The SMART Approach to Acute Ischemic Stroke Therapy

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Acute Ischemic Stroke

• Definitions and epidemiology
  – Acute ischemic stroke (AIS)

• Hyperacute (<6-8 hrs) AIS strategies and therapy
  – Approved therapies
  – Emerging therapies
  – The SMART rt-PA inclusion and exclusion criteria
  – Neuroimaging as a selection tool

• Healthcare infrastructure for stroke patient triage and care
  – Streamlining care
  – Telemedicine
Stroke Epidemiology and Facts

• 3rd leading cause of death and leading cause of disability in US

• Prevalence: ~750,000 strokes/year in US, 70% of patients survive

• Cost: ~$68 billion/year

• RF’s: >40 yrs, heart dz, HTN, tob, DM, HL, h/o TIA/stroke, obesity, drug use, recent childbirth, sedentary lifestyle
Stroke Epidemiology and Facts

• Sex:
  – ~60,000 more women than men have stroke/year
  – 60% of total stroke deaths are women

• Race:
  – African Americans twice likely to die from stroke, rate of first stroke double of Caucasians
  – AA males 3x likely to have ischemic stroke than same age grp of Caucasians
  – ~50% AA women will die of CV disease (hrt dz or stroke)
  – Asian Americans: increased risk of hemorrhagic stroke and intracranial atherosclerosis, but overall lower risk of death from stroke
Stroke Definitions

• Ischemic and hemorrhagic stroke:
  – Sudden neurologic damage
  – Caused by disturbance of circulation to the brain/spinal cord/retina

• Transient Ischemic Attack (TIA):
  – Temporary, focal neurologic deficit related to ischemia, lasting <24 hrs
  – Tissue-based def’n: transient episode of neuro dysfunction caused by ischemia without acute infarction

Stroke 2009; 40: 2276-2293
Etiologic Subtypes of Stroke and Frequency

Ischemic (85%)

Unknown (25%)

Embolism (20%)

Small Vessel Disease/ Lacunar (20%)

Thromboembolic (20%)

Hemorrhagic (15%)

Intracerebral hemorrhage (10%)

SAH: Aneurysm (5%)

Acute Ischemic Stroke (AIS): Hyperacute

- Strategies
- Approved therapies
- SMART Criteria
- Neuroimaging as a tool to identify best therapeutic option: cases
Acute Ischemic Stroke (AIS): Hyperacute Strategies

- Reperfusion and recanalization:
  - Drug therapy (rt-PA)
  - Devices
- Neuroprotection:
  - Pre-hospital (Mg++ Rx)
  - Post-hospital (hypothermia, hyperoxia?)
- Augmenting collateral flow and saving ischemic penumbra:
  - HTN’ive therapy
  - Devices
AIS Hyperacute Strategies: Saving “Tissue at Risk”

Tissue at risk or ischemic penumbra
AIS Hyperacute: Case 1

• History
  - 16 yo boy with h/o stroke 2006 (R MCA, no residual), migraine H/A
  
  - Last seen normal 13:30 noted to have L facial droop, slurred speech, poor balance while walking + severe H/A

  - PMH: neg stroke workup except for ?elevated Factor XIII; migraine H/A but uncomplicated; asthma

  - SH: basketball prodigy, no h/o drugs of abuse

• ED Assessment at 15:13:
  - MS: alert, very mild L neglect, orient x 3, language intact
  - CN: dense L facial droop, dysarthria
  - Motor: slower L FFM/FT; mild L dysmetria on FNF NIHSS ~5

• CT/CTA/CTP…
AIS Hyperacute: Case 1
CT
AIS Hyperacute: Case 1

MTT

CBV

CTP
What should we do?
AIS Hyperacute: Case 1

• Hospital Course:
  - After appropriate consent from mother…
  - Full dose IV tPA (0.9mg/kg) given at 16:00 (2.5hrs)
  - Follow-up exam in ICU: H/A persisted, but L facial droop and L wx/ataxia improved

• Follow-up:
  - Pt continued to improve neurologically
  - MRI and TTE performed following day…
AIS Hyperacute: Case 1
MRI

DWI
AIS Hyperacute: Case 1
MRI
FLAIR
AIS Hyperacute: Case 1
MRA
AIS Hyperacute: Case 1

• Hospital Course:
  - TTE and TEE: mitral valve mass (atrial side); mass consistent with vegetation or papillary fibroelastoma; valve itself is normal
  - Pt underwent CT surgery to remove mass…

• Follow-up:
  - Pathology of mass: thrombus
  - Hypercoag w/up performed, Heme/Onc consulted
  - Pt started on coumadin
  - Pt back to normal as outpt
AIS Hyperacute: Therapies

• Approved therapies
  – Thrombolysis: IV rt-PA
  – Mechanical embolectomy (approved devices but not proven therapy)

• Emerging therapies
  – Thrombolysis: IA rt-PA, combined IV and IA rt-PA, new fibrinolytics
  – New devices: U/S augmentation
  – Neuroprotection: hypothermia, neuroprotective drugs
  – Augmentation of collateral flow
Thrombolysis
Thrombolytic Therapy: Background

• Recombinant Tissue Plasminogen Activator (rt-PA, Alteplase, tPA)
  – Clot dissolving medication
  – Originally used in pt’s with MI
  – IV tPA approved by FDA for stroke use 6/96
  – Initially approved for use less than 3 hours after symptom onset, now safe to use up to 4.5 hrs
Thrombolysis with IV rt-PA: Clinical Outcomes

- 30-40% increase in chance of good outcome at 3 mth (39% rt-PA vs 26% placebo mRS 0-1 at 3 mth)
- Number needed to treat: 8 pt’s for one without significant disability
- 6.4% chance of symptomatic ICH (vs. 0.6%)
  - Overall mortality similar in both groups
  - ICH mostly in people with severe stroke
- Outcome depends upon:
  - Benefit seen in all subgroups
  - Severity of symptoms
  - Time to treatment
  - Other medical factors (i.e. blood pressure, general medical condition, brain imaging findings, recent bleeding/surgery etc)

NEJM 1995; 333: 1581-7
Time Window for IV rt-PA Extended: ECASS III

- Time of onset $\leq$ 3-4.5 hrs
  - More pts had favorable outcome at 90 days (52% vs. 45%; OR 1.34) with rt-PA
  - Similar to original rt-PA study (OR 1.7)
  - Different exclusion criteria: >80 yo, NIHSS>25, DM and prior stroke
- Safety:
  - Any ICH 27% vs. 17.6%, symptomatic ICH 2.4% vs. 0.2% in placebo (less than original study)
  - No change in mortality
- CPMC, AHA/ASA Guidelines: IV rt-PA window extended to 0-4.5 hrs

*NEJM 2008; 359: 1318-1329*  
*Stroke 2009; 40: 2945-48*
NINDS rt-PA Stroke Study:
Time to Treatment and Odds Ratio of Favorable Outcome

Minutes

Stroke Onset To Start of Treatment

Odds Ratio
Favorable Outcome

Benefit for rt-PA
No Benefit for rt-PA

μ

95% CI
OR

Marler et al; Neurology Dec, 2000
*Lancet 2004 (363): pooled analysis
Relative Contraindications to rt-PA

- Conditions that increases bleeding risk:
  - Anticoagulation (INR > 1.7), recent (< 30d) surgery/ head trauma or stroke, low platelets, other bleeding disorder, acute transmural MI
- Seizures at stroke onset
  - To avoid stroke mimics due to seizure (Todd’s paralysis)
- Uncontrolled BP >185/110
  - May tx with 1-2 doses IV BP meds within 10-15’
- Significant metabolic abnormality
  - To avoid stroke mimics due to metabolic derangement
- Rapidly resolving symptoms
  - Mild to moderate fluctuations common
- Major CT scan abnormality
  - Commonly over interpreted
- Significant dementia, short life expectancy

NEJM 1995; 333: 1581-7
Broadening Indications for rt-PA in Acute Stroke?

- Time of onset – up to 4.5 h and beyond?
  - Neuroimaging as a tool to select patients beyond 4.5hr?

- Defining “significant” neurological deficit
  - Simple rule: If you feel the deficit will impair the patient’s quality of life, then it is “significant”
    - Usually, NIHSS ≥ 4 (NIHSS maximum = 42) but will do NIHSS 0!!

- There many clinical situations showing benefit of IV rt-PA beyond guidelines (children, post-op, etc..) - requires further study!

- Recent data showing no significant risk in treating stroke mimics with rt-PA

*Stroke 2007: 38: 2612-18*
AIS Hyperacute: Case 2

- **91** year old female at remote hospital
- Acute aphasia, right sided weakness
- Symptom onset time: 15:15
- Past Medical History:
  - congestive heart failure
  - atrial fibrillation
  - **active bleeding hemorrhoids**
- Receiving warfarin: INR 2.5
Case 2: Examination

- Telemedicine consultation using remote video equipment: 16:15 (60 minutes)
- Exam: NIHSS=27 (right hemiplegia, aphasia, neglect, visual field cut)
- Non-Contrast Head CT: negative
What should we do?
Thrombolysis Contraindications in this Case

- Older Age (≥80)
- Large stroke (NIHSS >20)
- Anticoagulation (INR 2.5)
- Active Bleeding (hemorrhoids)
What should we do?
Case 2: Management

- Half dose IV rt-PA (0.45 mg/kg) administered at 17:30 (2h:15m)
- Transferred
- Upon arrival (3 hours later): Aphasia improved, right side strength is better (3/5)
- CTA/CTP performed
CT Perfusion (CTP)

- rMTT (tissue at risk)
- rCBV (damaged tissue)
CT Angiogram (CTA)
Case 2: Management and Outcome

• No further treatment
  – CTP: no tissue at risk
  – CTA: no large artery occlusion
• Patient experienced **full recovery**
• No bleeding
• MRI
Case 2: Diffusion Weighted MRI (DWI)
Conclusions

• IV rt-PA is **not** contraindicated in many patients who are frequently excluded from treatment including:
  – Age $>$80 (or $>$90)
  – Large strokes ($\text{NIHSS} > 20$)
  – Anticoagulated ($\text{INR} > 1.7$)
  – Active bleeding (mild)

• CTP/CTA useful in management

• Criteria for IV rt-PA need revision
  – Many more patients can be treated safely and effectively
  – **Use SMART criteria!!**
SMART
Simplified Management of Acute Stroke Using Revised Treatment Criteria

Courtesy of Dr. David Tong
Background

- Use of IV rt-PA for ischemic stroke is very low
  - 1.1-3% of all ischemic stroke patients\textsuperscript{1,2}
  - ~5-10% of stroke patients at stroke centers
- Highest published sustained treatment rate:
  - 15% at UT Houston stroke program\textsuperscript{3}

\textsuperscript{1} Ann Emerg Med, May 2007
\textsuperscript{2} Reed, Stroke 32(8); 2001
\textsuperscript{3} Arch Neurol 2001;58:2009–2013
The SMART Premise

- Current IV rt-PA treatment criteria are too strict
  - Clinical trial ≠ clinical practice
  - Exclusion criteria are not evidence based
  - Many centers’ exclusion criteria even more strict than guidelines

- Simplified Management of Acute Stroke using Revised Treatment Criteria (SMART)
  - Rethink exclusion criteria
  - Increase number of candidates for treatment
  - Streamline management
  - Use new technology to further increase treatment
    - CT perfusion (CTP)/CT angiography (CTA)
    - Telemedicine: inexpensive, accurate
Common IV rt-PA Contraindications That Are NOT SMART Criteria

- Stroke severity (mild or severe)
- Older Age ($\geq 80$)
- Presence of other asymptomatic brain lesions (e.g. tumor, aneurysm, subdural hematoma etc.)
- Improving symptoms (if still disabling)
- Stroke, head trauma, surgery, other bleeding or arterial puncture $< 3$ months
- Seizure
- Blood sugar (low or high)
- Elevated PTT/INR (on warfarin, heparin, LMWH)
- Pregnancy/children
- Dementia
- Renal failure, MI, other co morbidity
- Early infarct signs on CT
SMART: IV rt-PA

Absolute Exclusion Criterion

- Acute intracranial hemorrhage that is the cause of the patient’s symptoms
SMART: Frequency of Common Relative Contraindications

- Age (>79):
- Mild sx (NIHSS < 5):
- Improving/fluctuating:
- Time > 3-4.5h:
- Prior stroke:
- Dementia/low life expectancy:
- Anticoagulation:
- Recent surgery:
- Recent/active bleeding:
- Aneurysm/sdh/tumor:
- BP high:
- Unclear sx:
- Med illness (ie sepsis etc.):
- Recent catheterization:
- Trauma:
- Seizure:
- Language:

Percentage breakdown: 42%, 24%, 18%, 13%, 9%, 9%, 8%, 8%, 6%, 6%, 5%, 3%, 3%, 3%, 2%, 1%, 1%. 
SMART: Reduction of rt-PA Exclusions

- No NIHSS (stroke severity) cut offs
  - symptoms must be “disabling”
  - “mild strokes” cause significant morbidity/mortality
    - ~20-30% of “mild strokes” are disabling, especially if large artery occlusion present
    - Represent ~20-30% of acute stroke patients
    - Higher risk of subsequent deterioration
    - rt-PA effective in these patients
  - Severe strokes also benefit from IV rt-PA
- No age cut off
  - Older patients generally do worse, but still benefit from treatment

2. Nedeltchev Stroke. 2007;38:2531-2535
3. Barber, Neurology 2001;56:1015-1020
5. De Kayser, Stroke. 2007;38:2612-2618
SMART: Dealing with Stroke MIMICS

• If unclear it is a stroke, should you treat?
  – Risk of hemorrhage is very small (<1%)\(^1\-^4\)
  – Repercussion of missing treatment may be high
  – Mimics may constitute 10-23% of acute stroke rt-PA cases at high volume centers\(^1\)
    • Risk of bleeding is 0% in these cases
  – If you have not treated a stroke mimic with rt-PA, you are likely under treating

CPMC Thrombolysis Rate 6/06-12/09

- Outcomes: 59% independent (mRS ≤ 1)
- Symptomatic hemorrhage: 1.9%
- Mortality: 7.9%
- Mean age: 76 (NINDS: 66-69)
- Mean NIHSSS: 10
Using SMART Criteria: Our Hospital’s Results

• Between 7/06 and 12/09, 178 patients received thrombolysis
  – Represents 25-30% of ALL acute ischemic stroke patients at our hospital during this time
  – >95% of patients eligible for rt-PA RECEIVE it

• 135 patients (76%) treated with IV rt-PA alone using SMART criteria
SMART IV rt-PA Stroke
Patient Characteristics

• 49% male
• Mean NIHSS= 10
• Median age 76 years (NINDS age: 66-69)
  – 42% ≥ 80 years old
  – 13% ≥ 90 years old
• Median door to needle time: 58 minutes
• Median symptom onset time to treatment time:
  – 135 minutes (95% CI 65-195 minutes)
  – 21% >3h after symptom onset
SMART: High Number of Relative Treatment Contraindications

• On the basis of common IV rt-PA exclusion criteria **89%** of these patients would NOT have qualified for thrombolysis
  - 42% age $\geq$ 80 (13% $\geq$ 90)
  - 24% NIHSS $\leq$ 5 (41% NIHSS $\leq$ 7)
  - Average # contraindications: 1.4, (range 0-4)
  - 45% had more than one relative contraindication
C PMC Versus Major IV rt-PA Studies

Good Outcome (Rankin 0-2)*
- CPMC (n=135)*
  - 46%
- Average IV rt-PA (5 studies, n=8494)* **
  - 59%
- Average placebo (3 studies, n=1460) * **
  - 33%

Symptomatic ICH
- CPMC (n=135)*
  - 2% (2.2%)
- Average IV rt-PA (5 studies, n=8494)* **
  - 6.7%
- Average placebo (3 studies, n=1460) * **
  - 18%

Mortality
- CPMC (n=135)*
  - 13%
- Average IV rt-PA (5 studies, n=8494)* **
  - 18%
- Average placebo (3 studies, n=1460) * **
  - 7%

*Good outcome = Rankin 0-1 for NINDS/ECASS3 trial/CPMC data
** SITS-MOST/ECASS 3 excluded patients > 80 y, stroke > 1/3 MCA, or “severe”, NIHSS > 25, ECASS 3 also excluded DM + prior stroke

References:
- Lancet. 2007 Jan 27;369(9558):275-82
- Lancet. 2004;363:768-774
- NEJM 1995;333:1581-1587
AIS: Healthcare Infrastructure

- Streamlining stroke patient triage and care
- Telemedicine
**SMART: Streamlining the ED rt-PA Evaluation Process**

**Evaluation Elements Recommended by AHA/ASA¹**
- Patient history
- Noncontrast CT scan of the brain
- Physical examination
- Neurological examination using a formal stroke scale (eg, NIHSS)
- Diagnostic tests include, but are not limited to:
  - Electrocardiogram (ECG)
  - Prothrombin time (PT)/international normalized ratio (INR)
  - Blood glucose
  - Activated partial thromboplastin time (aPTT)
  - Serum electrolytes/renal function tests
  - Oxygen saturation, complete blood count, including platelet count

**Possible Expedited Protocol to Further Reduce Time to Treatment: CPMC Experience²-⁴**
- 1-hour time of arrival to IV rt-PA administration
- Stroke code alerts CT technologist to clear scanner
- 25 minutes to CT completion; 45 minutes for results; Stroke MD reads scans
- 45 minutes to lab results
- Stroke MD available 24/7, telemedicine evaluation possible if not in-house
- Do not wait for lab results for CTP/CTA, or for IV rt-PA if patient is not anticoagulated
- rt-PA ordered the minute CT negative for ICH; estimated weight used (and safe) for IV rt-PA
- No written consent required

*Based on study of 103 patients. CTP = computerized tomography perfusion, CTA = computed tomographic angiography

CPMC SMART: Rapid ED evaluation

- Door to CT completion: 15 minutes
- Door to needle: 62 minutes
- Symptom onset to needle: 135 minutes
- Requires strong commitment from hospital and staff
- Increases options for treatment
AIS Hyperacute: Case 4

- Male (79 years), chronic atrial fibrillation, on warfarin (INR 2.2)
  - History of prior stroke with residual, mild right visual field cut

- Acute onset left hemiparesis, right gaze preference

- Last considered well: 11:00 pm
  - Possibly okay at 12:00 midnight

- Collapsed going to bathroom: 1:30 am

- Arrival at local ED: 2:30 am; telestroke consult: 3:00 am
AIS: Case 4

- Examination
  - 0/5 left side, right gaze, left visual field, left facial, dysarthria, NIHSS=16

- CT hyperdense MCA dot sign

- Old left occipital stroke
• AIS: Case 4
Case 4: Contraindications?

- Anticoagulation?
- Uncertain time of onset?
- Age?
Case 4: Management

- Discussed treatment approach with patient and wife
- Patient treated: 4:00 AM

**Rationale**

- Stroke was severe and unlikely to improve spontaneously
- Far from IA treatment (at least 2 hours)
- There is no evidence that IA is better than IV
- There is no evidence anticoagulation increases bleeding risk significantly
  - IA generally always uses heparin!
AIS: Case 4

- Upon arrival at CPMC: 6:00 AM
  - Major improvement: NIHSS=2
  - CT/CTA/CTP
FS: CTA/CTP
AIS: Case 4 CTA/CTP
AIS: Case 4

- Despite M2 occlusion, no treatment

- Rationale:
  - CTP shows minimal if any hypoperfusion
  - Clinically, patient is near normal
  - If CTP had been abnormal, one would probably have proceeded (misery perfusion)

*M2 = second division middle cerebral artery.*
Case 4: Assessment Post-IV tPA
Case 4: Conclusions

■ Rethink your exclusions to IV rt-PA

■ CTP can aid substantially in treatment decisions and management (if only to reassure you of things)
SMART-TEL: **Optimizing Stroke Care Through Telemedicine**

Stroke centers provide quality stroke care but have limited reach. To address this, telemedicine plays a crucial role.

**Telemedicine**
- Well-established mechanism of providing specialized care beyond a hospital’s physical confines
- Uses technology to connect patient and physician with a remote specialist:
  - Telephone
  - Teleradiology
  - Videoconferencing
- The use of telemedicine for stroke care, termed ‘Telestroke’, now typically involves videoconferencing
- Results from the STRokE DOC study demonstrate video conferencing to be superior to telephone consultation in the treatment and management of stroke patients (98% vs 82%, \( P = 0.0009 \))
- Potential benefits of Telestroke include improved outcomes, reduced morbidity, and mortality

STRokE DOC = Stroke Team Remote Evaluation Using a Digital Observation Camera.
*Stroke* 2009;40;2635-2660
Conclusions

• Hyperacute stroke therapy still time-sensitive, several emerging therapies to expand treatment eligibility

• SMART Criteria may increase eligibility and benefit from IV rt-PA

• Stroke centers with 24/7 care and interventional services effective, telemedicine effective

• Neuroimaging is an important focus of research for acute stroke therapy

• Prevention and early detection are still essential first steps
CPMC Comprehensive Stroke Care Center
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Additional Slides
STROKE DOC Results

NIHSS Mean 9.5 vs. 7.7 (video vs. telephone)

*Odds ratio [OR] 10.9, 95% CI 2.7–44.6; p=0.0009

Lancet Neurol 2008; 7: 787–95
SMART: **IV not IA** Is Preferred Initial Treatment

- **Rationale:**
  - Time to reperfusion is likely more important than modality of reperfusion
    - IA treatment requires much more time to initiate compared with IV and is generally less available
  - No compelling data that IA is superior to IV, including in large artery occlusion or basilar occlusion
  - IA can always be added to IV (bridging/full dose)
  - IV first may “soften” clot, and make IA more effective
  - No good evidence that higher dose rt-PA causes more bleeding, especially if delayed
  - Data supporting IA thrombolysis is lower quality than that supporting IV
IV vs. IA therapy myths

- IA better than IV due to higher recanalization rate
  - Not been conclusively shown
  - Difficult to make a fair comparison (timing/severity/location)
  - Clinical outcomes may not be significantly different
- IA better >3h
  - ECASS 3 refutes this
- IA better in VB stroke
  - Similar outcomes in meta analysis\(^2\)
- IA superior if occlusion seen on CTA/MRA/CUS
  - See above, limited evidence
- DWI/PWI identifies good IA candidates
  - DEFUSE/EPITHET show IV rt-PA works in these patients

\(^1\) *Stroke.* 2007;38:2191-2195

SUPER SMART
(SUpplementing Perfusion To Enhance Recanalization)

- CPMC Protocol: Full Dose IV+IA rt-PA
- 7/07-6/10: 21 patients received full dose IV+IA
- All patients receive pre treatment CTP/CTA
- Median age 63 (43-94)
- Median NIHSS=15
- Revascularization: 95%
- Mean time to IA: 512 minutes (8.5 hours)
- Discharge mRS ≤ 2: 29%
- Symptomatic ICH: 5% (n=1)