Audio-Digest® EMERGENCY MEDICINE

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VASCULAR EMERGENCIES

ACUTE STROKE TREATMENT — Justin A. Sattin, MD, Stroke Fellow, University of California, San Diego, School of Medicine

Acute ischemic stroke: 80% of strokes ischemic, 20% hemorrhagic; frontotemporal brain lesions cause speech problems; cerebellar lesions cause balance problems; number of functions mediated by brain pose clinical challenge, compared to diseases with target pain and specific symptoms; patients with insensate brain often unaware of deficit

American Heart Association/American Stroke Association: *stroke warning signs* — sudden onset of 1) numbness and weakness, 2) confusion (covers fluent aphasia, *ie,* speaking gibberish), 3) visual loss in one or both eyes (visual field cut usual but monocular vision loss less common), 4) dizziness (suspicious if accompanied by dysarthria, diplopia, weakness, and sensory changes), 5) severe headache (intracerebral hemorrhage causes pain)

Left hemisphere stroke: causes aphasia; gaze deviation on left side; left hemisphere stroke sometimes followed by seizure that pins eyes to right side (eyes drift back to left when seizure ends); eyes will drift toward side of lesion in hemispheric infarction

Right hemisphere stroke: eyes drift right; left-sided visual field cut, weakness, sensory disturbance; issue of neglect unique to right hemisphere stroke; patient loses concept of leftness; rehabilitation difficult and patients do not do as well

Cerebellar stroke: causes dysarthria and ataxia

Brainstem stroke: associated with crossed signs; weakness and sensory loss on one side of face and opposite side of body concerning for brainstem stroke; illustrated by lateral medullary syndrome; presents with routine stroke signs

Hemorrhagic stroke: not qualitatively different from ischemic stroke; very high blood pressure (BP), *eg,* 260 mm Hg, and rapid decline in consciousness; flexor or extensor posturing

Medical emergency: need to recognize stroke as emergency like cardiac arrest; "code of a different flavor"

Clinical work-up: fresh set of vital signs, finger-stick glucose, electrocardiography (ECG), and noncontrast head computed tomography (CT)

Evaluation of stroke patient: seizure mimics stroke in ocular motility, so important for physician to obtain good history to rule out convulsion or epilepsy; also exclude hypoglycemia (can mimic stroke) and migraine; *anamnestic response* — symptoms of past stroke re-emerging due to another problem, *eg,* UTI; severity of new problem does not outstrip original problem; psychiatric symptoms may be present

Time of onset: ask relatives, witnesses; if "911" call placed, obtain time of call from emergency medical technician; sometimes detective work necessary (*eg,* man's receipt from store issued hours before stroke enabled physicians to estimate time of onset)

Computed tomography: confirms diagnosis (hemorrhagic or ischemic); in hyperacute settings, CT often normal (usual in patient with no history of stroke)

Proven treatments: *intravenous (IV) tissue plasminogen activator (tPA)* — National Institute of Neurological Disorders and Stroke (NINDS) ≈10 yr ago funded pivotal study in which tPA given as 10% bolus and 90% over 1 hr; results showed 10-fold higher hemorrhage rate in treatment arm than placebo arm; outcomes data in National Institutes of Health (NIH) Stroke Scale (NIHSS) showed tPA beneficial across board; relative benefit 50% on Modified Rankin scale (outcome measure used most by neurologists); number needed to treat (NNT) 7.7 (compares favorably with other medical interventions); mortality rate little lower for tPA but not statistically significant; *aspirin* — 2 trials (40,000 patients) showed aspirin can prevent death or nonfatal stroke in 1 of every 111 treated; does not compare to tPA result, so aspirin not viable alternative

Other treatments: *heparin* — not shown useful for acute stroke; study showed slight decrease in stroke recurrence offset by increase of same magnitude in hemorrhagic stroke

Neuroprotection: *hypothermia* — well-known neuroprotector; good data in cardiac arrest, conflicting data in traumatic brain injury; used in some surgical procedures; preclinical data available on brains with large infarctions not exposed to hypothermia and very small infarctions in brains exposed to hypothermia; pilot studies include one using surface cooling with blankets and one using catheter in femoral vein (catheter cools core temperature)

Intravascular Cooling for the Treatment of Stroke–Longer window (ICTus-L) trial: ongoing at speaker's center; patient presenting within 3 hr receives tPA (standard of care), then randomized to receive hypothermia or not; testing hypothesis that hypothermia will extend window for giving tPA and reduce bleeding risk

NXY 059: neuroprotective strategy under investigation; free radical scavenger made by AstraZeneca; testing for ischemic stroke and intracerebral hemorrage; *Stroke Acute Ischaemic NXY-059 Treatment (SAINT) I and II* — Saint I European version and Saint II US version of trial for ischemic stroke; data show adverse and serious events same for drug and placebo

Safety of tPA administration: recent study suggested one major impediment to stroke patients receiving tPA was clinicians' fear of hemorrhage risk; emergency department (ED) physicians, when polled, stated hemorrhage rate of 2% or 3% would make them more comfortable with using drugs

Magnetic resonance imaging (MRI) technologies: trial under way in which patients receive MRI, then device used for removal of clot; using Merci Retrieval (system), insert catheter, inflate balloon to occlude forward flow, snag clot on corkscrew-shaped device, retract it inside catheter, deflate balloon, and pull clot out

Intra-arterial thrombolysis: *Prolyse in Acute Cerebral Thromboembolism (PROACT) trial* — prourokinase (plasminogen activator) used within 6-hr window; agent squirted directly onto clot; had to have occlusion in M1 or M2 segments; results showed hemorrhage risk 10% at 24 hr up to 10 days, compared to risk of 2% rising over time in placebo arm; much higher than hemorrhage rate (0.6%) in IV tPA trial (attributed to more severe strokes in PROACT subjects); overall, positive trial on par with tPA trial; Food and Drug Administration (FDA) required second trial due to relatively small numbers

Hemicraniectomy: not proven therapy; in review of 140 patients, those <50 yr of age had reasonable chance of good outcome; all studies observational; physician can try approach if patient young, deteriorating, and family wants to pursue all avenues

Transcranial ultrasonography (US): can potentiate tPA; study pending

Laser therapy: appears to improve outcomes when delivered to brain, but reasons unclear; some animal data

Hypobaric O_2: in early testing stage

Estimated time to complete the educational process:			
Review Educational Objectives on page 3	5 minutes	Listen to audio program	60 minutes
Take pretest	10 minutes	Review written summary and suggested readings	35 minutes
		Take posttest	10 minutes

UPDATES IN STROKE AND TIA — Wade S. Smith, MD, Professor of Neurology, and Director, Neurovascular Service, University of California, San Francisco, School of Medicine

Stroke after transient ischemic attack (TIA): clinical view of TIA now as "unstable angina of the brain"

Clinical factors enhancing likelihood of stroke after TIA: 1) age >60 yr; 2) motor weakness (objective finding); 3) duration of TIA >10 min; 4) speech or language problem of any kind (*eg,* garbled speech); 5) diabetes; if none of 5 factors present at 90 days, no patient had stroke; when 5 present, 35% of patients had stroke within 90 days

What can be done for TIA patient: clinician should not miss 1) atrial fibrillation (ECG combined with review of systems questions sufficient to rule out in ED) or 2) carotid disease (not all settings have technology to noninvasively image carotid artery); for all other patients, give angiotensin-converting enzyme (ACE) inhibitor, statin, and antithrombotic agent (*eg,* aspirin, dipyridamole and aspirin [Aggrenox], clopidogrel [Plavix])

Standard of care: if no contraindication for antithrombotic drug, start with aspirin; if patient already on aspirin, change to clopidogrel 75 mg/day or Aggrenox (one tablet bid); ongoing trial (Prevention Regimen For Effectively avoiding Second Strokes [PRoFESS]) investigating whether clopidogrel or Aggrenox best therapeutic route; *atrial fibrillation* — put patients on warfarin (Coumadin); explain to patient Coumadin drug of choice

Outcome modification: if TIA related to carotid artery, risk for stroke within 30 days as high as 20%; do not wait weeks for carotid US and specialist follow-up; need to identify modifiable factors such as high BP and age early; clinician can revascularize, lower BP over time, treat glucose, keep temperature down, and utilize advanced rehabilitation techniques and stroke facilities to modify stroke outcome; identifying blood vessel blocked in brain now target issue (important outcome determinant in ischemic stroke [85% of all strokes] in light of new revascularization techniques for large vessel occlusions)

Bleeding in brain or ischemia: first question in traditional approach; heavily based on imaging; speaker advocates use of spiral CT followed by CT perfusion scan, which allows patients to be imaged with protocol lasting 25 min; can produce perfusion map of brain

CT angiography (CTA): gaining ground as standard of care; can go from vertex of skull through aortic arch down to diaphragm with single bolus of contrast (70 mL); *study* — speaker's experience of 2100 imaging studies using protocol; data on ≈1000 with follow-up creatinine; of ≈2 000 patients imaged, 2 required temporary hemodialysis due to contrast nephropathy (deemed "measurable risk" and practice continued for benefits of large-scale data collection); *reconstruction images* — data "phenomenal"; can peel bone away to view vessels; speaker's team prefers "thick nip" reconstruction images; black and white; sufficient to rule out carotid disease; can produce perisagittal reconstructions; can measure degree of stenosis accurately on cross-sectional images for which good correlation with catheter-based angiography; negative predictive value 100%; calcification of plaque may necessitate additional imaging studies; speaker endorses CTA screening for uncomplicated carotid disease; emerging use of angioplasty for risky intracranial vessels

Aneurysms: subarachnoid hemorrhage should be treated as emergency; never submitted for randomized trial; large movement to adopt endovascular route for treating aneurysm by putting coil inside aneurysm to thrombose it; avoids craniotomy but requires additional angiography

International Subarachnoid Aneurysm Trial (ISAT): published 2 yr ago, follow-up published recently in *Lancet*; investigated surgical *vs* endovascular treatment in randomized trial; surgery associated with higher mortality; study stopped due to mortality; rebleeding rates similar between 2 arms; more neurosurgeons starting to use coil on aneurysms, but still need to treat some aneurysms surgically; ideal to offer both treatment options

Intracranial hemorrhage due to hypertension: phase 2 trial published in *New England Journal of Medicine* investigated use of coagulation factor VIIa (NovoSeven) in patients with hypertensive intracranial bleed; hematoma expansion primary outcome; if CT performed within few hours of onset (*eg,* 3 hr), one third of patients have larger hematoma detected on CT at 6 hr; another trial explored prevention of hematoma expansion; showed hematoma expansion and mortality reduced if NovoSeven given within 4 hr (surprising outcome); speaker's group not using NovoSeven because not yet proven (phase 3 trial ongoing); may see development in this area

Ischemic stroke and tPA window: start secondary prevention at time of arrival; for thrombolysis and thrombectomy, can invoke time window of 0 to 3 hr used to study IV tPA; *New England Journal of Medicine* published results of trial in 1995 that showed patients randomized to tPA *vs* placebo within 3 hr have improved neurologic outcome at 90 days; number of scales indicated neurologic recovery improved if tPA given to proper patient, but not without risk; intracranial hemorrhage rate 6% in patients who received tPA, compared to 0.6% for placebo arm (10-fold increase; half of events fatal, and no difference in mortality)

Informed consent: speaker's group informs patients and their families about trial results; most patients elect tPA; if use off-label, inform patients; aim to foster medical system that can respond quickly and carry out ancillary testing and where patients can opt to "say no" to tPA

Use of tPA: emergency medical societies state tPA not standard of care; >50% of EDs in United States not giving tPA; liability issue; rare for ED physician to take on responsibility; key elements radiology and having neurologist willing to assist in protocol

Primary stroke centers: credentialed by Joint Commission on Accreditation of Healthcare Organizations (JCAHO); credential improves level of care in institution treating stroke; of >5000 major hospitals in United States, 500 to 600 have made application; next level comprehensive stroke center with interventional capabilities

Intra-arterial prourokinase: PROACT II randomized trial of intra-arterial recombinant prourokinase included patients that arrived in 3- to 6-hr window; aimed to safely open middle cerebral artery occlusion; 40% of patients achieved clinical end point, 25% did not (absolute clinical benefit 15%); problem intracranial hemorrhage; FDA has not approved prourokinase, so most centers using off-label intra-arterial tPA and urokinase to try to open vessels; difficult where large clot burden exists

Thrombectomy: next step; attempted in 1960s but morbid procedure so not pursued; longer catheters can now access all large vessels in neurovasculature; *case report* — young man with touch football injury and subsequent embolus; beyond tPA window on admission; patient underwent attempted thrombectomy for basilar artery occlusion (if untreated, mortality 90%); procedure carries risk of traumatizing vessels (requires blind stick to go through clot); *technique* — use balloon-guided catheter to introduce microwire through carotid into blocked vessel; pierce clot with wire; deliver nitinol memory wire which has distal corkscrew, and embed into clot; proximally, inflate balloon to arrest flow and fragmentation; pull back and use 100 mL syringe to vacuum out clot

Summary: catheter techniques work 48% of time; tPA intra-arterially can achieve opening 60% to 70% of time; pretreating with tPA, then using device known to be safe; most stroke neurologists believe IV tPA proven to improve outcome, and FDA approved label change to allow for acute ischemic stroke; prourokinase believed to work but not approved; thrombectomy not proven and not tested in randomized trial, so can be said to restore perfusion in ischemic stroke but not treat ischemic stroke (approved because device not drug)

Educational Objectives

The goal of this program is to educate the listener about emergency care for stroke and new diagnostic and treatment issues in transient ischemic attack (TIA) and stroke. After hearing and assimilating this program, the clinician will be better able to:

1. Evaluate a stroke patient using key diagnostic criteria.
2. Discuss the findings of the National Institute of Neurological Disorders and Stroke (NINDS) trial of tissue plasminogen activator (tPA) therapy and the implications for patients and families making decisions about stroke treatment.
3. List 5 clinical factors that enhance the likelihood of stroke after a transient ischemic attack (TIA).
4. Identify the risk factors and modifiable risk factors in determining a course of treatment for a patient with acute stroke.
5. Become aware of new uses of catheter techniques and computed tomography angiography in stroke.

Discussed on This Program

Aspirin (acetylsalicylic acid; ASA) [several trade names]
Coagulation factor VIIa (recombinant) [NovoSeven]
Clopidogrel bisulfate [Plavix]
Dipyridamole and aspirin [Aggrenox]
PROACT (Prolyse {recombinant prourokinase} in acute cerebral thromboembolism) (investigational)
Tissue plasminogen activator, recombinant (tPA)
Warfarin sodium [Coumadin]

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To locate lectures of related interest, or to see a complete listing of Audio-Digest CME Programs, including written summaries.

Suggested Reading

Adams HP Jr: Treatment of acute ischemic stroke: selecting th.right treatment for the right patient. *Eur Neurol* 45:61, 2001; **Ay H et al:** Transient ischemic attack: are there different types or classes? Risk of stroke and treatment options. *Curr Treat Options Cardiovasc Med* 8:193, 2006; **Berthet JP et al:** Acute carotid artery thrombosis: description of 12 surgically treated cases. *Ann Vasc Surg* 19:11, 2005; **Brown DL et al:** Survey of emergency physicians about recombinant tissue plasminogen activator for acute ischemic stroke. *Ann Emerg Med* 46:56, 2005; **Bruno A:** Predicting rtPA associated ICH in acute stroke. *Stroke* 35:2762; author reply 2762, 2004; Epub 2004 Oct 28. **Chuang YM et al:** Use of CT angiography in patient selection for thrombolytic therapy. *Am J Emerg Med* 21:167, 2003; **Deshmukh VR et al:** Intra-arterial thrombolysis for acute ischemic stroke: preliminary experience with platelet glycoprotein IIb/IIIa inhibitors as adjunctive therapy. *Neurosurgery* 56:46, 2005; **Frey JL:** Recombinant tissue plasminogen activator (rtPA) for stroke. The perspective at 8 years. *Neurologist* 11:123, 2005; **Furlan AJ et al:** When is thrombolysis justified in patients with acute ischemic stroke? A bioethical perspective. *Stroke* 28:214, 1997; **Giles MF et al:** Patient behavior immediately after transient ischemic attack according to clinical characteristics, perception of the event, and predicted risk of stroke. *Stroke* 37:1254, 2006; Epub 2006 Mar 30. **Gutierrez M et al:** Thrombolysis and neuroprotection in cerebral ischemia. *Cerebrovasc Dis* 21 Suppl 2:118, 2006; Epub 2006 May 2. **Imai K et al:** Successful thrombectomy in acute terminal internal carotid occlusion using a basket type microsnare in conjunction with temporary proximal occlusion: a case report. *AJNR Am J Neuroradiol* 26:1395, 2005; **Kent DM et al:** Sex-based differences in response to recombinant tissue plasminogen activator in acute ischemic stroke: a pooled analysis of randomized clinical trials. *Stroke* 36:62, 2005; Epub 2004 Nov 29. **Kwiatkowski T et al:** National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. The impact of imbalances in baseline stroke severity on outcome in the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study. *Ann Emerg Med* 45:377, 2005; **Pomerantz SR et al:** Computed tomography angiography and computed tomography perfusion in ischemic stroke: A step-by-step approach to image acquisition and three-dimensional postprocessing. *Semin Ultrasound CT MR* 27:243, 2006; **Reeves MJ et al:** Acute stroke care in the US: results from 4 pilot prototypes of the Paul Coverdell National Acute Stroke Registry. *Stroke* 36:1232, 2005; Epub 2005 May 12. Erratum in: Stroke. 2005 Aug;36(8):1820. **Smith WS:** Safety of mechanical thrombectomy and intravenous tissue plasminogen activator in acute ischemic stroke. Results of the multi Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, part I. *AJNR Am J Neuroradiol* 27:1177, 2006; **Suzuki S et al:** Use of multimodal MRI and novel endovascular therapies in a patient ineligible for intravenous tissue plasminogen activator. *Stroke* 36: e77, 2005; Epub 2005 Jul 28. **Sylaja PN et al:** Role of CT angiography in thrombolysis decision-making for patients with presumed seizure at stroke onset. *Stroke* 37:915, 2006; Epub 2006 Feb 2. **Tanne D et al:** Hemostatic activation and outcome after recombinant tissue plasminogen activator therapy for acute ischemic stroke. *Stroke* 37:1798, 2006; Epub 2006 Jun 8. **Toni D et al:** Specific therapies for ischaemic stroke: rtPA and others. *Neurol Sci* 26 Suppl 1:S26, 2005; **Zaidat OO et al:** Thrombolytic therapy of acute ischemic stroke: correlation of angiographic recanalization with clinical outcome. *AJNR Am J Neuroradiol* 26:880, 2005.

Faculty Disclosure

In adherence to ACCME guidelines, the Audio-Digest Foundation requests all lecturers to disclose any significant financial relationship with the manufacturer or provider of any commercial product or service discussed. For this issue, the faculty reported nothing to disclose.

Dr. Sattin spoke at *Critical Care,* held July 21-23, 2005, in San Diego, CA, and sponsored by the University of California, San Diego, School of Medicine. Dr. Smith spoke at *Topics in Emergency Medicine,* held October 24-27, 2005, in San Francisco, CA, and sponsored by the University of California, San Francisco, School of Medicine. The Audio-Digest Foundation thanks the speakers and the sponsors for their cooperation in the production of this program.

VASCULAR EMERGENCIES

*On a Test and Evaluation form, complete Pretest section **before** listening and Posttest section **after** listening.*

1. Heparin has not been shown to have any useful effect in the management of acute stroke.
   (A) True (B) False
2. As part of the National Institute of Neurological Disorders and Stroke (NINDS)-funded study 10 yr ago of tissue plasminogen activator (tPA) in stroke, what dosage of tPA was administered to the treatment arm?
   (A) tPA as 10% bolus; 90% over 1 hr
   (B) tPA as 50% bolus; 50% over 1 hr
   (C) tPA as 100% over 1 hr
   (D) None of the above
3. The NINDS study of tPA proved to be a turning point in stroke medicine by showing a:
   (A) Twenty-fold higher hemorrhage rate in the treatment arm
   (B) Higher mortality rate in the treatment arm
   (C) Relative benefit of 50% for tPA
   (D) Higher mortality in the placebo group
4. Results of 2 trials of aspirin in stroke involving 40 000 subjects showed:
   (A) Aspirin is not a viable alternative to tPA
   (B) Benefits greater than those for tPA in the NINDS tPA trial
   (C) Comparable benefits to tPA in the NINDS tPA trial
   (D) None of the above
5. Crossed signs are an indicator of _____ stroke.
   (A) Brainstem (C) Cerebellar
   (B) Hemorrhagic (D) Right hemisphere
6. Garbled speech or talking gibberish is 1 of 5 clinical factors that indicate a greater likelihood of a stroke after a transient ischemic attack (TIA).
   (A) True (B) False
7. If a TIA is related to the carotid artery, the risk for stroke within 30 days is as high as:
   (A) 5% (B) 10% (C) 15% (D) 20%
8. The Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial of intra-arterial prourokinase to open a middle cerebral artery occlusion found the main obstacle to achieving clinical end point in ischemic stroke was:
   (A) Intracranial hemorrhage (C) Intracranial clotting
   (B) Intracranial infarction (D) Increased intracranial pressure
9. The "tPA window" for patients to receive intravenous (IV) tPA that was shown to improve neurologic outcome at 90 days in a 1995 *New England Journal of Medicine* study refers to how many hours after a stroke event?
   (A) 0 to 2 (B) 0 to 3 (C) 0 to 6 (D) 3 to 6
10. Primary stroke centers are believed to provide their institutions with:
    (A) A credentialed, improved standard of stroke care
    (B) A nursing home
    (C) A way to cut administration and medical costs by treating more patients in fewer beds
    (D) An opportunity to test new pharmaceutical agents

Answers to Audio-Digest Emergency Medicine Volume 23, Issue 15: 1-A, 2-A, 3-A, 4-A, 5-B, 6-A, 7-A, 8-D, 9-A, 10-D

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