Stroke overview: Current and future treatments

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March 4, 2013

Disclosures

• None
• Discussion of investigational devices for acute stroke treatment
Objectives

- To become familiar with the spectrum and management of acute ischemic and hemorrhagic stroke subtypes.
- To correctly identify the signs/symptoms of stroke and perform a stroke-centered neurological exam/National Institutes of Health Stroke Scale (NIHSS).
- To know the time windows and treatment options for acute stroke interventions.

True or False?

- Acute stroke is the 3rd leading cause of death. True
- The time limit for IV-tPA is 4.5 hours. True
- IV-tPA is equally effective throughout the first 3 hours of stroke. False
- Lacunar infarcts do not benefit from IV-tPA. False
- The majority of patients with aneurysms will have a SAH. False
- The majority of SAH patients have an aneurysm. True
Epidemiology

• 4th leading cause of death
  – 2202 fewer deaths from stroke in 2008 than in 2007
• 795,000 strokes/year in U.S.
  – ~560,000 are first-time events
  – 60,000 more strokes in women than men/year
  – 1 in 4 patients dies within 1 year
  – 30-50% of survivors do not regain functional independence
  – 15-30% of survivors permanently disabled
• Cost of stroke in 2010: $73.7 billion

Panorama of stroke

• Ischemic stroke: 85%
  – Cardioembolic
  – Large-vessel atherosclerosis
  – Small-vessel occlusion
  – Other determined
  – Undetermined
• Hemorrhagic stroke: 15%
  – Subdural
  – Intraparenchymal
  – Subarachnoid

**Etiologies of ischemic stroke**

- **Atherosclerotic risk factors**
  - HTN
  - DM
  - Hyperlipidemia
  - Tobacco abuse (in past 5 years)
  - XRT
  - Homocystinuria
- **Dissection**
  - Trauma
  - Chiropractic manipulation
- **Hematologic**
  - Sickle cell disease
  - DVT
  - History of miscarriages
  - Livedo reticularis
  - Asymmetric radial pulses
- **Cardioembolism**
  - Atrial fibrillation
  - Ischemic/dilated cardiomyopathy
  - Mural thrombus/mass
  - IVDU
  - Atrial septal aneurysm
  - Paradoxical embolism/DVT/PFO
  - Association w/ Valsalva
  - Cancer
- **Miscellaneous**
  - Oral contraceptives
  - Recurrent headaches
  - Recent infection
  - Peripartum
  - HIV+
  - EtOH use
  - Family hx of any of above/premature stroke
  - Hearing loss
  - Uterine/bowel rupture or pneumothorax (suggests connective tissue disorder)

**Signs of posterior circulation ischemia**

- **Syndrome “doesn’t fit” a vascular territory**
  - This may not be an MCA infarct
  - This may not be an arterial infarct
  - Top-of-basilar syndromes usually embolic → infarcts in multiple vascular territories
- **May be nonfocal/subtle**
  - Drowsiness
  - Partial Wallenberg syndrome
  - “Blurry vision”
    - Homonymous hemianopia
    - Diplopia
    - Amaurosis fugax
    - Transient visual obscurations (TVOs)
- **Often progressive**
- **Fluctuation not uncommon**
- **Declining level of consciousness heralds worsening prognosis**
- **Recent headache/neck pain**
  - Dissection
  - Migrainous stroke
  - Venous thrombosis
- **Seizure less common but does occur**
  - Embolic etiology
  - Venous thrombosis
Common signs of posterior circulation ischemia

- Ataxia
- Lethargy – *may be progressive*
- Dysarthria – pa-ta-ka
- Diplopia
- Cranial nerve deficits
- Gaze deviation – *away from stroke*
- Crossed signs
  - ipsilateral facial droop/numbness
  - contralateral hemiparesis/numbness

NIHSS

[Images of illustrations showing various assessments for NIHSS]

http://learn.heart.org
Knowledge of tPA for acute stroke among Michigan adults

- 32.2% aware of tPA
  - 52.7% knew of 3-hour window
  - 1 in 6 adults aware of time-sensitive nature
- Awareness greater among middle-aged adults (55-64 yrs), women, Caucasians, higher income
- 27.6% - can state 3 warning signs

EMS arrival makes a difference

- 22.3% of U.S. has access to PSC within 30 min. (55.4% within 60 min.)
- Air ambulances increase likelihood of arriving within 60 min. to 79.3%
- Austria: 21,712 stroke pts (4.1% helicopter) – OR 3.6 of receiving thrombolysis vs. indirect ambulance w/ ER MD (OR1.5)
- Pts aged 15-49 yrs: arrival by ambulance is associated with receiving stroke intervention ($p < 0.005$)
  - No difference if presenting hospital had Primary Stroke Center (PSC) certification

Time is brain. Quantified.

- Typical #neurons in human forebrain = 22 billion
- In large-vessel stroke, **1.9 million** neurons are lost every minute without recanalization
- Brain ages 3.6 years/hour of untreated stroke

**IV-tPA (recombinant tissue plasminogen activator)**

- Approved by FDA in 1995 for ischemic stroke within <3 hrs. onset
- ↓incidence favorable outcome at 3 mo. with ↑time interval from stroke onset to start of treatment
- Nationwide tPA rates 2-3%

<table>
<thead>
<tr>
<th></th>
<th>0-90 min</th>
<th>91-180 min</th>
<th>181-270 min</th>
<th>271-360 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number needed to tx for benefit (NNTB)</td>
<td>3.6</td>
<td>4.3</td>
<td>5.9</td>
<td>19.3</td>
</tr>
<tr>
<td>Number needed to tx for harm (NNTH)</td>
<td>65</td>
<td>38</td>
<td>30</td>
<td>14</td>
</tr>
<tr>
<td>Help-to-harm</td>
<td>18.1</td>
<td>8.8</td>
<td>5</td>
<td>0.7</td>
</tr>
</tbody>
</table>


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**Get With the Guidelines**

- American Stroke Association: **Goal Door-to-Needle (DTN) time <60 min >80% of time**
- Of 129,431 stroke pts. presenting within 3 hrs. of sx onset, 24, 504 (19.7%) received IV-tPA
- Mean DTN 79.3 min, median 78 min
- Group with DTN <60 min were more likely to
  - meet door-to-CT complete ≤25 min.
  - be at hospital with annual stroke volume >300 pts. (*p* 0.003)
  - be at hospital giving IV-tPA >20 times/yr. (*p* <0.001)
  - older (*p* <0.001), female (*p* 0.001), African-American (*p* 0.001)
  - arriving by ambulance (*p* 0.1275) on-hours (*p* <0.001)

*Circulation 2011;123(7):750-8.*
**Improved outcomes in DTN <60 min**

<table>
<thead>
<tr>
<th></th>
<th>DTN &lt;60 min (n=6790)</th>
<th>DTN &gt;60 min (18,714)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>8.6%</td>
<td>10.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any tPA complic</td>
<td>8%</td>
<td>9%</td>
<td>0.0065</td>
</tr>
<tr>
<td>sICH</td>
<td>4.7%</td>
<td>5.6%</td>
<td>0.0017</td>
</tr>
</tbody>
</table>

*After adjustment, each 15-min. reduction in door-to-needle time was associated with 5% lower odds of dying.*

*Circulation 2011;123(7):750-8.*

**Stroke workup**

- CT head w/o contrast
- MRI head w/o gadolinium
- MRA/CTA head/neck
- 2D echocardiogram w/ bubble study eval. mural thrombus/atrial septal aneurysm/PFO
- Telemetry eval. arrhythmia
- Fasting lipids
- (Trans-esophageal echocardiogram eval. left atrial appendage thrombus/aortic arch)
Stroke workup in patients <55 yrs.

- CBC, chemistry, ESR, CRP
- PT/PTT/INR
- RPR/VDRL
- Homocysteine, lactic acid, Lp(a)
- Toxicology
- Sickle cell prep
- Pregnancy test
- EKG
- CT head w/o contrast
- MRI head w/o gadolinium
- MRA/CTA head/neck
- TTE/TEE with bubble study
- CSF
- ANA, ANCA, cryoglobulins, HIV
- Transcranial Doppler
- Cerebral angiography
- Brain/meningeal biopsy
- Hypercoagulable w/u
  - Protein C & S
  - Antithrombin III
  - Activated Protein C resistance
  - Factor V Leiden mutation
  - Antiphospholipid Ab
  - Prothrombin 20210A gene mutation
  - Fibrinogen
  - MTHFR C677T

Intra-arterial therapy (IAT): why? when?

- Poor IV-rtPA recanalization rates for proximal arterial occlusion
  - Internal carotid artery (ICA): 10%
  - Proximal middle cerebral artery (MCA): 24-30%
- IA-rtPA: local delivery of fibrin-selective agent → less systemic effect of hypofibrinogenemia
- Mechanical strategies
  - ↓use of thrombolitics: possibly ↓symptomatic intracranial hemorrhage (sICH)
  - Extend treatment window
  - ↑surface area accessible to fibrinolytic agents
  - Clot retrievers possibly more efficient at removing mature clot or cholesterol/calcium emboli
## Acute stroke: Interventional tools

<table>
<thead>
<tr>
<th>&lt;4.5 hours</th>
<th>&lt;8 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>• IV-rtPA</td>
<td>• Merci (Mechanical Embolus Retrieval in Cerebral Ischemia) retriever</td>
</tr>
<tr>
<td>• Intra-arterial therapies</td>
<td>• Thromboaspiration (Penumbra)</td>
</tr>
<tr>
<td></td>
<td>• Stent</td>
</tr>
<tr>
<td></td>
<td>• Balloon angioplasty</td>
</tr>
<tr>
<td></td>
<td>• Stentriever</td>
</tr>
<tr>
<td></td>
<td>– Solitaire</td>
</tr>
<tr>
<td></td>
<td>– Trevo</td>
</tr>
<tr>
<td></td>
<td>– 3D Separator</td>
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<tr>
<td></td>
<td>– Mindframe</td>
</tr>
<tr>
<td></td>
<td>– Surpass</td>
</tr>
<tr>
<td></td>
<td>– Revive IC</td>
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</tbody>
</table>

### <6 hours

- Intra-arterial therapies
  - IA-rtPA
  - Mechanical

### <4.5 hours
- IV-rtPA
- Intra-arterial therapies

### <8 hours
- Merci (Mechanical Embolus Retrieval in Cerebral Ischemia) retriever
- Thromboaspiration (Penumbra)
- Stent
- Balloon angioplasty
- Stentriever
  - Solitaire
  - Trevo
  - 3D Separator
  - Mindframe
  - Surpass
  - Revive IC

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**Thrombectomy is time-dependent**

![Graph showing the relationship between time from symptom onset to angiographic reperfusion and probability of good clinical outcome.](image)

*Neurology 2009;73:1066-72.*
Mechanical thrombectomy

**MERCI**

- Mechanical grasp of clot with a cork screw like device
- First device approved for mechanical extraction HDE
- Benchmark for all future mechanical device trials

**PENUMBRA**

- Proximal aspiration of clot in fragments
- Safer and more effective than MERCI
- Used in conjunction with other methods
Mechanical thrombectomy

- Mechanical clot extraction by a self-expanding, fully retrievable stent
- Safer and more effective than MERCI, comparable to Penumbra
- Used in conjunction with other methods (SOLUMBRA)
- Faster recanalization times

Mechanical thrombectomy

- Mechanical clot extraction by self-expanding, fully retrievable stent
- Similar in design, technique, outcomes to SOLITAIRE
- Used in conjunction with other methods
Mechanical thrombectomy

- Mechanical clot extraction by a self-expanding fully retrievable stent with internal partitions to grasp clot
- Similar in intent with stentriever, but different in design
- Currently under investigation

Acute stroke clinical trials

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Recanalization</th>
<th>SICH</th>
<th>mRS 2</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS</td>
<td>-</td>
<td>6%</td>
<td>28%</td>
<td>24%</td>
</tr>
<tr>
<td>PROACT II</td>
<td>66%</td>
<td>10.9%</td>
<td>40%</td>
<td>25%</td>
</tr>
<tr>
<td>IMS II</td>
<td>60%</td>
<td>9.9%</td>
<td>46%</td>
<td><strong>16%</strong></td>
</tr>
<tr>
<td>MERCI</td>
<td>48%</td>
<td>7.8%</td>
<td>28%</td>
<td>44%</td>
</tr>
<tr>
<td>PENUMBRA</td>
<td><strong>82%</strong></td>
<td>11%</td>
<td>25%</td>
<td>33%</td>
</tr>
<tr>
<td>POST (PENUMBRA)</td>
<td>84%</td>
<td>7%</td>
<td>40%</td>
<td>25%</td>
</tr>
<tr>
<td>MULTI MERCI</td>
<td>68%</td>
<td>9.8%</td>
<td>36%</td>
<td>34%</td>
</tr>
<tr>
<td>TREVO</td>
<td>78%</td>
<td>5%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>SWIFT (SOLITAIRE)</td>
<td><strong>83%</strong></td>
<td>11%</td>
<td><strong>58%</strong></td>
<td><strong>18%</strong></td>
</tr>
<tr>
<td>TREVO 2</td>
<td><strong>86%</strong></td>
<td>6.8%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>IMS III</td>
<td><strong>65-81%</strong></td>
<td>6.2%</td>
<td>40.8%</td>
<td>19.1%</td>
</tr>
</tbody>
</table>
**LICA occlusion**

**Intracranial hemorrhage**

- Extra-axial
  - Subdural
  - Subarachnoid
- Intra-axial
  - Intraparenchymal
  - Intraventricular
Saccular aneurysms

- **Location**
  - Anterior communicating A: 30-35%
  - Posterior communicating A: 25%
  - MCA bifurcation: 20%
  - BA apex: 10%
- **2-5% population**
- **Factors influencing aneurysm rupture:**
  - Cocaine/amphetamine use
  - Uncontrolled HTN
  - Smoking
**Pial AVMs: Epidemiology**

- Congenital
- 3rd-6th decades, males=females
- Rarely familial (Osler-Weber-Rendu & Sturge-Weber syndromes)
- 2% multiple
  - Wyburn-Mason syndrome
  - Osler-Weber-Rendu syndrome

**Aneurysmal subarachnoid hemorrhage (SAH)**

- 30,000 cases/year
- 30-50% patients die before arriving to hospital
- 50% of survivors sustain irreversible brain injury
- Females > males
- Complications: rebleeding vasospasm, strokes, seizures, low sodium, hydrocephalus
- Risk of re-bleeding if aneurysm not secured: 2%/day x first 48 hours, 1-2%/day x first 2 weeks, 50% at 6 months
Treatment of intracranial aneurysms

• Endovascular
  – Coil embolization
  – Balloon remodeling + coiling
  – Stent-assisted coiling
  – Onyx®-500 embolization

• Surgical clip ligation

Angiography – Right internal carotid artery aneurysm
**Pial AVMs: Pathophysiology**

- Embryonic error of angiogenesis at capillary level
- Serpiginous mass of dilated feeding arteries, nidus, dilated draining veins
- Electron microscopy: abnormal elastic lamina/internal lamella, hyalinized venous walls

**Pial AVMs: Presentation**

- Presentation
  - ICH – 50% (ICH>IVH>SAH)
  - Seizures – 25%
  - Ischemia (steal phenomena)
  - Headaches
- Annual hemorrhage rate: 1-4%
- Mortality after 1st ICH: 10-29% (up to 50% for posterior fossa ICH)
- Re-hemorrhage rate in 1st year: 6-17%
Pial AVMs: CT/MR

- CT
  - Slightly hyperdense serpiginous vascular structures
  - Calcification (30%)
- MR
  - Gliosis/adjacent atrophy from steal
  - Hemosiderin from prior micro-hemorrhages
  - Slow-flowing components poorly demonstrated by non-enhanced MRA
  - Mass effect uncommon (unless ICH present)

Pial AVMs - Calcifications
Pial AVMs: Angiography

- *Sine qua non*: early draining vein
- 85% supratentorial (MCA>ACA>PCA territories), 15% infratentorial
- 10-15% have pre-/intra-nidal aneurysms
- 10-15% may also have dural (ECA) supply
- Gold standard to evaluate for small AVM

Spetzler-Martin III AVM
Spetzler-Martin III AVM

Spetzler-Martin III AVM
Spetzler-Martin III AVM

AVMs: Treatment

• Surgery
• Pre-operative embolization (liquid embolic agent/glue) + surgery
• Embolization alone (if few feeders)
• Radiosurgery
• Observation
Dural AVFs

- AV shunt involving dura, not parenchyma
- Females:males::3:1
- Acquired
  - Idiopathic (most common)
  - Venous thrombosis
  - Trauma
  - Infection
  - Hypercoagulable state
  - Prior neurosurgery
- Presenting symptoms
  - Pulsatile tinnitus
  - HA
  - Cranial nerve palsies
  - Focal neurological deficits
  - Dementia (venous congestive encephalopathy)

Dural AVFs

- Feeders
  - ECA branches
  - Tentorial/dural branches ICA
  - Meningeal branches VA
  - Pial branches (rarely)
Angiography

- Normal on post-bleed-day #0 and #10
- Angiogram 3 months later: +dural arteriovenous fistula