott TG, Furlan AJ, et al. Guidelines for thrombolytic therapy for acute stroke: A supplement to the guidelines for the management of patients with acute ischemic stroke: A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke*. 1996; 27:1711-8.
3. Practice advisory: Thrombolytic therapy for acute ischemic stroke - Summary statement: Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 1996; 47:835-9.
4. Adams, HP Jr, Adams RJ, Brott T, et al. Guidelines for the Early Management of Patients With Ischemic Stroke. A Scientific Statement From the Stroke Council of the American Stroke Association. *Stroke* 2003; 34:1056-1083.