Acute Stroke Treatment—Update for 2008

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The Stroke Pandemic

Stroke Subtypes

- Hemorrhagic 15%
  - Subarachnoid
  - Intraparenchymal
- Other 4%
- Cryptogenic 26%
- Atherosclerotic 17%
- Cardioembolic 17%
- Lacunar 21%
- Ischemic 85%


Impact of Stroke in the USA

- Stroke Survivors
  - Return to normal 10%
  - Hemiparetic 48%
  - Unable to walk 22%
  - Complete/partial dependence 24-53%
  - Aphasic 12-18%
  - Clinically depressed 32%

TIA or Stroke

• True TIA are brief attacks lasting a few minutes-hours
• Longer attacks up to 24 hours with resolution of clinical symptoms are often ischemic stroke
• MRI demonstrates abnormalities in 50-70% cases

Event Risk Within 3 Months After TIA

Independent risk factors for stroke within 90 days after TIA:
- Age > 60 years
- Diabetes mellitus
- Duration of episode greater than 10 min
- Weakness
- Language impairment with the episode

Early Treatment of TIA Reduces Risk of Stroke

- Oxfordshire Study
- Phase I
  - 310 patients referred to stroke clinics with initial treatment plan initiated on return
- Phase II
  - 289 patients direct access to stroke clinics and treatment initiated on day 1
- Stroke at 90 days was reduced by 80% with early treatment
- ARR at 90 days 10.3-2.1= 8.2%

What is an Acute Ischemic Stroke?
Diffusion-Perfusion Mismatch

- rCBF
- TTP
- DWI
Hemodynamics—Acute Period

• Normal CO2 vasodilatory response may disappear
• Impaired autoregulation
• Reductions in CPP (even in normal range) can produce reduced CBF
• Cerebral steal (decreased CBF in ischemic area b/c of vasodilation elsewhere)
• Inverse steal
• These changes may persist for several weeks or more

Ischemic Penumbra:
Hypoperfused Area of Focal Ischemia That May Be Salvaged by Timely Intervention

The Penumbra and Imaging

• Perfusion Weighted MRI correlates with but may often overestimate the size of the penumbra
• May be inaccurate data—many studies assessed final infarct volume on day 7
  – Infarct may shrink between days 1 and 7
BP is a Double-Edged Sword

- High BP maintains perfusion to organs in times of stress
- Low BP may help to guard against bleeding out

BP is a Double-edged Sword

- High BP is long-term risk factor for vascular disease
- High BP predisposes for ICH and may expand hematomas
- Hypertensive encephalopathy
- Low BP at risk of syncope
- Extreme low BP → watershed infarcts
- Low BP in AIS may produce poor flow, worsening stroke
Blood Flow Dynamics and Brain Ischemia

- Cerebral blood volume (CBV)
  - 80-85% venular
  - 10-15% arterial
    - The most responsive portion to CPP changes
  - 5% capillary

Cerebral Perfusion Pressure

**CPP = MAP - ICP**
Cerebral Autoregulation

- Compensatory mechanism to maintain cerebral blood flow (CBF)
- Adjusts for CPP of 70-150
- Mediated by changes in CVR
  - When CPP decreases, vasodilation of small arteries, arterioles ensues
  - A 10% decrease in MAP produces only 2-7% drop in CBF

![Cerebral Autoregulation Diagram](image-url)
Oxygen Extraction

- If MAP drops below threshold, O2 extraction fraction (OEF) increases to compensate
  - Normally, only 30-40% of O2 to brain is used for energy production
  - After this reserve is exhausted, cellular damage results

Cerebral Autoregulation Factors

Adapted with permission from Varon J and Marik PE. Chest. 2000;118:214-227.
Blood Pressure in Ischemic Stroke

Acute elevations of BP are common in stroke
- Seen in 85% of patients
- Often declines spontaneously in first 24-48 hours

Cerebral autoregulation is defective in most stroke patients

Acutely lowering BP can expand area of ischemia
- Supported by PET studies
- Supported by clinical experience
- Supported by ASA guidelines

Ischemic Stroke

- Cerebral autoregulation may be lost
- Chronic hypertensive patients are accustomed to higher BP—curve shifted to the right
- Patients may have concomitant cardiac disease
- Hypertension may resolve spontaneously
  - May be important to maintain adequate perfusion pressures
  - Usually not treated unless
    - SBP >220, DBP >120 or MAP >130 mmHg
    - Or concomitant medical conditions—acute MI, aortic dissection, hypertensive encephalopathy, severe LV failure
    - Or if thrombolytic Rx to avoid hemorrhage

Predicting Tissue Viability

• Would have enormous value in making treatment decisions
• Areas of increased OEF may represent the penumbra
  – Increased OEF implies reduced blood supply relative to O2 demand but with metabolically active cells
  – Data that reperfusion within 1 hour improves CMRO2
• Determination of thresholds for CBF and CMRO2 below which tissue is likely to die
  – Suffers from many technical problems

CT perfusion

Mean transit time (MTT)  Blood volume (BV)
Acute Stroke Treatment

- **Acute treatment**
  - Thrombolysis
  - IV/IA/TPA/ others
  - Mechanical Clot Disruption
  - Anticoagulation, antiplatelet agents
  - Neuroprotection
  - Hypothermia

- **Secondary prevention**
  - Risk factors modification
  - Medical vs. surgical interventions

**Scenario #1**

- 68 yo man, h/o hypertension
- 2 hrs right sided weakness (face=arm>leg), Broca’s aphasia
- BP 190/88, INR 1.0, normal labs o/w
- NIHSS=12
Scenario #1

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Stroke Unit: The Ideal

- Acute stroke patients should be admitted to a stroke unit
- Tools in a stroke unit
  - Telemetry
  - Care maps
  - Experienced nurses
  - Prevent aspiration pneumonia, DVT, infection
  - Multidisciplinary team
- All TIA patients admitted if they present within 48 hours or have multiple TIAs
Key Elements of a Primary Stroke Center

- Director
- Stroke team 24/7
- Stroke unit
- Care maps
- Rapid CT and lab testing
- Neurosurgery within 2 hours
- Track outcomes
- Education – public and private
Stroke Unit Care

- Meta-analysis of 23 trials comparing organized stroke unit care with general ward care

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds ratio</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (1 year)</td>
<td>0.86</td>
<td>.005</td>
</tr>
<tr>
<td>Death or institutionalized care</td>
<td>0.8</td>
<td>.0002</td>
</tr>
<tr>
<td>Death or dependency</td>
<td>0.78</td>
<td>.0003</td>
</tr>
</tbody>
</table>

- No increase in length of stay
- Conclusion: Stroke unit care associated with lower odds of death or dependency


Overall Benefits and Risks of IV tPA for Stroke

- Benefit: neurologically normal at 3 months
  - 55% relative increase
  - 12% absolute increase
- Very robust effect: NNT = 8
- Risk of symptomatic ICH was 6.4%
- The overall benefits include the ICHs
- Risk of ICH can be reduced by closely following the tPA protocol

Efficacy of tPA by Stroke Subtype

- Small vessel
- Large vessel
- Cardioembolic

% with good outcome

Time Is Brain: Effects of tPA vs. Time

- Odds ratio for favorable outcome at 3 months
- Minutes from stroke onset to start of treatment
- Benefit for rt-PA
- No benefit for rt-PA
- Benefit for rt-PA
- No benefit for rt-PA
Prospective Studies

- Patients with little or no response to rtPA at 24 hours had poor recovery at 3 months
- Results of the German Stroke Registry Study Group that followed 1796 patients treated with rt-PA at 225 hospitals between 2000-2002
- Hueschmann PU JAMA, Oct:2004

Studies to Extend IV t-PA Beyond 3-Hour Time Window

Efficacy Analyses

- ECASS II: 0- to 6-hour time window; primary outcome modified Rankin 0 to 1
- ATLANTIS: 3- to 5-hour time window; primary outcome Barthel of 95 to 100
- Both studies prospective, randomized, double-blinded


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Using tPA in Routine Clinical Practice

• Overall only about 3%-4% of stroke patients receive tPA—mostly due to time delays
• Efficacy similar to NINDS trial
• Rate of ICH: 4%-6%
• Risk of ICH increases with protocol violations
  – Time >3 hours
  – Poor blood pressure control
  – Using prohibited agents
  – Wrong dose
    • 0.9 mg/kg
    • Maximum dose: 90 mg
  – Elevated blood sugar also increases risk

Results of Anticoagulation: Meta-analysis

• No significant difference in 2-week mortality (8.5% in AC group vs. 8.7% in controls)
• Total new strokes identical between 2 treatment groups: 4.1%
• No evidence of heterogeneity among various studies or agents

Anticoagulation for Acute Ischemic Stroke

- Urgent *routine* anticoagulation with goal of improving neurologic outcome or preventing early recurrence not recommended
- More study is required before recommendation can be made regarding immediate anticoagulation in specific patient groups
  - Large-vessel atherothrombosis
  - High risk of recurrent embolism
- Not recommended for moderate or severe stroke
  - High risk of intracranial bleeding
- Contraindicated within 24 hours of tPA


Scenario #2

- 60 yo woman, h/o Afib
- 4 hrs right sided weakness (face=arm>leg), global aphasia
- BP 100/52, INR 1.0, normal labs o/w
- NIHSS=16
Intra-arterial Thrombolysis
PROACT-11

• Prourokinase
• Intraarterial: 9mg r-proUK
• 0-6 hrs
• Angiographic MCA occlusion

PROACT-11: RESULTS

• Bleeding rate and recanalization

<table>
<thead>
<tr>
<th>outcome</th>
<th>recan</th>
<th>mortality</th>
<th>bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>40%</td>
<td>66%</td>
<td>27%</td>
<td>10% with</td>
</tr>
<tr>
<td>25%</td>
<td>18%</td>
<td>25%</td>
<td>10% without</td>
</tr>
</tbody>
</table>
Intraarterial Thrombolysis

- ICA occlusion
- MCA main Stem occlusion
- Basilar Artery Occlusion
- Thrombolysis beyond 3 hours

Should Every Ischemic Stroke Seen Within 3 hours be Thrombolysed?

- Not a benign therapy
- Completed stroke stand to gain very limited benefit
- It would be useful to define possible salvageable tissue before attempting thrombolysis
t-PA Protocol

**Emergency Department:**
- Reconfirm time of onset
- Obtain written consent
- Page neurology resident and neurology attending
- Alert CT for immediate scan
- Page neuroradiologist on call
- Start labs: PT, PTT, INR, Platelets, Blood Glucose
- EKG
- Racial Hemocult

**Exclusion Criteria:**
- Central hemorhage
- Intracranial hemorhage
- Subarachnoid/thoracic hemorrhage
- Recent CVA < 3 months
- Recent SAH
- Recent AVM
- Recent SCA
- Recent WMC
- Recent intracranial hemorrhage
- NIHSS Scale > 22 (see attached)
- Lacunar syndrome
- Rapid improvement
- Insular ribbon sign or loss of basal ganglia definition
- PTT > 15
- PT > 15
- Palatostis < 100,000
- Blood glucose > 400 or < 50
- EKG (recent MI)
- Inclusion criteria met
- Consent form signed
- Administer t-PA
- AM/PM

**NIH Stroke Scale**

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>Level of Consciousness</td>
</tr>
<tr>
<td>2.</td>
<td>LOC Questions</td>
</tr>
<tr>
<td>3.</td>
<td>LOC Commands</td>
</tr>
<tr>
<td>4.</td>
<td>Best Horizontal Gaze</td>
</tr>
<tr>
<td>5.</td>
<td>Visual Fields</td>
</tr>
<tr>
<td>6.</td>
<td>Facial Palsy</td>
</tr>
<tr>
<td>7.</td>
<td>Motor: Right Arm</td>
</tr>
<tr>
<td>8.</td>
<td>Motor: Left Arm</td>
</tr>
<tr>
<td>9.</td>
<td>Motor: Right Leg</td>
</tr>
<tr>
<td>10.</td>
<td>Motor: Left Leg</td>
</tr>
<tr>
<td>11.</td>
<td>Limb Ataxia</td>
</tr>
<tr>
<td>12.</td>
<td>Sensation</td>
</tr>
<tr>
<td>13.</td>
<td>Best Language</td>
</tr>
<tr>
<td>14.</td>
<td>Dysarthria</td>
</tr>
<tr>
<td>15.</td>
<td>Extinction &amp; Inattention</td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td></td>
</tr>
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</table>
NIHSS: Correlates with Outcome

- 3-6 excellent, regardless of treatment (90%)
- 16-22: 40% excellent outcome
- Lacunar strokes 30% greater chance of an excellent outcome
- High NIHSS >23 associated with increased chances of hemorrhage
- Intracranial hemorrhage carries a > 50% mortality

Blood Pressure Management

- **If rt-PA is an option**
  S<185mm, D <105

- **If rt-PA is not an option**
  Avoid lowering the blood pressure unless
  1.  S> 220 D> 120
  2.  MAP> 130
  3.  Signs of CHF or Renal Failure
Hyperglycemia & Hyperthermia

- Control of blood glucose and elevated temperature improve outcome and reduce infarct size
- Controlled hypothermia may reduce mortality but better devices are required to reduce complications
Hyperthermia

- Large Metananalysis
- 9 studies, 3,790 patients
- Power to detect 9% increase in mortality in pyrexial group (37.4-38) was 99%
- Hyperthermia was associated with increased mortality
- OR 1.16 (CI 0.99-1.43 P< 0.00000001)
- Hajat et al: Stroke, 2000; 31: 410

Mechanical Clot Disruption

- Endovascular energy emitting devices
- PT Angioplasty
- Endovascular Thrombectomy
- Merci tested 28 patients/7 US centers
- Median NIHSS 22
- 43% complete recanalization
- 21% more when intraarterial rt-PA added
- Merci2: 150 patients 53.3 recanalization with embolectomy
- SICH 7.8%
- Improved outcome in recanalized patients
IA Reperfusion Therapy

• IA is an option for selected, severe patients < 6 h or < 3 not candidates for IV tPA (Class I; B)
• Treatment requires SC and qualified INR (Class I; C)
• Contraindications for IV tPA (surgery) Class IIa; C)
• Should not preclude IV tPA (Class III; C)
• 68 y/o female with history of peripheral vascular disease, hypertension and atrial fibrillation

• While watching TV with husband, patient began having a left facial droop and left sided weakness. Her husband noticed this and called 911

• Patient presented to ER with left-sided weakness, left facial droop, and no movement of left upper extremity. Neurologic exam also revealed right gaze deviation; the patient could not move her eyes past midline.

• Pre NIHSS = 13

• A non-contrast CT of the brain was obtained on arrival at the ER and it identified a dense right middle cerebral artery sign, without significant loss of gray-matter differentiation an indication that this patient was an interventional candidate

• She was not a candidate for IV tPA because she was on Coumadin for an artificial valve

• Angiography revealed a complete occlusion of the right M1 middle cerebral artery and the distal branches
• Immediately after the procedure, the patient was identified to have increased movement of the left lower and upper extremities
• Patient didn’t qualify for acute rehab and is home doing well
• (outpt therapy)
UK Protocol (one of)

- **0-3 hours**
  - CT +/- CTA +/- Perfusion CT
  - IV rt-PA
  - Contraindications for IV-tpa? IA procedure vs. clinical trials (if eligible)
- **3-8 hours**
  - CT +/- CTA +/- Perfusion CT
  - High suspicion and/or confirmed occlusion? Proceed with IA intervention
  - Consider enrollment in clinical trials
  - For basilar artery, what is there to lose beyond 8 hours?

Treatment in Acute Stages

- Thrombolytics (Intravenous or Intraarterial)
- Minimal interference with BP unless symptomatic or rt-PA
- Temperature control
  - Maintain normal temperature
- Aggressive control of hyperglycemia
- Anticoagulation
  - Heparin only for DVT prophylaxis
  - No proven use for full dose IV heparin
- Antiplatelet agents may reduce recurrence
Conclusions

• Intravenous Rt-PA is effective in reducing stroke morbidity in the right patient within 3 hours
• Intra-arterial rt-PA (not FDA approved) might be better for ICA or MI MCA occlusions, basilar occlusions
• MERCI device for clot disruption may be used with/without IA-rt-PA
• Multimodal therapy is an option
• Newer medications and devices may further improve stroke outcome
  – We are investigating these