Emergency Assessment of Acute Ischemic Stroke

Indication
Activase® (alteplase) is indicated for the treatment of acute ischemic stroke. Exclude intracranial hemorrhage as the primary cause of stroke signs and symptoms prior to initiation of treatment. Initiate treatment as soon as possible but within 3 hours after symptom onset.

Important Safety Information
Contraindications
Do not administer Activase to treat acute ischemic stroke in the following situations in which the risk of bleeding is greater than the potential benefit: current intracranial hemorrhage (ICH); subarachnoid hemorrhage; active internal bleeding; recent (within 3 months) intracranial or intraspinal surgery or serious head trauma; presence of intracranial conditions that may increase the risk of bleeding; bleeding diathesis; and current severe uncontrolled hypertension.

Please see Important Safety Information throughout and the accompanying full Prescribing Information.

Genentech
A Member of the Roche Group

www.activase.com
Common symptoms of acute ischemic stroke include:

- Abrupt onset of hemiparesis, monoparesis, or quadriparesis
- Hemisensory deficits
- Monocular or binocular visual loss
- Visual field deficits
- Diplopia
- Dysarthria
- Facial droop
- Ataxia
- Vertigo
- Nystagmus
- Aphasia
- Sudden decrease in the level of consciousness
Conditions that may mimic stroke

- Central nervous system (CNS) abscess
- CNS tumor
- Complicated migraine
- Drug toxicity
- Hypertensive encephalopathy

- Hypoglycemia
- Psychogenic conditions
- Seizures
- Wernicke's encephalopathy
EMS management of patients with suspected stroke²

<table>
<thead>
<tr>
<th>On scene</th>
<th>In transit</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Manage CABs (chest compressions-airway-breathing)—give oxygen, if needed</td>
<td>• Rapid transport to closest PSC or CSC; in some instances, this may involve medical transport and hospital bypass*</td>
</tr>
<tr>
<td>• Perform prehospital stroke assessment</td>
<td>• Bring witness, family member, or caregiver, if possible</td>
</tr>
<tr>
<td>• Establish and record exact time when patient last seen normal</td>
<td>• Alert receiving emergency department (ED)</td>
</tr>
<tr>
<td>• If possible, bring witness to hospital. Alternatively, record name and phone number (preferably cell phone number) of witness</td>
<td>• Check and record blood glucose to assess for hypoglycemia</td>
</tr>
<tr>
<td>• Identify current medications taken by patient, especially any anticoagulants, and recent illnesses, surgery, or trauma</td>
<td>• Establish cardiac monitoring and intravenous (IV) access, if possible</td>
</tr>
</tbody>
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*If no such centers exist, patient should be brought to the most appropriate institution that provides emergency stroke care.
CSC=comprehensive stroke center; EMS=emergency medical services; PSC=primary stroke center.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Normal:</th>
<th>Abnormal:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial Droop</td>
<td>Both sides of face move equally</td>
<td>One side of face does not move as well</td>
</tr>
<tr>
<td>Arm Drift</td>
<td>Both arms move equally or not at all</td>
<td>One arm drifts compared with the other, or does not move at all</td>
</tr>
<tr>
<td>Speech</td>
<td>Patient uses correct words with no slurring</td>
<td>Slurred or inappropriate words or mute</td>
</tr>
</tbody>
</table>
Los Angeles Prehospital Stroke Screen (LAPSS) criteria

- Age >45 years
- History of seizures or epilepsy absent
- Symptom duration <24 hours
- At baseline, patient is not wheelchair bound or bedridden
- Blood glucose between 60 mg/dL and 400 mg/dL
- Obvious asymmetry (left vs right) in any of the following 3 exam categories:
  - Facial smile/grimace (equal, droop)
  - Grip (equal, weak grip, no grip)
  - Arm strength (equal, drifts down, falls rapidly)
1a. Level of Consciousness (LOC)

0 = Alert; keenly responsive
1 = Not alert, but arousable by minor stimulation
2 = Not alert; requires repeated stimulation to attend or is obtunded and requires strong or painful stimulation to make movements
3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic

The investigator must choose a response if full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages, etc. A score of 3 is given only if the patient makes no movement (other than reflexive posturing) in response to noxious stimuli.

1b. LOC Questions

Ask the patient: “What month is it?” “How old are you?”

0 = Answers both questions correctly
1 = Answers 1 question correctly
2 = Answers neither question correctly

Score only the initial answer (there is no credit for being close). Patients unable to speak due to intubation, orotracheal trauma, severe dysarthria, language barrier, etc, are scored 1. Aphasic and stuporous patients are scored 2.
1c. LOC Commands

Ask the patient to: “Open and close your eyes.” “Grip and release your hand.”

0 = Performs both tasks correctly
1 = Performs 1 task correctly
2 = Performs neither task correctly

Substitute another 1-step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to the command, the task should be demonstrated to him or her (pantomime) and the results scored (i.e., follows none, 1, or 2 commands). Patients with trauma, amputation, or other physical impediments should be given suitable 1-step commands. Only the first attempt is scored.

2. Best Gaze (only horizontal movement tested)

Establish eye contact and ask the patient to: “Follow my finger.”

0 = Normal
1 = Partial gaze palsy
2 = Forced deviation or total gaze paresis is not overcome by oculocephalic maneuver

Appropriate for aphasic patients. Score voluntary or reflexive horizontal eye movements (do not perform caloric test). Test patients with ocular trauma, bandages, preexisting blindness, etc, for reflexive movement and a choice made by the investigator. Patients with conjugate deviation of the eyes (overcome by voluntary or reflexive activity) and those with isolated peripheral nerve paresis (cranial nerve III, IV, or VI) are scored 1.
3. **Visual Fields**

*Use confrontation, finger counting, or visual threat.*

**Confront upper/lower quadrants of visual field.**

- **0** = No visual loss
- **1** = Partial hemianopia
- **2** = Complete hemianopia
- **3** = Bilateral hemianopia

Test patients with unilateral blindness or enucleation in remaining eye. Patients with clear-cut asymmetry, including quadrantopia, are scored 1. Blind patients are scored 3. Test again using double simultaneous stimulation. Score 1 for extinction and record under item 11.

4. **Facial Palsy**

*Through words or pantomime, encourage the patient to:*

- **“Show me your teeth.”**  
- **“Raise your eyebrows.”**  
- **“Close your eyes.”**

- **0** = Normal symmetrical movements
- **1** = Minor paralysis (flattened nasolabial fold, asymmetry on smiling)
- **2** = Partial paralysis (total or near-total paralysis of lower face)
- **3** = Complete paralysis of one or both sides

If possible, remove facial bandages, orotracheal tube, tape, etc, before testing. In poorly responsive patients, score symmetry of grimace in response to noxious stimuli.
5. **Motor Arm**

Alternately position the patient’s arms. Extend each arm with palms down (90 degrees if sitting, 45 degrees if supine).

- **0** = No drift
- **1** = Drift
- **2** = Some effort vs gravity
- **3** = No effort vs gravity
- **4** = No movement
- **UN** = Amputation or joint fusion

Test each arm in turn (nonparetic arm first). Drift is scored if arm falls before 10 seconds. Score untestable (UN) only for patients with amputations or joint fusions of the shoulder.

6. **Motor Leg**

Alternately position the patient’s legs. Extend each leg (30 degrees, always while supine).

- **0** = No drift
- **1** = Drift
- **2** = Some effort vs gravity
- **3** = No effort vs gravity
- **4** = No movement
- **UN** = Amputation or joint fusion

Test each leg in turn (nonparetic leg first). Drift is scored if leg falls before 5 seconds. Score UN only for patients with amputations or joint fusions of the hip.
7. **Limb Ataxia**

Ask patient (eyes open) to: “Touch your finger to your nose.”
“Touch your heel to your shin.”

- **0** = Absent
- **1** = Present in 1 limb
- **2** = Present in 2 limbs
- **UN** = Amputation or joint fusion

Perform finger-nose-finger and heel-shin tests on both sides to determine unilateral cerebellar lesion. Score 0 for patients who are paralyzed or cannot understand the commands. Score 1 or 2 only if ataxia is disproportionate to weakness. Score UN only for patients with amputation or joint fusions.

8. **Sensory**

Test as many body parts as possible (arms [not hands], legs, trunk, face) for sensation using pinprick or noxious stimulus (in the obtunded or aphasic patient).

- **0** = Normal
- **1** = Mild-to-moderate sensory loss
- **2** = Severe to total sensory loss

Score sensory loss due to stroke only. Stuporous and aphasic patients are scored 0 or 1. Patients with brain-stem stroke and bilateral sensory loss, quadriplegic patients who do not respond, and comatose patients (item 1a = 3) are scored 2. A score of 2 is only given when severe or total loss of sensation is clearly demonstrated.
9. **Best Language**

Using pictures and a sentence list (see following cards), ask the patient to:

“Describe what you see in this picture.”
“Name the items in this picture.”
“Read these sentences.”

0 = No aphasia
1 = Mild-to-moderate aphasia
2 = Severe aphasia
3 = Mute, global aphasia

Patients with visual loss can be asked to identify and describe objects placed in their hand. Intubated patients should be asked to write their answers. The examiner must choose a score for stuporous or uncooperative patients. Comatose patients (item 1a = 3) are scored 3. A score of 3 is only given if the patient is mute and unable to follow 1-step commands.
NIHSS testing card—picture description

(NIHSS information on pages 7-17)

NIHSS testing card—naming list

(NIHSS information on pages 7-17)

You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.
10. Dysarthria

Using a simple word list (see next card), ask the patient to:
“Read these words.” “Repeat these words.”

0 = Normal articulation
1 = Mild-to-moderate dysarthria
2 = Severe dysarthria
UN = Intubated or other physical barrier

Patients with severe aphasia can be scored based on the clarity of articulation of their spontaneous speech. Score UN only for patients who are intubated or have other physical barriers to speech. Do not tell patients why they are being tested.

11. Extinction and Inattention

Sufficient information to determine these scores may have been obtained during the prior testing.

0 = No abnormality
1 = Visual, tactile, auditory, spatial, or personal inattention
2 = Profound hemi-inattention or extinction to more than 1 modality

Lack of patient response and inattention may already be evident from the previous items. Score 0 if the patient has a severe visual loss preventing visual double simultaneous stimulation, but the response to cutaneous stimuli is normal, or if the patient has aphasia but does appear to attend to both sides. The presence of visual or spatial neglect or anosognosia may also be evidence of abnormality.
NIHSS testing card—word list

MAMA
TIP-TOP
FIFTY-FIFTY
THANKS
HUCKLEBERRY
BASEBALL PLAYER
• Noncontrast brain CT or brain magnetic resonance imaging (MRI)
• Blood glucose
• Oxygen saturation
• Serum electrolytes/renal function tests*
• Complete blood count, including platelet count*
• Markers of cardiac ischemia*
• Prothrombin time (PT)/international normalized ratio (INR)*
• Activated partial thromboplastin time (aPTT)*
• Electrocardiogram*

*Although it is desirable to know the results of these tests before administering alteplase, fibrinolytic therapy should not be delayed while awaiting results unless: 1) there is clinical suspicion of a bleeding abnormality or thrombocytopenia, 2) the patient has received heparin or warfarin, or 3) the patient has received other anticoagulants (direct thrombin inhibitors or direct factor Xa inhibitors).

AHA=American Heart Association; AIS=acute ischemic stroke; ASA=American Stroke Association; CT=computed tomography.
AHA/ASA 2013 Guidelines: additional diagnostic tests for *selected* patients with suspected AIS$^2$

- Thrombin time and/or ecarin clotting time if it is suspected the patient is taking direct thrombin inhibitors or direct factor Xa inhibitors
- Hepatic function tests
- Toxicology screen
- Blood alcohol level
- Pregnancy test
- Arterial blood gas tests (if hypoxia is suspected)
- Chest radiography (if lung disease is suspected)
- Lumbar puncture (if subarachnoid hemorrhage is suspected and CT scan is negative for blood)
- Electroencephalogram (if seizures are suspected)
Recommendations from AHA/ASA 2013 Guidelines

• Evidence indicates that persistent in-hospital hyperglycemia during the first 24 hours after stroke is associated with worse outcomes than normoglycemia, and thus, it is reasonable to treat hyperglycemia to achieve blood glucose levels in a range of 140 to 180 mg/dL and to closely monitor to prevent hypoglycemia in patients with acute ischemic stroke (*Class Ila; Level of Evidence C*)

• It is reasonable to follow the current American Diabetes Association recommendation to maintain blood glucose in a range of 140 to 180 mg/dL

• Subcutaneous insulin protocols can safely lower and maintain blood glucose levels below 180 mg/dL in acute stroke patients

• Hypoglycemia (blood glucose < 60 mg/dL) should be treated in patients with acute ischemic stroke (*Class I; Level of Evidence C*). The goal is to achieve normoglycemia

Class I=conditions for which there is evidence and/or general agreement that the procedure or treatment is useful and effective; Class Ila=conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment, but where the weight of evidence or opinion is in favor of the procedure or treatment; Level of Evidence C=consensus opinion of experts.
Blood pressure (BP) management in patients with acute ischemic stroke

Recommendations from AHA/ASA 2013 Guidelines
If patients are otherwise eligible for acute reperfusion therapy except that BP is uncontrolled*:

• Labetalol 10-20 mg IV over 1-2 minutes, may repeat 1 time; or

• Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5-15 minutes, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or

• Other agents (hydralazine, enalaprilat, etc) may be considered when appropriate

If BP cannot be controlled, do not administer alteplase.*

In patients with markedly elevated BP who do not receive fibrinolysis, a reasonable goal is to lower BP by 15% during the first 24 hours after onset of stroke. The level of BP that would mandate such treatment is not known, but consensus exists that medications should be withheld unless the systolic BP is >220 mm Hg or the diastolic BP is >120 mm Hg (Class I; Level of Evidence C).

*The 2013 AHA/ASA guidelines for the management of patients with acute ischemic stroke define hypertension (elevated blood pressure) associated with alteplase eligibility as systolic >185 mm Hg or diastolic >110 mm Hg.

Please see Important Safety Information throughout and the accompanying full Prescribing Information.
Intravenous rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for selected patients who may be treated within 3 hours of onset of ischemic stroke (Class 1; Level of Evidence A).

In patients eligible for intravenous rtPA, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible. The door-to-needle time (time of bolus administration) should be within 60 minutes from hospital arrival (Class 1; Level of Evidence A).

Class I=conditions for which there is evidence and/or general agreement that the procedure or treatment is useful or effective; Level of Evidence A=data derived from multiple randomized clinical trials or meta-analyses.
NIH-recommended response times for acute ischemic stroke

Since 2015, the Joint Commission has required DTN of ≤60 minutes in 50% of all eligible AIS patients receiving Activase® (alteplase)\textsuperscript{6}

Target: Stroke has established a more aggressive goal\textsuperscript{7}:
- DTN within 60 minutes in at least 75% of patients
- DTN within 45 minutes in at least 50% of patients

Door to treatment in ≤60 min\textsuperscript{2,8}

<table>
<thead>
<tr>
<th>≤0</th>
<th>≤10</th>
<th>≤15</th>
<th>≤25</th>
<th>≤45</th>
<th>≤60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected stroke patient arrives at ED</td>
<td>Initiate MD evaluation and labwork</td>
<td>Notify stroke team (including neurologic expertise)</td>
<td>Initiate imaging scan Review patient history and establish time of last known well/symptom onset Assess using NIHSS</td>
<td>Interpret imaging scan and labs Review patient eligibility for Activase*</td>
<td>Give Activase bolus and initiate infusion in eligible patients*</td>
</tr>
</tbody>
</table>

*Initiate treatment with Activase as soon as possible but within 3 hours after symptom onset.

Patient selection for Activase® (alteplase) therapy

- Activase is indicated for the treatment of acute ischemic stroke
- Exclude intracranial hemorrhage as the primary cause of stroke signs and symptoms prior to initiation of treatment
- Initiate treatment as soon as possible but within 3 hours after symptom onset

Please see Important Safety Information throughout and the accompanying full Prescribing Information.
Contraindications to Activase therapy

Do not administer Activase to treat acute ischemic stroke in the following situations in which the risk of bleeding is greater than the potential benefit:

☐ Current intracranial hemorrhage
☐ Subarachnoid hemorrhage
☐ Active internal bleeding
☐ Recent (within 3 months) intracranial or intraspinal surgery or serious head trauma
☐ Presence of intracranial conditions that may increase the risk of bleeding
☐ Bleeding diathesis*
☐ Current severe uncontrolled hypertension

*The 2016 AHA/ASA scientific rationale for the inclusion and exclusion criteria for IV alteplase in AIS (an adjunct to the 2013 AHA/ASA guidelines for the early management of patients with AIS) also advises against treatment with IV alteplase in patients:

- With a platelet count <100,000/mm³, INR >1.7, aPTT >40 seconds, or PT >15 seconds
- Who have a history of warfarin use and an INR >1.7
- Who have received a treatment dose of low-molecular-weight heparin within the previous 24 hours
- Who are taking direct thrombin inhibitors or direct factor Xa inhibitors, unless the laboratory tests are normal or the patient has not received a dose of these agents for >48 hours

INR=international normalized ratio, PT=prothrombin time.
The recommended dose of Activase® (alteplase) is 0.9 mg/kg (not to exceed 90-mg total dose) infused intravenously over 60 minutes with 10% of the total dose administered as an initial bolus over 1 minute.
**Indication**
Activase is indicated for the treatment of acute ischemic stroke (AIS). Exclude intracranial hemorrhage as the primary cause of stroke signs and symptoms prior to initiation of treatment. Initiate treatment as soon as possible but within 3 hours after symptom onset.

**Important Safety Information**

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Do not administer Activase to treat acute ischemic stroke in the following situations in which the risk of bleeding is greater than the potential benefit: current intracranial hemorrhage (ICH); subarachnoid hemorrhage; active internal bleeding; recent (within 3 months) intracranial or intraspinal surgery or serious head trauma; presence of intracranial conditions that may increase the risk of bleeding; bleeding diathesis; and current severe uncontrolled hypertension.

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Warnings and Precautions

Bleeding
Activase® (alteplase) can cause significant, sometimes fatal, internal or external bleeding, especially at arterial and venous puncture sites. Avoid intramuscular injections and trauma to the patient. Fatal cases of hemorrhage associated with traumatic intubation in patients administered Activase have been reported. The concomitant administration of heparin and aspirin with and following infusions of Activase for the treatment of AIS during the first 24 hours after symptom onset has not been investigated. Because heparin, aspirin, or Activase may cause bleeding complications, carefully monitor for bleeding, especially at arterial puncture sites. Hemorrhage can occur 1 or more days after administration of Activase, while patients are still receiving anticoagulant therapy. If serious bleeding occurs, terminate the Activase infusion.

In the following conditions, the risks of bleeding with Activase are increased and should be weighed against the anticipated benefits: recent major surgery or procedure; cerebrovascular disease; recent intracranial hemorrhage; recent gastrointestinal or genitourinary bleeding; recent trauma; hypertension; high likelihood of left heart thrombus; acute pericarditis;
**Warnings and Precautions (cont’d)**

**Bleeding (cont’d)**
subacute bacterial endocarditis; hemostatic defects including those secondary to severe hepatic or renal disease; significant hepatic dysfunction; pregnancy; diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions; septic thrombophlebitis or occluded AV cannula at seriously infected site; advanced age; and patients currently receiving oral anticoagulants, or any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

**Orolingual Angioedema**
Orolingual angioedema has been observed during and up to 2 hours after infusion in patients treated for AIS. In many cases, patients received concomitant angiotensin-converting enzyme inhibitors. Monitor patients treated with Activase during and for several hours after Activase infusion for orolingual angioedema. If angioedema develops, discontinue the Activase infusion and promptly institute appropriate therapy.

Please see Important Safety Information throughout and the accompanying full Prescribing Information.
Warnings and Precautions (cont’d)

**Cholesterol Embolization**
Cholesterol embolism, sometimes fatal, has been reported rarely in patients treated with thrombolytic agents; the true incidence is unknown. It is associated with invasive vascular procedures and/or anticoagulant therapy.

**Coagulation Tests May be Unreliable during Activase® (alteplase) Therapy**
Coagulation tests and/or measures of fibrinolytic activity may be unreliable during Activase therapy unless specific precautions are taken to prevent *in vitro* artifacts.

**Adverse Reactions**
The most frequent adverse reaction associated with Activase AIS therapy is bleeding.

Although exploratory analyses of the AIS clinical studies suggest that severe neurological deficit (National Institutes of Health Stroke Scale [NIHSS > 22]) at presentation was associated with an increased risk of intracranial hemorrhage, efficacy results suggest a reduced but still favorable clinical outcome for these patients.

Allergic-type reactions, e.g., anaphylactoid reaction, laryngeal edema, orolingual angioedema, rash, and urticaria have been reported.
Monitor BP

- Every 15 minutes for 2 hours from the start of alteplase therapy;
- Then every 30 minutes for 6 hours; and
- Then every hour for 16 hours

If systolic BP is 180-230 mm Hg or diastolic BP is 105-120 mm Hg, administer:

- 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 is not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside.

Please see Important Safety Information throughout and the accompanying full Prescribing Information.
Perform neurologic assessment\textsuperscript{2}

The use of a stroke rating scale, preferably the NIHSS, is recommended.

- Repeat every 15 minutes during the 1-hour infusion to monitor for neurologic deterioration

Check for major and/or minor bleeding

All body secretions should be tested for occult blood.\textsuperscript{11}

- Major bleeding: intracranial, retroperitoneal, gastrointestinal, or genitourinary hemorrhages\textsuperscript{12}

- Minor bleeding: gums, venipuncture sites, hematuria, hemoptyisis, skin hematomas, or ecchymosis\textsuperscript{12}

- Arterial and venous punctures should be minimized and checked frequently\textsuperscript{9,11}
Monitor blood pressure every 15 minutes during the 1-hour infusion

- Once intravenous alteplase is given, the blood pressure must be maintained below 180/105 mm Hg to limit the risk of ICH.
- Administer antihypertensive medications to maintain blood pressure at or below these levels.

Discontinue infusion and obtain an emergency CT scan if the patient develops severe headache, acute hypertension, nausea, or vomiting or has a worsening neurologic examination.

Monitor for signs of orolingual angioedema

If angioedema is noted, promptly institute appropriate therapy and discontinue alteplase infusion.
Continue to monitor for neurologic deterioration\textsuperscript{2,12}
- Every 15 minutes for the first hour after the infusion is stopped
- Every 30 minutes for the next 6 hours
- Hourly from the eighth postinfusion hour until 24 hours after the infusion is stopped

Continue to check for major and/or minor bleeding\textsuperscript{12}

Continue to monitor and control blood pressure\textsuperscript{2,12}
- Every 15 minutes for the first hour after the infusion is stopped
- Every 30 minutes for the next 6 hours
- Hourly from the eighth postinfusion hour until 24 hours after the infusion is stopped
Obtain a follow-up CT scan or MRI at 24 hours before starting anticoagulants or antiplatelet agents.²

Continue to monitor for signs of orolingual angioedema⁹
References