Title:	**Evaluation and Management of Acute Ischemic Stroke: IV tPA**
Number:	**CSC-1**
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Source
This protocol is adapted primarily from the American Heart Association/American Stroke Association guidelines statements on the treatment of acute ischemic stroke.

Treatment Goal
All eligible patients, based on the criteria below, should be given IV tPA as soon after stroke onset as possible, whether or not there are plans to proceed to acute endovascular therapy.

Time Goals
- Door to CT: < 25 minutes
- Door to CT interpretation: < 45 minutes
- Door to needle: < 60 minutes

Inclusion Criteria
- Diagnosis of acute ischemic stroke causing significantly disabling neurological deficit; the following should typically be considered disabling, despite low NIHSS:
  - Complete hemianopsia (≥ 2 on NIHSS question 3)
  - Severe aphasia (≥ 2 on NIHSS question 9)
  - Visual or sensory extinction (≥ 1 on NIHSS question 11)
  - Any weakness limiting sustained effort against gravity (≥ 2 on NIHSS question 5 or 6)
  - Any deficit leading to total NIHSS score > 5
  - Any deficit considered potentially disabling in the view of the patient and the treating practitioner. Clinical judgment is required.
- Onset of symptoms < 4.5 hours before beginning treatment (see below for additional restrictions on treatment in 3-4.5 hr window)
- Age ≥ 18 years

Exclusion Criteria

- Significant head trauma or prior stroke in the 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 BP (SBP > 185 mm Hg or DBP > 110 mm Hg)
- Active internal bleeding
- Acute bleeding diathesis, including but not limited to
    - Platelet count < 100,000/mm^3 (*In patients without history of thrombocytopenia, treatment with IV tPA can be initiated before availability of platelet count but should be discontinued if platelet count is < 100,000/mm^3.*)
    - Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal*
    - LMWH dose within the previous 24 hours
    - Current use of anticoagulant with INR > 1.7 or PT > 15 seconds (*In patients without history of recent use of oral anticoagulants or heparin, treatment with IV tPA can be initiated before availability of coagulation tests results but should be discontinued if INR > 1.7 or PT is abnormally elevated by local laboratory standards.)*
- Current use of direct thrombin inhibitors or direct factor Xa inhibitors within the prior 48 hours, unless the following laboratory tests are normal: aPTT, INR, platelet count, AND thrombin time (TT) (or ecarin clotting time, ECT) in patients on dabigatran or anti-Xa activity in patients on a factor Xa inhibitor (rivaroxaban, apixaban, edoxaban, fondaparinux).
- Blood glucose < 50 mg/dl (2.7 mmol/L)
- CT demonstrates multilobar infarction (hypodensity > 1/3 cerebral hemisphere)

Relative Exclusion Criteria

1. Recent experience suggests that under some circumstances – with careful consideration and weighing of risks and benefits – patients may receive fibrinolytic therapy despite 1 or more relative contra-indications. Consider risk to benefit of IV tPA administration carefully if any of these relative contra-indications is present:
    - Only minor or rapidly improving stroke symptoms (clearing spontaneously)
    - Pregnancy (*This item is included based on guidelines, however, we do not consider pregnancy alone to be a contra-indication.*[3])
    - Early postpartum period (< 14 days after delivery)
    - Seizure at onset with postictal residual neurologic impairments
    - Major surgery or serious trauma within the previous 14 days
    - Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
    - Recent acute myocardial infarction (within previous 3 months)

Additional Relative Contra-Indications for Patient Considered for Treatment in the 3-4.5 Hour Window

2. Age > 80 years
3. NIHSS > 25
4. Taking oral anticoagulants regardless of the INR
5. History of both diabetes and prior ischemic stroke

Pre-Treatment Evaluation

- Temperature, pulse, BP, respirations
- Physical exam / neurologic exam with NIHSS
- EKG
- CBC with platelets, basic metabolic panel, INR, LFTs, aPTT may be ordered. Only the assessment of blood glucose must precede the initiation of IV alteplase in all patients. IV alteplase should not be delayed while waiting for hematologic or coagulation testing if there is no reason to suspect an abnormal test.[4]
- Urine HCG in women of child-bearing potential
- Blood for type and screen
- Stroke-protocol head CT: Head CT with CTA of the head and neck vessels.

Pre-Treatment Management of BP

At the time of initiation of infusion of IV tPA, BP should be ≤ 185/110. If BP is greater than this, then use IV labetalol or nicardipine or another appropriate agent for immediate BP control. See full protocol for BP management before and after IV tPA administration (Appendix A).

The Infusion

6. Weight may be estimated
7. Dose: 0.9 mg/kg (maximum dose of 90 mg)
8. Give 10% as a bolus over 1 minute followed by the remaining 90% as a continuous infusion over 60 minutes; using Smart pump (see Dose Table, Appendix B)
9. If the patient develops symptoms of ICH (e.g. headache, nausea, vomiting, or new focal symptoms or signs), discontinue infusion and obtain a STAT non-contrast head CT.

Post-Treatment Management

- NeuroICU admission for monitoring for at least 24 hours after IV tPA
- Vital signs and neuro assessments every 15 minutes for 2 hours from the start of tPA therapy, then every 30 minutes for 6 hours, and then every hour for 16 hours
- Strict control of BP for 24 hours based on the protocol (Appendix A)
- Pulse oximeter; oxygen cannula or mask to maintain O_2 saturation ≥ 95%
- Acetaminophen 650 mg PO/PR every 4 hours for T > 99.4; cooling blanket for T > 102; set to avoid shivering (see Shivering Treatment Protocol)
- If considering antiplatelet agents or anticoagulants in the first 24 hours, verify fibrinogen > 100, aPTT < 80
- No Foley catheter, nasogastric tube, arterial catheter or central venous catheter for 24 hours, unless absolutely necessary
- STAT head CT for any worsening of neurologic condition

For acute stroke immediately after diagnostic angiography

- If a femoral arterial sheath is in place, DO NOT REMOVE IT. The sheath should remain sutured in place while tPA is given. Consider immediate endovascular therapy as an alternative to IV tPA, if the sheath can be accessed and the Interventional Neuroradiology Staff are immediately available. If not, and the patient is eligible for IV tPA, administer full dose (0.9 mg/kg, to maximum 90 mg). In all cases, leave the sheath in place and check STAT CBC, aPTT, INR, and fibrinogen. Monitor the groin site and flank for the development of a hematoma, follow vital signs and Hb/Hct for evidence of blood loss. If a hematoma forms or there is evidence of blood loss, page Vascular Surgery (pager #11950) and apply pressure until hemostasis is achieved. If bleeding continues, give RiaSTAP (pooled fibrinogen) (see Protocol: Guidelines for the Management of Symptomatic Hemorrhage After Alteplase, Appendix C). Vascular Surgery may choose to repair the artery surgically. If no bleeding occurs, the sheath can be removed after 24 hours. If the patient is anticoagulated and cannot be reversed, Vascular Surgery will surgically close the artery in the OR.

For acute stroke days or weeks after transfemoral diagnostic angiography

- If a femoral arterial sheath has been pulled within 2 weeks of stroke onset, carefully weigh the risk of bleeding against the benefits of IV tPA therapy. If tPA is given, notify Vascular Surgery prior to drug administration. Monitor the groin site and flank for the development of a hematoma, and closely and follow vital signs and Hb/Hct for evidence of blood loss. (Occult blood loss may occur into the retroperitoneal space.) If a hematoma forms or there is evidence of acute blood loss, notify Vascular Surgery and apply direct pressure until hemostasis is achieved. If occult blood loss is suspected, obtain an abdominal CT to look for retroperitoneal hematoma. If bleeding continues, give RiaSTAP (pooled fibrinogen) (see Protocol: Guidelines for the Management of Symptomatic Hemorrhage After Alteplase, Appendix C).

For symptomatic intracranial hemorrhage after IV tPA infusion

- If the neurological examination worsens or there is another reason to suspect intracranial hemorrhage, obtain a STAT head CT.
- Check CBC, INR, aPTT, fibrinogen, and D-dimer.
- Follow the protocol: Guidelines for the Management of Symptomatic Hemorrhage After Alteplase, (Appendix C)
- If heparin is being given, give protamine sulfate 1 mg/100 U heparin received in the prior 3 hours (Give 10 mg test dose slowly IVP over 10 minutes and observe for anaphylaxis; if stable, give the entire calculated dose slow IVP; maximum dose 50 mg)
- Consider administration of platelets if:
    - The patient was taking aspirin prior to tPA administration
    - Platelets < 100K
- May consider aminocaproic acid (Amicar) for severe uncontrolled bleeding (administered initially at 5 g given over 1 hour, followed by 1 g/hr for 5-8 hours or until bleeding is controlled; maximum dose is 24 g/24 hr) (*amicar DAG link*)
- Institute frequent neuro checks and therapy for acutely elevated ICP as needed.

References

1. Jauch EC, et al. Guidelines for the early management of patients with acute ischemic stroke. Stroke 2013; 44:870-947.

2. Demaerschalk BM, et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke. Stroke 2016;47:581-641

3. Razmara, et al. Cerebrovascular complications of pregnancy and the postpartum period. Curr Cardiol Rep 2014;16:532-

4. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the american heart Association/American stroke association. *Stroke*. 2018;49(3):e46-e99.

Appendix A: Treatment of Elevated BP Before and After Administration of IV tPA[1]

Patients otherwise eligible for acute reperfusion therapy, except that BP is > 185/110 mm Hg:

- 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 5-10 minutes, maximum 15 mg/h; when desired BP is reached, adjust to maintain proper BP limits; or
- Other agents (hydralazine, enalaprilat, etc) may be considered when appropriate

If BP is not maintained at or below 185/110 mm Hg, do not administer tPA.

Management of BP during and after tPA or other acute reperfusion therapy to maintain BP at or below 180/105 mm Hg:

- Monitor BP every 15 minutes for 2 hours from the start of tPA therapy, then every 30 minutes for 6 hours, and then every hour for 16 hours
- If SBP > 180 mm Hg or DBP > 105 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 is not controlled by the above regimen or if DBP > 140 mm Hg, consider IV Na nitroprusside (begin at a low dose of 5 microg/min to avoid precipitous drop in BP and titrate upwards every few minutes to achieve desired BP). Dose range: 0.25 – 10 microg/kg/min

Appendix B: tPA Weight-Dose Chart for Treatment of Acute Ischemic Stroke

Note: 1 vial contains 100 mg tPA. This is mixed with 100 cc of sterile water to make a solution of 1 mg/ml.

Weight (kg)	*Weight (lbs)*	*Total Dose (mg)*	*Bolus Dose (mg)*	*Infusion Dose (mg)*	*Infusion Rate (mg/hr)*
40-41	88-91	36	4	32	32
42-43	92-95	38	4	34	34
44-45	96-100	40	4	36	36
46-47	101-104	41	4	37	37
48-49	105-108	43	4	39	39
50-51	109-113	45	5	40	40
52-53	114-117	47	5	42	42
54-55	118-122	49	5	44	44
56-57	123-126	50	5	45	45
58-59	127-130	52	5	47	47
60-61	131-135	54	5	49	49
62-63	136-139	56	6	50	50
64-65	140-144	58	6	52	52
66-67	145-148	59	6	53	54
68-69	149-152	61	6	55	55
70-71	153-157	63	6	57	57
72-73	158-161	65	7	58	58
74-75	162-166	67	7	60	60
76-77	167-170	68	7	61	61
78-79	171-174	70	7	63	63
80-81	175-179	72	7	65	65
82-83	180-183	74	7	67	67
84-85	184-188	76	8	68	68
86-87	189-192	77	8	69	69
88-89	193-196	79	8	71	71
90-91	197-201	81	8	73	73
92-93	202-205	83	8	75	75
94-95	206-210	85	9	76	76
96-97	211-214	86	9	77	77
98-99	215-218	88	9	79	79
≥ 100	≥ 219	90	9	81	81

tPA Bolus Dose Rate Chart for Acute Stroke Therapy

Dose	***Pump Settings***	***Duration***	***Volume Setting***
4 mg	120 ml/hr	2 minutes	4 ml
5 mg	150 ml/hr	2 minutes	5 ml
6 mg	180 ml/hr	2 minutes	6 ml
7 mg	210 ml/hr	2 minutes	7 ml
8 mg	240 ml/hr	2 minutes	8 ml
9 mg	270 ml/hr	2 minutes	9 ml

Appendix C: Guidelines for the Management of Symptomatic Hemorrhage After Alteplase (tPA)

Source
This protocol was developed by the Stroke Division in collaboration with the BWH Pharmacy.

- STAT head CT, if ICH is suspected
- Consult Neurosurgery for ICH
- Check CBC, PT, PTT, platelets, and D-dimer. Repeat every 2 hours until bleeding is controlled
- Check fibrinogen STAT
- **If a serious head bleed suspected post tPA administration, initiate fibrinogen concentrate (RiaSTAP ®) and administer 2 vials STAT** (each vial contains estimated 900 mg to 1300 mg of fibrinogen); **do not need to wait for initial fibrinogen level prior to RiaSTAP® administration** ***(if RiaSTAP® not available, administer 20 units of cryoprecipitate STAT*)**
    - **If the initial fibrinogen level comes back less than or equal to 100 mg/dL, administer additional 2 vials of RiaSTAP® *(if RiaSTAP® not available, administer additional 20 units of cryoprecipitate STAT*)**
    - If the initial fibrinogen level is greater than 100 mg/dL, check a post administration fibrinogen level before re-dosing
- Check a second fibrinogen level 1 hour post administration of either 2 or 4 vials of RiaSTAP® (or total cryoprecipitate administered)
    - If fibrinogen level comes back less than 200 mg/dL, administer additional 2 vials of RiaSTAP ® (or additional 20 units of cryoprecipitate if RiaSTAP® not available)
- Fibrinogen levels can be repeated every 2 hours until bleeding is controlled
- After adequate fibrinogen replacement, patient can be assessed for need of fresh frozen plasma (FFP). FFP administration is usually not needed in reversing symptomatic hemorrhage after alteplase, but can be considered if:
    - Fibrinogen greater than 100 and PT or PTT still prolonged
    - Patient was anticoagulated prior to alteplase administration
    - If FFP deemed necessary, give 2 units every 6 hours for 24 hours
- Consider administering platelets if:
    - Patient was taking aspirin prior to alteplase administration
    - Platelets < 100K
- May consider aminocaproic acid (Amicar®) administered initially at 5 grams given over 1 hour, followed by 1gram/hr for 5-8 hours or until bleeding is controlled. Maximum dose is 24grams/24hours as a last resort (*amicar DAG link*)
- Institute frequent neurochecks and therapy of acutely elevated ICP, as needed