Practical Considerations in the Early Treatment of Acute Stroke

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Disclosures

Consultant – Novartis
Procter & Gamble

Advisory Board – Maquet/Datascope

Editor – Neurology ALERT
Stroke Facts – AHA 2012

- 800,000 new strokes per year in US
- 30% will die within one year
- 2nd leading cause of death world-wide
- #1 cause of permanent disability
- 5,000,000 stroke survivors
- 50% decline in incidence over 30 yrs.
- 4th leading cause of death in US
**Stroke Classification**

**Mechanisms of Stroke**

- Athero-thrombotic/embolic: 44%
- Cardio-embolic: 21%
- Small Vessel Disease: 19%

**Ischemic**

- Hypertensive: 5%
- Amyloid Angiopathy: 3%
- Other: 2%

**Hemorrhagic**

- Aneurysmal: 3%
- AVM*-related: 1%
- Other: 2%

Subarachnoid (6%)

Intracerebral (10%)

*AVM=arteriovenous malformation


Source: NCHS and NHLBI.
Is She Just Too Old For This?

New parents over 50—child-rearing’s final frontier.

By Lisa Miller
Trends in Pregnancy Hospitalizations 1994-2004 in the U.S.
Kuklina et.al. CDC. Stroke 2011

Queried National Inpatient Sample for all hospitalizations – pregnancy and stroke

From 1994-95 compared to 2006-07

47% increase for antepartum period
83% increase for postpartum period
Why the increase in pregnancy-associated stroke?

- **Age** - older women becoming pregnant. 
  > age 35 increased from 19% to 25%
- **Hypertension** in postpartum group increased from 28% to 41%
- Heart disease
- Obesity
- Diabetes
- Multiple births
Carotid atherosclerosis
Prevalence of high blood pressure in Adults by age and sex (NHANES: 2005-2006). 
Source: NCHS and NHLBI.
At Risk for Stroke?
Cardiac Risk Factors for Stroke
(40% of strokes < age 60)

- Atrial Fibrillation
- Valvular Heart Disease
  MVP, endocarditis, prosthetic valves
- Intracardiac Congenital Defects
  PFO, ASD, AS aneurysm
- Acute Myocardial Infarction
  (AHA/ASA Guidelines, 2006)
<table>
<thead>
<tr>
<th>Test or procedure</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Antiphospholipid syndrome</td>
<td>Lupus anticoagulant, anticardiolipin, and anti-β-2 glycoprotein antibodies*</td>
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<tr>
<td>Systemic lupus erythematosus, other connective tissue diseases, Wegener’s granulomatosis, Churg-Strauss syndrome</td>
<td>ANA, anti-ds-DNA, ENAs, complement, ANCA</td>
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<tr>
<td>Specific infections</td>
<td>Serum titres for syphilis, borrelia, zoster virus, hepatitis B and C virus, and HIV infection†</td>
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<tr>
<td>Hepatitis C virus, other cryoglobulinemias</td>
<td>Cryoglobulins</td>
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<tr>
<td>Illicit drugs</td>
<td>Serum and urine toxicological screening</td>
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<tr>
<td>Primary CNS and other vasculitis, CNS and systemic infections</td>
<td>CSF examination</td>
</tr>
<tr>
<td>Hyperhomocysteinaemia</td>
<td>Homocysteine concentrations</td>
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<tr>
<td>Specific deficiencies</td>
<td>Antithrombin III, protein S or C concentrations‡</td>
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<tr>
<td>Specific mutations</td>
<td>Factor V Leiden, prothrombin G20210A mutations</td>
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<tr>
<td>Sickle-cell disease</td>
<td>Haemoglobin electrophoresis§</td>
</tr>
<tr>
<td>Several inflammatory, infectious and genetic diseases, retinocerebral arteriopathies</td>
<td>Ophthalmological examination</td>
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<tr>
<td>Primary CNS and other medium and large-vessel vasculitis, non-atherosclerotic arteriopathies</td>
<td>Intra-arterial cerebral angiography¶</td>
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<tr>
<td>Periarteritis nodosa</td>
<td>Abdominal and renal angiography</td>
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<tr>
<td>Takayasu’s disease</td>
<td>Aortic PET</td>
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<tr>
<td>Primary CNS vasculitis</td>
<td>Cerebromeningeal biopsy</td>
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<tr>
<td>Fabry’s disease</td>
<td>GLA activity</td>
</tr>
<tr>
<td>CADASIL</td>
<td>Skin biopsy</td>
</tr>
<tr>
<td>MELAS</td>
<td>Muscle biopsy</td>
</tr>
<tr>
<td>Specific genetic diseases (Fabry’s, CADASIL, HANAC syndrome, MELAS, etc)</td>
<td>Genetic tests</td>
</tr>
</tbody>
</table>
MODIFIABLE RISK FACTORS for STROKE

- Previous Stroke or TIA
- Hypertension
- Cardiac Disease *
- Diabetes* and Glucose Metabolism
- Hypercholesterolemia
- Carotid Artery Disease
- Cigarette Smoking
- Lifestyle Factors (obesity, physical inactivity, diet, illicit drug use, emotional stress)
- Oral contraceptives

* Including: atrial fibrillation, sinoatrial disorder, recent acute myocardial infarction, marantic or subacute bacterial endocarditis, cardiac tumors, left atrial enlargement and valvular disorders, both native and artificial
+ Glucose status

Goals of Emergency Treatment

- Rapid recognition & treatment of focal ischemia
- Medication for neuronal protection
- Restoration of blood flow to ischemic regions
Signs of Acute Stroke

The Cincinnati Prehospital Stroke Scale

**Facial Droop** (have patient show teeth or smile):
- **Normal** — both sides of face move equally
- **Abnormal** — one side of face does not move as well as the other

**Arm Drift** (patient closes eyes and holds both arms straight out for 10 seconds):
- **Normal** — both arms move the same or both arms do not move at all (other findings, such as pronator drift, may be helpful)
- **Abnormal** — one arm does not move or one arm drifts down compared with the other

Left: normal. Right: stroke patient with facial droop (right side of face).

**Abnormal Speech** (have the patient say “you can’t teach an old dog new tricks”):
- **Normal** — patient uses correct words with no slurring
- **Abnormal** — patient slurs words, uses the wrong words, or is unable to speak

Left: normal. Right: one-sided motor weakness (right arm).

**Interpretation:** If any 1 of these 3 signs is abnormal, the probability of a stroke is 72%.
Neuroprotection

- Thousands of compounds have been tested in the laboratory.
- Hundreds of compounds have been tested in clinical trials—billions of $$ spent.
- So far, none have demonstrated any significant clinical benefits.
- The latest failure—SAINT I, II.
Reperfusion of the ischemic brain is the most effective therapy for acute ischemic stroke ever known and ever likely to be discovered.

Molina & Saver
Stroke 2005;36:2311
REVERSIBLE AND IRREVERSIBLE ISCHEMIC THRESHOLDS

In Monkeys

Intracerebral Blood Flow

(ml/100 gm/min)

Reversible Paralysis

Infarction

Hours

0 1 2 3 >4

20

10

0

Factors That Influence Outcome After Focal Brain Ischemia

1. Duration of Ischemia
2. Degree of Collaterals
3. Animal Species
4. Arterial Blood Pressure
5. $p \text{O}_2$
6. Hematocrit
7. Glucose
8. Core Temperature
**Algorithm for Suspected Stroke**

**EMS assessments and actions**
- Immediate assessments performed by EMS personnel include
  - **Cincinnati Prehospital Stroke Scale** (includes difficulty speaking, arm weakness, facial droop)
  - **Los Angeles Prehospital Stroke Screen**
  - Alert hospital to possible stroke patient
  - Rapid transport to hospital

**Immediate general assessment:**
- 10 minutes from arrival
  - Assess ABCs, vital signs
  - Provide oxygen by nasal cannula
  - Obtain IV access; obtain blood samples (CBC, electrolytes, coagulation studies)
  - Check blood sugar; treat if indicated
  - Obtain 12-lead ECG; check for arrhythmias
  - Perform general neurological screening assessment
  - Alert Stroke Team: neurologist, radiologist, CT technician

**Immediate neurological assessment:**
- 25 minutes from arrival
  - Review patient history
  - Establish onset (<3 hours required for fibrinolytics)
  - Perform physical examination
  - Perform neurological examination:
    - Determine level of consciousness (Glasgow Coma Scale)
    - Determine level of stroke severity (NIH Stroke Scale or Hunt and Hess Scale)
  - Order urgent noncontrast CT scan (door-to-CT scan performed: goal <25 minutes from arrival)
  - Read CT scan (door-to-CT read: goal <45 minutes from arrival)
  - Perform lateral cervical spine x-ray (if patient comatose/history of trauma)
Does CT scan show intracerebral or subarachnoid hemorrhage?

Data

Probable acute ischemic stroke
- Review for CT exclusions: are any observed?
- Repeat neurological exam: are deficits variable or rapidly improving?
- Review fibrinolytic exclusions: are any observed?
- Review patient data: is symptom onset now >3 hours?

Decision

If high suspicion of subarachnoid hemorrhage remains despite negative findings on CT scan, perform lumbar puncture. Fibrinolytic therapy is contraindicated following a lumbar puncture.

Drug

Patient remains candidate for fibrinolytic therapy?

Yes

- Review risks/benefits with patient and family: If acceptable — Begin fibrinolytic treatment (door-to-treatment goal <60 min):
  - Monitor neurological status: emergent CT if deterioration
  - Monitor BP; treat as indicated
  - Admit to critical care unit
  - No anticoagulants or antiplatelet treatment for 24 hours

No

Consult neurosurgery

Blood on LP

Initiate actions for acute hemorrhage
- Reverse any anticoagulants
- Reverse any bleeding disorder
- Monitor neurological condition
- Treat hypertension in awake patients

No blood on LP

- Initiate supportive therapy as indicated
- Consider admission
- Consider anticoagulation
- Consider additional conditions needing treatment
- Consider alternative diagnoses

No to all of above
Transient Ischemic Attacks

What is the risk of stroke?

• One in nine patients will have a stroke within 90 days of TIA (ER diagnosis)
• Half of all strokes occur in the first two days
• Risk with atrial fibrillation is 11%
• Risk with >70% ICA stenosis is 25%

(JAMA 2000;284:290/Arch Neurol 1995;52:246)
Early Questions?

Too much emphasis on the NIHSS!!

- What is the vascular anatomy?
- What is the true age of the acute infarct?
- Is there large vessel, proximal stenosis?
- Is there a cardiac source of embolism? (40% < age 60 have cardiogenic embolism)
- Is the deficit disabling?
CT or MR?

How fast is your hospital?

How responsive are your radiologists?
Acute Therapy for Ischemic Stroke

- Antiplatelet therapy
- Anticoagulant therapy
- Hemodynamic manipulations
- Thrombolysis – IV and IA
- Angioplasty/Stenting
- Mechanical Clot Removal
- Surgical Interventions
General Care & Treatment

- ABCs
- Temperature
- Cardiac Monitoring & Treatment
- Arterial Hypertension
- Arterial Hypotension
- Hyperglycemia
- Hypoglycemia
- Intracranial Hypertension
NINDS rt-PA Stroke Study

- 624 patients treated with 0.9 mg/kg/hour
- Treated in less than three hours; ½ less than 90 minutes
- t-PA group: 31-50% complete recovery
- Control: 20-38% complete recovery
- ICH: 6.4% v. 0.6%
- Mortality: 17% v. 20%
Time window can be extended to 4 ½ hours for intravenous rTPA, but is that the best therapy we have to offer?

(ASA/AHA Stroke 2009;40;2945-2948)
<table>
<thead>
<tr>
<th>Time Range</th>
<th>Odds Ratio (O.R.)</th>
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<tbody>
<tr>
<td>0-90 minutes</td>
<td>2.8</td>
</tr>
<tr>
<td>90-180 minutes</td>
<td>1.6</td>
</tr>
<tr>
<td>180-270 minutes</td>
<td>1.4</td>
</tr>
</tbody>
</table>
ECASS -III

Exclusion Criteria

Age > 80 years
Warfarin use regardless of INR
NIHSS > 25
History of prior stroke and diabetes

(ASA/AHA Stroke 2009;40;2945-2948)
Intravenous Thrombolysis

Disadvantages –

• Short time window
• Poor recanalization of carotid-T, MCA stem, basilar, vertebral
• Systemic exposure to TPA causes bleeding problems
Sources: SPEED QA logs and Get with the Guideline Stroke Registry.

Note: 
1. Time in Minutes are based on median calculations.
2. Target times are based on Brain Attack Coalition’s recommendations & National Institute of Neurological Disorders and Stroke (NINDS) for Primary Stroke Centers.
Intraarterial Thrombolysis

- t-PA, urokinase, or prourokinase
- 75% partial or complete thrombolysis
- PROACT II trial randomized to heparin (1996)
  - treated 3-6 hours after onset
  - MCA occlusion
  - 67% re-opened
  - ICH: 10% v. 2%

Bridging protocol – IV to intraarterial
Acute Ischemic Stroke-CTA

85 yo with left hemiplegia at 3 hours

Non-contrast CT

CT Angiogram
CT Perfusion Studies

CBF

CBV

MTT
Intra-arterial TPA

Angio

Post TPA
24 hours after IA-TPA

Follow-up CT
Mechanical Thrombectomy

MERCI retriever
FDA Approved in 2004
Concentric Medical, Inc, Mountain View, California

Penumbra system
FDA Approved in 2008
Penumbra, Inc. Alameda, California

Advantages over chemical thrombolysis:
1. Lessens or avoids use of chemical thrombolysis, reducing risk of ICH
2. Extends treatment window beyond 6 hours
3. Faster recanalization   (Courtesy of Dr. Daniel Berlin)
Controversial Therapies for Ischemic Stroke

1. Hemicraniectomy for Large Hemispheral Infarcts
2. Induced Hypertension for Ischemic Stroke
3. Therapeutic Hypothermia for Ischemic Stroke
Middle cerebral artery infarction
Tatu, 1998

- MCA perforating branches
- PoCA perforating branches
- Thalamoperforating branches
- Thalamogeniculate branches
- Medial PChA
- Lateral PChA
- Insular zone
Hemicraniectomy
High Risk for Herniation

• Gaze deviation, hemiplegia and neglect with NIHSS > 15
• Hemiplegia and global aphasia with NIHSS > 20
PLUS nausea or vomiting
  CT hypotensity > 50% MCA ± ACA or PCA
Angiography shows carotid “T” occlusion
Hemicraniectomy Algorithm

• Repeat CT in 6-12 hours
  If complete MCA plus ACA or PCA, consider hemicraniectomy

• Watch for decreasing LOC and anisocoria; repeat CT; midline shift
  >10 mm, consider hemicraniectomy
Vahedi, et.al.
Hemicraniectomy Trials

<table>
<thead>
<tr>
<th>At one Year</th>
<th>Surgery</th>
<th>Medical</th>
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</thead>
<tbody>
<tr>
<td>Survived</td>
<td>78%</td>
<td>29%</td>
</tr>
<tr>
<td>mRS ≤ 4</td>
<td>75%</td>
<td>24%</td>
</tr>
<tr>
<td>mRS ≤ 3</td>
<td>43%</td>
<td>21%</td>
</tr>
<tr>
<td>mRS = 4</td>
<td>31%</td>
<td>2%</td>
</tr>
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</table>

10X increased risk of disability; unable to walk or attend to bodily needs
Time Is Brain !