OPENING THE WINDOW OF TIME IN
STROKE THERAPY
New Evidence for the Emergency Department

Course Chair:
ANDY S. JAGODA, MD
Professor and Chair
Department of Emergency Medicine
Mount Sinai School of Medicine
New York, NY
Meeting the Criteria for Intravenous Thrombolysis

Kama Gulum, MD
Department of Emergency Medicine
University of California San Diego
Meeting the Criteria for Intravenous Thrombolysis

Objectives

1. Understand the time-critical nature of acute ischemic stroke
2. Understand factors at play in using intravenous thrombolysis safely
3. Understand how extremes of severity and age impact thrombolysis decision-making in the ED
“Time is brain”

Table 5. ED-Based Care

<table>
<thead>
<tr>
<th>Action</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Door to physician</td>
<td>≤10 minutes</td>
</tr>
<tr>
<td>Door to stroke team</td>
<td>≤15 minutes</td>
</tr>
<tr>
<td>Door to CT initiation</td>
<td>≤25 minutes</td>
</tr>
<tr>
<td>Door to CT interpretation</td>
<td>≤45 minutes</td>
</tr>
<tr>
<td>Door to drug (≥80% compliance)</td>
<td>≤60 minutes</td>
</tr>
<tr>
<td>Door to stroke unit admission</td>
<td>≤3 hours</td>
</tr>
</tbody>
</table>
t-PA: Time-to-treatment and Efficacy

NINDS parts 1 and 2
ECASS I
ECASS II
ECASS III
Pooled data analysis
ATLANTIS part A
ATLANTIS part B
EPIPHET

Meta-analysis

Individual patients in individual trials

Meta-analysis

Individual trial outcomes

“Super-good”

“Good”

“Bad”

RESULT

“Good”

Pooled analysis

Individual patients in individual trials

Pooled analysis – “mega-trial”

Individual patients pooled together

RESULT

“Good”

“More reliable results can be expected if individual data are available for a pooled analysis…”

t-PA: Time-to-treatment and Efficacy

• Lees pooled analysis (N = 3,670)
  – Increased t-PA efficacy with earlier administration
    • No further efficacy demonstrated after 4.5 hours
  – Mortality benefit seen with t-PA administration
    • This benefit decreased the later t-PA was administered
    • Risk of administration after 4.5 hours may outweigh benefit

t-PA: Time-to-treatment and Efficacy

- At anytime t-PA is administered, there is a risk of symptomatic hemorrhage
Using t-PA safely; Exclusion Criteria
Using t-PA safely
Exclusion criteria

**t-PA exclusion criteria**

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**“Leaky brain or leaking body”**
- Significant *head trauma* or prior *stroke* in previous 3 months
- Symptoms suggest *subarachnoid* hemorrhage
- Recent *intracranial* or intraspinal *surgery*
- Active *internal bleeding*
- *Arterial puncture* at noncompressible site in previous 7 days

**“Bad brain”**
- Intracranial *neoplasm*, *arteriovenous* malformation, or *aneurysm*
- History of *previous intracranial hemorrhage*
- CT demonstrates multilobar infarction (*hypodensity >1/3 cerebral hemisphere*)

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Using t-PA safely
Exclusion criteria

t-PA exclusion criteria

**Bleeding diathesis**
- Platelet count <100,000/mm³
- Heparin within 48 hours, with elevated aPTT
- Current use of anticoagulant with INR >1.7 or PT >15 seconds
- Direct thrombin inhibitors or direct factor Xa inhibitors with “elevated sensitive laboratory tests”

**Miscellaneous**
- Blood glucose concentration <50 mg/dL (2.7 mmol/L)
- Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)

Using t-PA safely
Exclusion criteria

**RELATIVE t-PA exclusion criteria**

**Relative exclusions**
- Minor or rapidly improving symptoms
- Pregnancy
- Seizure at onset with residual neurological impairments
- Major surgery or serious trauma within previous 14 days
- Recent GI or GU hemorrhage (within previous 21 days)
- Recent AMI (within 3 months)

**For treatment at 3 – 4.5 hours**
- Aged >80 years
- Severe stroke (NIHSS>25)
- Taking an oral anticoagulant regardless of INR
- History of both diabetes and prior ischemic stroke

Using t-PA safely; treatment decisions

- Is the patient too severe?
- Is the patient too mild?
- Is the patient too old?
Using t-PA safely
Treatment decisions

Symptomatic hemorrhage risk with t-PA

Bad outcome at 3 months, if untreated

Is the patient too mild?


Using t-PA safely
Treatment decisions

Is the patient too mild?

"MILD"

Not so mild: 6 mos
Not mild at all: 6 hrs

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Using t-PA safely

Treatment decisions

Is the patient too mild?

“MILD”

Not so mild: 6 mos

Not mild at all: 6 hrs

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Consideration:
the "low NIHSS score" stroke
with a devastating effect on livelihood

Not so mild: 6 mos

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Using t-PA safely

Treatment decisions


Is the patient too mild?

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Using t-PA safely

Treatment decisions

- Depression
- Impaired executive function
- Unmeasured motor dysfunction

- Not so mild: 6 mos
- Not mild at all: 6 hrs

"The calm before the storm"

"MILD"

Is the patient too mild?

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Using t-PA safely

Treatment decisions

Is the patient too mild?

Not mild at all: 6 hrs

"The calm before the storm"

ACA-to-MCA collaterals in an MCA stroke

http://neuroangio.org/neuroangio-topics/intracranial-collateral-pathways/

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Using t-PA safely

Treatment decisions

- Rapid improvement

  +

- Large-vessel occlusion or stenosis on imaging (especially if present while deficit is mild)

  OR

- Symptoms consistent with a large vessel occlusion/cortical stroke

  ...is associated with subsequent deterioration

---


Using t-PA safely
Treatment decisions

Is the patient too severe?

Use in Acute Ischemic Stroke
In addition to the previously listed conditions, the risks of alteplase therapy to treat acute ischemic stroke may be increased in the following conditions and should be weighed against the anticipated benefits:

- Patients with severe neurological deficit (e.g., NIHSS > 22) at presentation. There is an increased risk of intracranial hemorrhage in these patients.
- Patients with major early infarct signs on a computerized cranial tomography (CT) scan (e.g., substantial edema, mass effect, or midline shift).
Using t-PA safely
Treatment decisions

Is the patient too severe?

NIHSS

Imaging
# Using t-PA safely

## Treatment decisions

### Is the patient too severe?

<table>
<thead>
<tr>
<th>NIHSS</th>
<th>ICH (%)</th>
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<tbody>
<tr>
<td>1 – 5</td>
<td>2%</td>
</tr>
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Using t-PA safely
Treatment decisions

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Imaging

Kama Gulum, MD
# Using t-PA safely

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*Kama Gulumia, MD*
Using t-PA safely
Treatment decisions

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Imaging

> 1/3 the territory of the MCA
Using t-PA safely
Treatment decisions

NIHSS
Risk of symptomatic ICH by baseline NIHSS in NINDS
<table>
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Is the patient too severe?

Imaging
> 1/3 the territory of the MCA?

Time since onset
00:00:00

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Using t-PA safely
Treatment decisions

Is the patient too old?
Using t-PA safely
Treatment decisions

Is the patient too old?

YOUNG

OLD fare worse with stroke


Using t-PA safely
Treatment decisions

Is the patient too old?

YOUNG

Less aggressive workups & treatment

OLD fare worse with stroke

Using t-PA safely
Treatment decisions

Is the patient too old?

YOUNG
- Do better with t-PA

OLD
- Fare worse with stroke
- Still benefit too


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Using t-PA safely
Treatment decisions

Is the patient too old?

Young

Old

Old fare worse with stroke

Young do better with t-PA

Old still benefit too


Using t-PA safely
Treatment decisions

Is the patient too old?

YOUNG

DO NOT DISTURB

OLD
fare worse
with stroke

OLD
still benefit
too

YOUNG
do better
with t-PA

Age >80 = increased ICH risk with t-PA


Using t-PA safely

Treatment decisions


Is the patient too old?

YOUNG

do better
with t-PA

OLD

still
benefit
too

Age >80 ≠ increased ICH risk with t-PA

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Using t-PA safely

Treatment decisions


Using t-PA safely

Treatment decisions

Is the patient too mild?

Is the patient too severe?

Is the patient too old?

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events/Number of patients</th>
<th>Adjusted Odds Ratio (99% CI)</th>
<th>Adjusted p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rt-PA</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤80</td>
<td>331/698 (47.4%)</td>
<td>346/719 (48.1%)</td>
<td>0.92 (0.67-1.26)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>223/817 (27.3%)</td>
<td>188/799 (23.5%)</td>
<td>1.35 (0.97-1.88)</td>
</tr>
<tr>
<td>NIHSS Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>221/304 (72.7%)</td>
<td>232/308 (75.3%)</td>
<td>0.85 (0.52-1.38)</td>
</tr>
<tr>
<td>6-14</td>
<td>276/728 (37.0%)</td>
<td>268/724 (37.0%)</td>
<td>1.08 (0.81-1.45)</td>
</tr>
<tr>
<td>15-24</td>
<td>50/402 (12.4%)</td>
<td>33/421 (7.8%)</td>
<td>1.73 (0.93-3.20)</td>
</tr>
<tr>
<td>≥25</td>
<td>7/81 (8.6%)</td>
<td>1/65 (1.5%)</td>
<td>7.43 (0.43-129.00)</td>
</tr>
</tbody>
</table>

IST-3 collaborative group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet. 2012;379(9834):2352-63
Summary

TIME REALLY IS BRAIN:
- Minute-by-minute reduction of good outcome with t-PA, until it’s gone by 4.5 hours from onset

Is the patient too mild?
- WATCH OUT FOR:
  - Small strokes with big consequences
  - Rapid improvement of cortical/large artery strokes

Is the patient too severe?
- < 3 hours: Careful with NIHSS > 22
- 3 – 4.5 hrs: Avoid NIHSS > 25
- Anytime: Avoid hypodensity >1/3 hemisphere on CT

Is the patient too old?
- < 3 hours: “Never too old”, but careful with age > 80
- 3 – 4.5 hrs: Be very careful with age > 80
How Policy Affects Practice in Stroke Therapy

ANDY S. JAGODA, MD
Professor and Chair
Department of Emergency Medicine
Mount Sinai School of Medicine
New York, NY
Key Questions

- Are there guidelines that assist in clinical decision making? How good are they?
  - ACEP/AAN Clinical Practice Guidelines
  - AHA/ASA Guidelines for the Early Management of Adults with Ischemic Stroke
- Have policy and guidelines changed outcomes?
Evidence-based Guidelines

• Define the clinical question
  – Focused question better than global question
  – Outcome measure must be determined

• Grade the strength of evidence

• Incorporate practice patterns, available expertise, resources and risk:benefit ratios
Two Separate Questions

- How strong is the evidence from one study?
  - Critical appraisal

- How strong is the combined evidence from multiple studies?
  - Synthesis
  - Consistency in magnitude, direction

- Greater risk, cost, implausibility require greater evidence
Evidence-based Guidelines: Limitations

- Different groups can read the same evidence and come up with different recommendations
- Outcome measure can be major factor
  - MTBI
  - t-PA in stroke
  - Steroids in spinal trauma
Description of the Process

- Different societies use different classification schemes which may impact applications of the recommendation
- ASA / AHA
Description of the ACEP Process

- Strength of evidence (Class of evidence)
  - I: Randomized, double-blind interventional studies for therapeutic effectiveness; prospective cohort for diagnostic testing or prognosis
  - II: Retrospective cohorts, case control studies, cross-sectional studies
  - III: Observational reports; consensus reports

- Strength of evidence can be downgraded based on methodological flaws
Description of the ACEP Process

- Strength of recommendations:
  - A / Standard: Reflects a high degree of certainty based on Class I studies
  - B / Guideline: Moderate clinical certainty based on Class II studies
  - C / Option: Inconclusive certainty based on Class III evidence
Description of the ASA Process: Levels of Evidence

- **Level A**
  - Data from many large, randomized trials

- **Level B**
  - Data from fewer, smaller randomized trials, careful analyses of nonrandomized studies, observational registries

- **Level C**
  - Expert consensus

Description of the ASA Process: Classes of Recommendations

I  IIa  IIb  III

- Intervention is useful and effective
- Evidence conflicts/opinions differ but leans toward efficacy
- Evidence conflicts/opinions differ; neutral statement
- Intervention is not useful/effective and may be harmful

Why Don’t Physicians Follow Clinical Practice Guidelines?

- Review of 76 articles dealing with adherence
- Barriers to physician adherence identified:
  - Lack of familiarity
  - Lack of agreement
  - Lack of access to intervention or resource
  - Lack of confidence that an intervention will change the outcome
  - Patient related barriers

2006 Recommendations for Use of Thrombolytic Agents

- American Academy of Emergency Medicine
  - “Insufficient evidence”

- Society for Academic Emergency Medicine
  - “Insufficient evidence”

- National Heart, Lung and Blood Institute
  - 0 - 3 hrs (Grade IA)
  - 3+ hrs not recommended

- American Heart Association
  - 0 - 3 hrs t-PA is recommended (Grade IA)

- American College of Emergency Physicians
  - “Insufficient evidence at this time to endorse the use of intravenous t-PA...when systems are not in place”
  - t-PA may be an efficacious therapy...if used according to NINDS criteria

2014 Recommendations for Use of Thrombolytic Agents

- American Academy of Emergency Medicine
  - 0 - 3 confirmed benefit
  - 3 - 4.5 suggested benefit

- Society for Academic Emergency Medicine
  - Rescinded statement

- National Heart, Lung and Blood Institute/American Heart Association
  - 0 - 3 hrs (Grade IA)
  - 3 - 4.5 hrs (Grade 1B)

- American College of Emergency Physicians
  - 0 - 3 hrs t-PA should be offered (Level A)
  - 3 - 4.5 hrs t-PA should be considered (Level B)

AAEM. Clinical practice statement: t-PA and stroke. 4.12.10
Thrombolysis for Acute Ischemic Stroke

- 27 trials; 10,187 participants
- “People given clot dissolving drugs were more likely to have recovered from their stroke and to be independent, especially if they had been treated within the first 3 hours”
- “Older people benefited as much as younger people”
- “The treatment is very effective if started within 3 hours of stroke and definitely improves outcome if given up to 4.5 hours after stroke”

Do the BAC’s Criteria for Stroke Centers Improve Care for Ischemic Stroke?

- Questionnaire regarding the BAC 11 elements sent to 34 academic medical centers
  - 85% had a recognized stroke team
  - 85% had a stroke unit
  - 16,853 acute ischemic stroke cases between 1999 - 2001
    - 2.4% received t-PA
- Written protocols were associated with increased t-PA use

Houston Paramedic and Emergency Stroke Treatment and Outcome Study

- Educational interventional study: 1999 - 2001
  - Phase 1 – Baseline data collection
  - Phase 2 – Educational program to paramedics, public messaging, community screening

- Cases per month increased from 74 to 89
- Paramedic diagnostic accuracy increased from 61% to 79%
- Patients arriving within 120 minutes of symptom onset increased from 58% to 62%
- Use of t-PA increased with a range from 6.8% to 17.2%
  - 3.7% hemorrhage rate

Temporal Trends In Patient Characteristics and Treatment Among Acute Ischemic Stroke Patients at GWTG Stroke Hospitals

- Analysis of 1,093,895 acute stroke patients from the GWTG registry from 2003 to 2011
- 50,798 treated with t-PA
- Door-to-image time decreased from a median of 24 to 20 minutes
- Door-to-needle time decreased from a median of 81 min to 72 min
- t-PA use increased from 4% to 7% in all AIS patients
  - 42% to 77% eligible patients

Key Points

- Alteplase is an FDA approved treatment for acute ischemic stroke and its use in the appropriate setting is a recommendation by ACEP, AAEM, AAN, ASA/AHA, ESO, NICE
- A decision not to use alteplase in the appropriate setting is acceptable but clinical decision-making must be well supported in the medical record
IV t-PA or Endovascular Procedures – Assessing the Evidence

PHILIP B. GORELICK, MD MPH FACP

Professor, Translational Science & Molecular Medicine
Michigan State University College of Human Medicine
Medical Director, Mercy Health Hauenstein Neurosciences
Grand Rapids, MI
Learning Objectives

The learner will be able to discuss the following new evidential sources in relation to acute ischemic stroke treatment:

1. Intravenous tissue plasminogen activator (IV t-PA)
2. Endovascular clinical trials
3. Future directions
Background Information
# Time is Brain – Quantified

**Estimated Loss of Key Nerve Tissue in a Typical Large Artery Hemisphere AIS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Neurons Lost</th>
<th>Synapses Lost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Stroke</td>
<td>1.2 billion</td>
<td>8.3 trillion</td>
</tr>
<tr>
<td>Per Hour</td>
<td>120 million</td>
<td>830 billion</td>
</tr>
<tr>
<td>Per Minute</td>
<td>1.9 million</td>
<td>14 billion</td>
</tr>
<tr>
<td>Per Second</td>
<td>32,000</td>
<td>230 million</td>
</tr>
</tbody>
</table>

AIS = Acute Ischemic Stroke

Onset to Treatment Time with IV t-PA
Need for Speed in Acute Ischemic Stroke

Setting
- AHA/ASA Get With The Guidelines: Stroke program registry of 58,353 t-PA treated patients

Results
- Faster onset to treatment time in 15 minute increments led to:
  1. Reduced in-hospital mortality (OR=0.96; 95% CI: 0.95, 0.98*)
  2. Symptomatic intracranial bleeding (OR=0.96; 95% CI: 0.95, 0.98*)
  3. Increase of independent ambulation at discharge (OR=1.04; 95% CI: 1.03, 1.05*)
  4. Discharge to home (OR=1.03; 95% CI: 1.02, 1.04*)

Conclusion: Rapidity or treatment significantly influences outcomes with IV t-PA in AIS
*P<.001

The Latest Evidence Supporting Use of IV t-PA
Effect of Treatment Delay, Age, and Stroke Severity on the Effects of IV Thrombolysis with Alteplase for Acute Ischemic Stroke: A Meta-analysis of Individual Patient Data from Randomized Trials*

*NINDS A&B, ECASS I-III, ATLANTIS A&B, EPITHET, IST-3

# Effect of Alteplase for Good Outcome (mRS 0-1) by Treatment Delay, Age, and Stroke Severity-1

<table>
<thead>
<tr>
<th>Treatment Delay</th>
<th>Alteplase (n=3391)</th>
<th>Control (n=3365)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 3.0 hrs</td>
<td>32.9%</td>
<td>23.1%</td>
<td>1.75 (1.35, 2.27)*</td>
</tr>
<tr>
<td>&gt;3.0 ≤4.5 hrs</td>
<td>35.3%</td>
<td>30.1%</td>
<td>1.26 (1.05, 1.51)</td>
</tr>
<tr>
<td>&gt;4.5 hrs</td>
<td>32.6%</td>
<td>30.6%</td>
<td>1.15 (.95, 1.40)</td>
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<td>≤80</td>
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<td>1.25 (1.10, 1.42)</td>
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<tr>
<td>&gt;80</td>
<td>17.6%</td>
<td>13.2%</td>
<td>1.56 (1.17, 2.08)</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 4</td>
<td>68.7%</td>
<td>58.9%</td>
<td>1.48 (1.07, 2.06)</td>
</tr>
<tr>
<td>5 - 10</td>
<td>47.7%</td>
<td>43.0%</td>
<td>1.22 (1.04, 1.44)</td>
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Effect of Alteplase for Good Outcome (mRS 0-1) by Treatment Delay, Age, and Stroke Severity-3

Bottom line

- Irrespective of age, stroke severity, and despite an increased risk of fatal ICH early after treatment, alteplase significantly improves odds of a good outcome after stroke within 4.5 hours

UT Houston Mobile Stroke Unit

- Diagnostic Equipment
  - Portable CT scanner (CereTom)
  - Point-of-care laboratory system
  - Teleradiology/Teleneurology connection

The Need for Speed
Speeding up “Door-to-Needle Time”

Slide courtesy of James Grotta, MD, April 2014.
Endovascular Trials in Acute Ischemic Stroke (AIS)

3 Recent Negative Trials Back to Back to Back
# 3 Recent Negative Endovascular Trials in AIS

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Question</th>
<th>Comment</th>
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<tr>
<td>Intervventional Management of Stroke III (IMS-III):</td>
<td>Is endovascular therapy after administration of IV t-PA in moderate-to-severe AIS more effective (and safe) compared to IV t-PA alone within 3 hours after symptom onset?</td>
<td>Primary Endpoint mRS ≤2: Endovascular 40.8% IV t-PA 38.7% (P= 0.70) Predefined Endpoints NIHSS 8-19 or ≥20 (P-value= 0.27)</td>
</tr>
</tbody>
</table>
| Mechanical Retrieval and REcanalization of Stroke Clots Using Embolectomy (MR RESCUE) | 1. Does presence of substantial penumbral tissue predict patients most likely to respond to mechanical embolectomy?  
2. Do embolectomy patients have improved functional outcome compared to randomized controls? | P= not significant for either question (penumbra or embolectomy) |
| SYNTHESIS Expansion                        | AIS patients within 4.5 hours randomized to endovascular therapy (IA thrombolysis with t-PA, mechanical clot disruption or retrieval or a combination of approaches vs. IV tPA) | For mRS (0,1), P= .16 |

Criticisms of These Trials

Was the optimal population targeted?
1. Presence of target vessel occlusion?
2. Presence of target salvageable tissue?
3. Fast and effective reperfusion?
4. Other criticisms

Time to Reperfusion and Good Clinical Outcome: Multivariable Model

- Every 30-minute delay in reperfusion results in a 10% relative reduction in a good clinical outcome on the mRS (0 - 2)
- Conclusions
  1. Good clinical outcome associated with angiographic reperfusion with IA therapy that is time dependent
  2. Faster endovascular reperfusion in IMS III may have yielded a positive result (Mean time from onset to IA end/reperfusion: 325 (5 hrs 25 min): range: 180 - 418
  3. Speed of treatment must be emphasized in future reperfusion trials

Khatri P, et al. ISC Platform Presentation February 2013
Better Engineering Leading to Better Results for Recanalization and Reperfusion

SWIFT and TREVO 2 Trial
“Stent Retrievers”
Solitaire Flow Restoration Device Versus the Merci Retriever in Patients with Acute Ischaemic Stroke (SWIFT): A Randomised, Parallel-group, Non-inferiority Trial

TREVO-2

SWIFT

Current/Future Directions

1. Additional neuroimaging and other factors to better understand the role of:
   A. Collateral blood flow patterns
   B. Clot burden & clot characteristics
   C. Re-visit penumbra & diffusion/perfusion mismatch (volume of infarction vs. tissue at risk), and wake up strokes
   D. Better device technologies
   E. Means to reduce IV t-PA-associated brain hemorrhage

2. Additional trials to prove devices improve efficacy
   A. SWIFT PRIME (IV tPA vs. IV t-PA and the Solitaire device)
   B. Different trial design to answer criticisms

SWIFT PRIME = Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (clinicaltrials.gov NCT01657461)
1. Intravenous thrombolysis remains 1st line therapy for eligible patients with AIS

2. Treatment in the early time window is important

3. Irrespective of age, stroke severity, and despite an increased risk of fatal ICH early after treatment, alteplase significantly improves odds of a good outcome after stroke within 4.5 hours of administration

4. Clot retrieval devices are available for clinical use according to FDA “clearance” status, however, additional study is needed to prove efficacy and safety of the devices in AIS

Case 1

Determining Eligible Candidates for IV t-PA

Ischemic Stroke Presenting 0 to 3 Hours Post Symptom Onset

Andy S. Jagoda, MD
Specific Objectives

- Review current recommendations for t-PA in patients presenting with acute ischemic stroke within 3 hours of symptom onset
- Discuss imaging options for patients presenting with acute ischemic stroke
- Discuss risk/benefit of patients presenting with mild deficits from an acute ischemic stroke
Case 1

- 28-year-old ballerina presents to the emergency department complaining of acute onset of headache, vomiting, left face numbness, right-sided weakness, and feeling off balance
- Symptoms started 1 hour prior to arrival
- No past medical history
- She was in a minor motor vehicle accident 48 hrs prior
- Medications: Birth control pill
Case 1

- 118/68 mmHg
- 16 breaths/min
- Pulse: 68 beats/min
- pOx: 98%
- Blood glucose 110 mg/dL
- NIHSS 4
  - Mild left-face droop = 1
  - Slight drift on upper and lower right extremity = 2
  - Mild loss of sensation on right face = 1
Question 1: Do you do a HINTS evaluation as part of your neurologic exam in patients with suspected posterior circulation stroke?

1. Yes
2. No
3. I don’t know what a HINTS evaluation is
HINTS Testing

- Performed in patients who are symptomatic
- Head Impulse – eyes remain focused on object (vestibular ocular reflex)
  - Normal in stroke
  - Abnormal in peripheral problems (catch up saccades) because the vestibular nerve is not working
- Nystagmus – fast phase change direction in stroke
  - Benign conditions beat in only one direction
  - Central lesions: direction changing nystagmus
- Test of Skew - vertical disconjugate gaze
  - Alternate cover change – avoids fixation

www.emcrit/misc/posterior-stroke-video/
HINTS

- CT misses from 60% to 90% of acute ischemic strokes in the brainstem or cerebellum.
- MRI with diffusion-weighted imaging is more reliable than CT, but still misses from 15% to 20% of patients with posterior circulation stroke in the early period.
- HINTS is reported to be up to 99% sensitive when performed by an experienced clinician.

Question 2: Which of the following is the most likely cause of acute ischemic stroke in this 28 year old woman who has no medical problems?

1. Cervical artery dissection
2. Vertebral artery dissection
3. Cocaine abuse
4. Patent foramen ovale
5. Hypercoagulable state due to birth control pill
Question 3: If vertebral artery dissection is considered as the cause of an acute ischemic stroke, what is the emergent imaging of choice?

1. Noncontrast CT
2. CT angiography head and neck
3. MRI head
4. MRA head and neck
5. Not sure
Imaging in Acute Ischemic Stroke

- Non-contrast head CT is generally the first test in acute ischemic stroke, but has limitations.
- P’s of acute stroke imaging: Parenchyma (brain), Pipes (vasculature), Perfusion (blood flow), and Penumbra (at-risk tissue).
- Sequence studies: Non-contrast head CT, CT angiography (CTA) of the head and neck, and perfusion CT (CTP).
- Enhances the sensitivity of emergent CT neuroimaging for acute ischemic processes.
- Identifies patients who may benefit from endovascular interventions.
Imaging in Acute Ischemic Stroke

- Emergency imaging of the brain is recommended before initiating any specific therapy to treat acute ischemic stroke (IA).
- CT perfusion and MRI perfusion and diffusion imaging including measures of infarct core and penumbra may be considered for the selection of patients for acute reperfusion therapy beyond the time windows for IV t-PA (IIb).
- Noninvasive imaging of the cervical vessels should be performed routinely as part of the evaluation of patients with suspected TIA (IA).

Question 4: Would you give t-PA to this patient with a NIHSS 4 and a vertebral artery dissection?

1. Yes
2. No
3. Not sure
Minor Stroke: To Lyse or Not To Lyse?

..NO
Relative Exclusion Criteria:
“Only minor or rapidly improving stroke symptoms (clearing spontaneously)”

..YES (?)
NIHSS\(\leq 6\) better outcome with t-PA \((P=0.047)\)

BUT...
Treating all mild AIS patients with IV t-PA could potentially save up to $200 million in the USA alone.

ACEP/AAN Clinical Policy: Use of Intravenous t-PA for the Management of Acute Ischemic Stroke in the Emergency Department

- Level A Recommendation: “In order to improve functional outcomes, IV tPA should be offered to acute ischemic stroke patients who meet NINDS inclusion/exclusion criteria and can be treated within 3 hours of symptom onset”*
  - NINDS exclusion: Rapidly improving or minor symptoms

*The effectiveness of t-PA has been less well established in institutions without the systems in place to safely administer the medication

AHA / ASA 2013 Recommendation

- Use of intravenous fibrinolysis in patients with conditions of mild stroke deficits, rapidly improving stroke symptoms, major surgery in the preceding 3 months, and recent myocardial infarction may be considered and potential increased risk should be weighed against the anticipated benefits (Class IIb, Level C).

Case 1 (continued)

- Patient received t-PA without improvement
- One hour later she became “unresponsive” and unable to move all extremities
- She was able to blink appropriately in response to “yes/no” questions
- Repeat CTA showed no hemorrhage and evidence of basilar artery thrombus
Question 5: At your hospital what would you do?

1. Activate the neuro-interventional team
2. Transfer to a comprehensive stroke center
3. Admit to the ICU
4. Not sure
Case 1 (continued)

- Patient did not receive any additional intervention
- She remains “locked-in” 3 years post event with tracheostomy and peg
Conclusions

• High quality evidence supports the use of t-PA for acute ischemic stroke
• The HINTS evaluation is useful for identifying posterior circulation strokes
• A low NIHSS score is not a contraindication for tPA and risk must be weighed against benefit and quality of life
• Young patients with no history of DM or hypertension, with a normal head CT are at low risk for sICH
• Patients with cervical artery dissection are candidates for tPA if the dissection is extra-cranial
• The role of endovascular interventions for acute ischemic stroke are still being defined
Current Status of Telemedicine in Stroke Care

Joshua N. Goldstein, MD, PhD, FACEP

Associate Professor, Harvard Medical School
Director, Center for Neurologic Emergencies
Department of Emergency Medicine
Massachusetts General Hospital
Boston, MA
How Busy is the Average Emergency Department?

<table>
<thead>
<tr>
<th>Number of Visits per Year</th>
<th>Number of Emergency Departments</th>
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<tbody>
<tr>
<td>&lt;10k</td>
<td>1718</td>
</tr>
<tr>
<td>10-19k</td>
<td>1150</td>
</tr>
<tr>
<td>20-29k</td>
<td>822</td>
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<td>40-49k</td>
<td>299</td>
</tr>
<tr>
<td>&gt;50k</td>
<td>375</td>
</tr>
</tbody>
</table>
“Higher” Volume EDs

- Proportion of higher-volume (≥8,760 visits/year) EDs differed by region
  - Percentage of high-volume EDs by region, 2001:
    - Southern States: 72% of 1,328 total EDs
    - Midwestern States: 55% of 1,425 total EDs
    - Western States: 66% of 890 total EDs
    - Northeastern States: 89% of 713 total EDs

“Lower” Volume EDs

- Low volume (<8,760 visits/year)
- States with the lowest ED volume (2001):
  - Hawaii
  - South Dakota
  - Utah
- 83% of low-volume EDs were located in a rural setting

Why Telestroke?

- Provides “acute stroke specialist” availability remotely
- Cost effective means to staff a low-frequency, high-impact event
- Concentrate the expertise (high-volume providers but at low-volume sites)
- Standardize care across a range of centers
Advantages of Video Over Telephone
Telestroke

Video: “Best Gaze”

*Video available for download at the “Resources” link for this program

Partners Telestroke
telestroke.massgeneral.org
Ability to See Subtle Findings

Video:
“Motor Arm”

*Video available for download at the “Resources” link for this program

Partners Telestroke
telestroke.massgeneral.org
The Telestroke "Hub and Spoke" Model
Models of Telestroke Care

- Hospital-based hub and spoke
- For-profit, telemedicine company-based hub and spoke
- Multi-point acute telestroke consult
- Hub-less private practice physicians

Class I, Level A Recommendations

- HQ-VTC systems are recommended for performing an NIHSS-telestroke examination in non-acute stroke patients, and this is comparable to an NIHSS-bedside assessment.

- The NIHSS-telestroke examination, when administered by a stroke specialist using HQ-VTC, is recommended when an NIHSS-bedside assessment by a stroke specialist is not immediately available for patients in the acute stroke setting, and this assessment is comparable to an NIHSS-bedside assessment.

- FDA approved teleradiology systems are recommended for timely review of brain CT scans in patients with suspected acute stroke.

- Review of brain CT scans by stroke specialists or radiologists using teleradiology systems approved by the FDA (or equivalent organization) is useful for identifying exclusions for thrombolytic therapy in acute stroke patients.

• Class I, Level of Evidence B
  – In a telestroke network, FDA-approved teleradiology systems can be effective in supporting rapid imaging interpretation in time for thrombolysis decision making.
  – A stroke specialist using HQ-VTC should provide a medical opinion regarding the use of IV t-PA in patients with suspected stroke when on-site stroke expertise is not immediately available.
  – When the lack of local physician stroke expertise is the only barrier to the implementation of inpatient stroke units, telestroke consultation via HQ-VTC is recommended.
  – Assessment of occupational, physical, or speech disability in stroke patients by allied health professionals via HQ-VTC systems using specific standardized assessments is recommended when in-person assessment is impractical.

Class II, Level of Evidence A
- HQ-VTC is reasonable for performing a general neurological examination by a remote examiner with inter-rater agreement that is comparable to that between different face-to-face examiners.

Class IIb, Level of Evidence C
- Compared with traditional bedside evaluation and use of intravenous t-PA, the safety and efficacy of intravenous t-PA administration based solely on telephone consultation without CT interpretation via teleradiology are not well-established.

Telestroke Challenges

- Financial Sustainability
  - Costs of infrastructure
  - Who is paying?

- Human Resources Sustainability
  - Time and effort on both sides (hub and spoke teams)
  - Licensure and credentialing barriers
  - Can the technology be leveraged to support other purposes including education, networking, etc?
Common Barriers

**Imaging**
- Routine Testing
- Reliability of Connections

**Stakeholder Buy-In**
- Getting MDs More Comfortable Using System

**Video**
- Reliability, Image Quality
- Routine Testing of Connections, Endpoint Upgrades

**Workflow**
- Improving “Door-to-Needle” Time
Lessons Learned: Best Practices to Consider

• Have a clinical champion at both ends
• Have Emergency Department support
• Standardize clinical care protocols
• “Over” train spoke hospital staff
• Make contingency plans for technology failures
• Sign transfer agreements
• Establish reporting and feedback mechanisms
Challenges to Telemedicine for Stroke

- First and foremost
  - Business model
- Next consideration
  - Hardware
  - Credentialing
  - Backup
  - Secondary services
  - Integration into regional stroke systems of care
  - Integration into other eHealth initiatives
The Future

- Telemedicine from the ambulance?
OPENING THE WINDOW OF TIME IN
STROKE THERAPY
New Evidence for the Emergency Department

Course Chair:
Andy S. Jagoda, MD
Professor and Chair
Department of Emergency Medicine
Mount Sinai School of Medicine
New York, NY