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**ED Patient Neuroprotection:**  
*What neuroprotection strategies do we as emergency physicians utilize in the ED?*


Edward Sloan, MD, MPH, FACEP



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**IEME**  
**Current Concepts in Emergency Care**  
*Maui, HI*  
*December 4, 2006*

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**Edward P. Sloan, MD, MPH**  
**FACEP**

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*Department of Emergency Medicine*  
**University of Illinois College of Medicine**  
**Chicago, IL**

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**Attending Physician**  
**Emergency Medicine**

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*Our Lady of the Resurrection Hospital*

**Chicago, IL**

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Foundation for Education and Research  
in Neurological Emergencies

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**Disclosures**

- Consultant to Baxter, Eisai, King Pharma, Novo Nordisk
- Speaker's bureau Eisai
- FERNE President and Board Chair
- ACEP Clinical Policy Committee
- FERNE support from Astra Zeneca, Eisai, Novo Nordisk, UCB Pharma

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## Thanks You

- IEME
- Marvin Wayne, MD (and Joan)
- The FERNE staff:
  - Charri
  - Carla
  - Jonathan
  - Li
- All of you

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## Global Objectives

- Maximize patient outcome
- Utilize health care resources well
- Optimize evidence-based medicine
- Enhance ED practice
  - Better processes
  - Better sense of well being
  - Better understanding of who we are and what we do

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## Sessions Objectives

- State key questions and concepts
- Why perform neuroprotection?
- What global neuroprotection do emergency physicians provide?
- What specific disease states?
- What specific therapies?
- What lies ahead?

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## ED Ischemic Stroke Patient Neuroprotection: *What neuroprotection strategies do we utilize and what might be the role of NXY-059?*

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## Case Presentation...

- 64 year old presents to ED
- L Hemiparesis and aphasia
- Symptoms onset 45 minutes ago
- No headache or trauma
- History of TIA x 1, similar symptoms
- Hx DM, smoker
- No recent illness

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## ED Neuroprotection: *Key Concepts*


- Outcome related to infarct volume
- Need to limit infarct size
- Aggressively Rx ischemic penumbra
- ED MD is the best neuroprotectant
- Specific neuroprotectants tested
- SAINT-I clinical trial showed benefit
- Specific questions to be addressed

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### ED Neuroprotection: Key Concepts

- Outcome related to infarct volume

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### Stroke Volume and Outcome

- Vessel occlusion
- Infarct core
- Ischemic penumbra
  
- How large is the core in the ED?
- What is the penumbra conversion?
- Do ED therapies limit infarct growth?

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### ED Neuroprotection: Key Concepts

- Outcome related to infarct volume
- Need to limit infarct size

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### Limiting Stroke Volume

- Enhance perfusion
- Treat hypoxia, hypotension
- Limit ischemic cascade effects
- Prevent complications

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### ED Neuroprotection: Key Concepts

- Outcome related to infarct volume
- Need to limit infarct size
- Aggressively Rx ischemic penumbra

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### Aggressively Rx Ischemic Penumbra


- Maximize cerebral perfusion
- Provide optimal substrates, O2
- Avoid cell death
- Maintain intact blood brain barrier

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### Cerebral Perfusion

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- $CPP = MAP - ICP$
- Cerebral perfusion pressure
- Mean arterial pressure
- Intracranial pressure

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### Cerebral Perfusion

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- $CPP = MAP - ICP$
- $MAP = 2/3 DBP + 1/3 SBP$
- 150/90
- $MAP = 2/3 (90) + 1/3 (150) = 110$
- If MAP = 110 mmHg, ICP 20 mmHg
- CPP then equals 90 mmHg

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### Cerebral Perfusion

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- Cerebral blood flow auto-regulation
- CPP maintained over range of MAPs
- Pathological ICP elevations limited
- Unless...
- Hypertensive emergency with upregulation of acceptable BPs
- Local infarct with edema, greater ICP

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### Mean Arterial Pressure

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- 120 / 75    MAP = 90 mmHg
- 210 / 120    MAP = 150 mmHg
- 185 / 110    MAP = 136 mmHg
- How much MAP therapy is OK?
- What MAP is optimal in acute stroke?
- How to avoid watershed infarct?

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### Mean Arterial Pressure

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- 20-25% reduction acutely is optimal
- MAP of 140-150
- 25% reduction 30-40 mm Hg
- MAP optimally should be 110-120
- Perhaps as low as 100, but no lower

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### Mean Arterial Pressure

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- 170/100
- $MAP = 2/3 (90) + 1/3 (150) = 122$
- 150/90
- $MAP = 2/3 (90) + 1/3 (150) = 110$
- 140/84
- $MAP = 2/3 (90) + 1/3 (150) = 102$

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## Mean Arterial Pressure

- 20-25% reduction acutely is optimal
- Some reduction is likely unless a true hypertensive emergency
- Patients will otherwise achieve their own steady state
- Pay attention to vital signs, hydration status, overall status
- Labetalol, IVF, sedation, ABCs

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## Watershed Infarct

wa-ter-shed (wô t r-sh d) *n.*

1. A ridge of high land dividing two areas that are drained by different river systems. Also called *water parting*.
2. The region draining into a river, river system, or other body of water.
3. A critical point that marks a division or a change of course; a turning point:

watershed infarction *n.*  
 Infarction of the cerebral cortex in an area of blood supply between two major cerebral arteries.



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## ED MD: Best Neuroprotectant



## ED MD: Best Neuroprotectant

- Available 24/7

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## ED MD: Best Neuroprotectant

- Available 24/7
- Effectively able to diagnose infarct

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## ED MD: Best Neuroprotectant

- Available 24/7
- Effectively able to diagnose infarct
- Systems expert; able to make things happen quickly

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## ED MD: Best Neuroprotectant

- Available 24/7
- Effectively able to diagnose infarct
- Systems expert; able to make things happen quickly
- Focus on acute interventions

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## ED MD: Best Neuroprotectant

- Available 24/7
- Effectively able to diagnose infarct
- Systems expert; able to make things happen quickly
- Focus on acute interventions
- Know our limitations

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## ED MD: Best Neuroprotectant

- Available 24/7
- Effectively able to diagnose infarct
- Systems expert; able to make things happen quickly
- Focus on acute interventions
- Know our limitations
- We can be trained

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## ED MD Neuroprotection

- Manage the airway

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## ED MD Neuroprotection

- Manage the airway
- ETI, rapid sequence induction


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### ED MD Neuroprotection

- Manage the airway
- ETI, rapid sequence induction
- Manage hypotension


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### ED MD Neuroprotection

- Manage the airway
- ETI, rapid sequence induction
- Manage hypotension
- Manage hypertension


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### ED MD Neuroprotection

- Manage the airway
- ETI, rapid sequence induction
- Manage hypotension
- Manage hypertension
- Treat metabolic abnormalities


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### ED MD Neuroprotection

- Manage the airway
- ETI, rapid sequence induction
- Manage hypotension
- Manage hypertension
- Treat metabolic abnormalities
- Diagnose and lower elevated ICP


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### ED MD Neuroprotection

- Manage the airway
- ETI, rapid sequence induction
- Manage hypotension
- Manage hypertension
- Treat metabolic abnormalities
- Diagnose and lower elevated ICP
- Prevent and treat seizures


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### ED MD Neuroprotection


- Manage the airway
- ETI, rapid sequence induction
- Manage hypotension
- Manage hypertension
- Treat metabolic abnormalities
- Diagnose and lower elevated ICP
- Prevent and treat seizures
- We first do no harm

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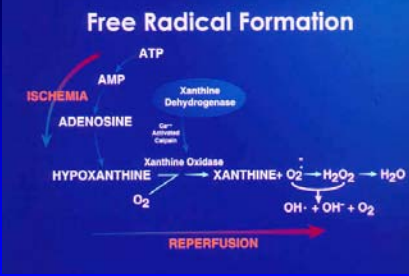



### ED Neuroprotection: Key Concepts

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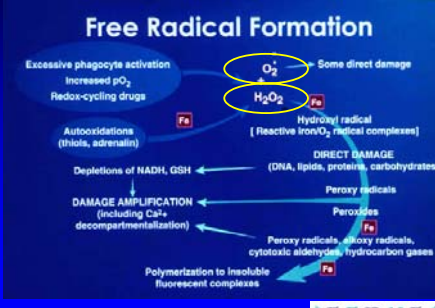
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### Stroke Pathophysiology: Free Radical Formation




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### Stroke Pathophysiology: Free Radical Formation



**Tirilazad**  
**Citicoline**  
**Ebselen**  
**NXY-059**


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### Neuroprotection 1955-2000

Trials of Neuroprotection Agents in Stroke:  
1955-2000


|                               |        |
|-------------------------------|--------|
| Neuroprotective Agents Tested | 49     |
| RCTs Performed                | 114    |
| Patients Enrolled             | 21,445 |
| Trials with Positive Results  | 0      |

This year, first positive primary endpoint trial...and the end to another potential neuroprotectant.)

Kidwell CS et al. *Stroke* 32(6):1349-59. Edward Sloan, MD, MPH, FACEP 


### Why have neuroprotection agents failed in human trials?

- Wrong theoretical concept
- Treatment initiated too late
- Stroke heterogeneity
- Wrong drug action
- Doses too low
- Trials underpowered
- Wrong outcome measures
- Insensitive statistical techniques

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## NXY-059 (Cerovive)

ORIGINAL ARTICLE

**NXY-059 for Acute Ischemic Stroke**

Kennedy R. Lees, M.D., Justin A. Zivin, M.D., Tim Ashwood, Ph.D., Antonio Davalos, M.D., Stephen M. Davis, M.D., Hans-Christoph Diener, M.D., James Grotta, M.D., Patrick Lyden, M.D., Ashfaq Shuaib, M.D., Hans-Göran Härdemark, M.D., and Warren W. Wasiewski, M.D., for the Stroke-Acute Ischemic NXY Treatment (SAINT I) Trial Investigators\*  
 2006;354(6):588-600.

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## NXY – 059 Characteristics

- NXY-059 (Cerovive) is an intravenous, nitrone-based, free radical trapping agent
- Preclinical trials positive in rats/primates
- Effective after 4 hours of ischemia
- Significant dose response

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## SAINT I Trial

(Stroke – Acute Ischemic – NXY-059 Treatment)

- RCT Design
  - 72 hr treatment window
  - NXY-059 vs placebo
  - Target plasma concentration ~260 µM
  - 158 centers across 24 countries
    - Europe, Asia, Australia, New Zealand, South Africa

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## SAINT I Trial

(Stroke – Acute Ischemic – NXY-059 Treatment)

- Eligibility
  - CT/MR consistent with AIS
  - Previous independence
  - NIHSS ≥6 including limb weakness
    - t-PA permitted
  - < 6hr ictus to treatment
    - Forced allocation to achieve mean time from onset to start of treatment ≤ 4 hrs

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## SAINT I Primary Outcome Variable:

### Change in Modified Rankin Scale

**At 90 Days**

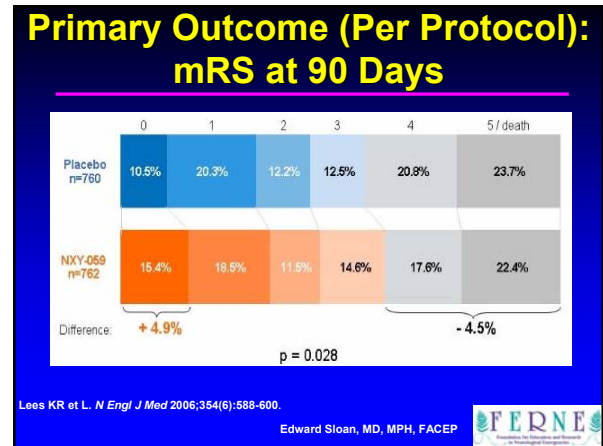
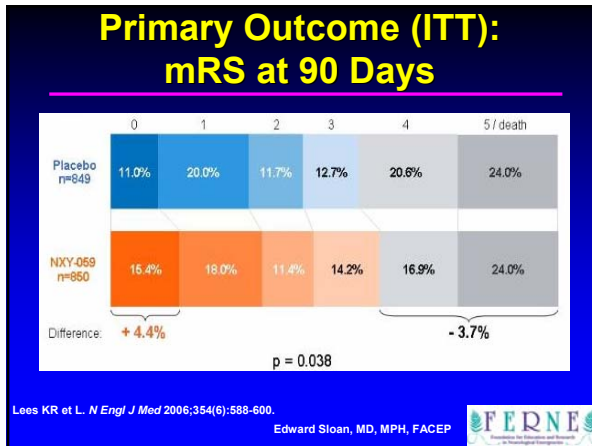
|   |   |                                 |
|---|---|---------------------------------|
| Symptom free  | 0 | Symptom free                    |
| Symptomatic, but performing previous activities             | 1 | Able to do all usual activities |
| Unable to do some previous activities, but independent      | 2 | Able to look after self         |
| Requires some help, but can walk without assistance         | 3 | Able to walk without assistance |
| Needs assistance with walking and attending to bodily needs | 4 | Not bedridden                   |
| Bedridden, incontinent, requires constant care              | 5 | Bedridden / Death               |

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## SAINT I Secondary Outcome Variables

- mRS at 7 and 30 days
- NIHSS change on days 7 and 90
- Barthel Index on days 7, 30, and 90
- Safety
- Day 90 SIS-16 and Four Domains
- Day 90 EQ-5D

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### NXY-059 Number Needed to Treat: Benefit Using mRS Shift Analysis

|                  |            |
|------------------|------------|
| Lowest Possible  | 7.9        |
| Highest Possible | 16.7       |
| Expert Panel     | 9.8        |
| Expert Panel     | 8.7 – 10.9 |

Saver J. *UCLA Stroke Center*. Edward Sloan, MD, MPH, FACEP

### NXY-059 Number Needed to Treat: Benefit Using Outcome Dichotomy

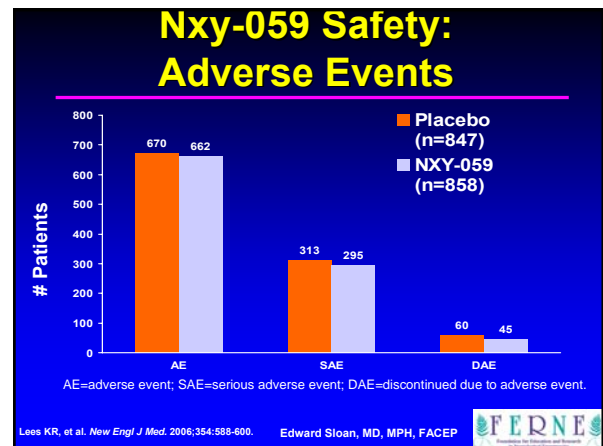
| mRS        | NNT |
|------------|-----|
| 0 vs 1-6   | 23  |
| 0-1 vs 2-6 | 42  |
| 0-2 vs 3-6 | 48  |
| 0-3 vs 4-6 | 28  |

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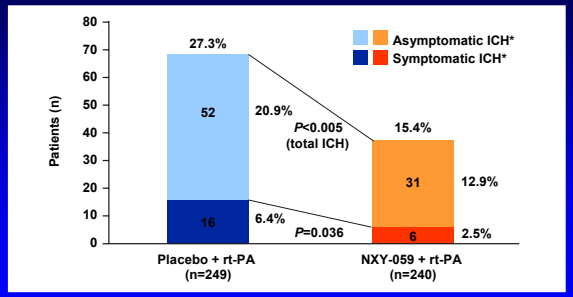
### SAINT I Clinical Endpoints

| Endpoint                   | P Value |
|----------------------------|---------|
| Rankin shift               | 0.038   |
| Rankin dichotomized        | 0.17    |
| Improvement in NIHSS       | 0.86    |
| Barthel Index dichotomized | 0.14    |
| Stroke Impact Scale        | 0.08    |
| Euro QOL Index             | 0.06    |
| QOL Visual Analogue Scale  | 0.05    |

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### ICH After IV tPA Thrombolysis: (SAINT –I Post Hoc Analysis)



Edward Sloan, MD, MPH, FACEP  
Lees KR, et al. New Engl J Med. 2006;354:588-900.

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### Neuroprotectant Questions

- Will SAINT-II reproduce results?
- Will the NNT be comparable?
- Will safety data be comparable?
- Will the tPA / ICH data compare?
- How to explain BBB information?
- What cost will the results justify?

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### Saint II Overview

- No improvement in 3 month functional outcome in NXY-059 pts.
- No decreased rate of ICH in tPA treated patients with NXY-059 use.
- No apparent post-hoc benefit identified such that continued study of any subgroup is warranted.

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### Saint II Answers

- Will SAINT-II reproduce results? No.
- Will the NNT be comparable? No.
- Will safety data compare? Unknown.
- Will the tPA / ICH data compare? No.
- How to explain BBB info? No need.
- What cost are justified? None.

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### Conclusions

- We encounter many pts with diseases that require neuroprotection
- We as emergency physicians routinely provide neuroprotection
- Neuroprotection reduces ischemic stroke infarct volume, complications
- Morbidity of other disease states also reduced due to ED neuroprotection
- Patient outcomes improved

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**Questions?**

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312 413 7490

ferne\_teme\_2006\_sloan\_neuroprotection\_120406\_finalcd  
1/23/2007 3:47 PM

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Overview

**FERNE: Mission Statement**

- Patients with neurological emergencies deserve quality emergency care.
- Quality scientific research.
- Case-oriented, evidence-based medical education on optimal acute neurological care.
- Use of technology to break down space and time barriers

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Education

**Educational Activities to Date**

- 63 Meetings
- 181 Speakers
- 393 Lectures
- 370+ Lectures on the FERNE website
- 13 Lectures on the EMedHome website
- 97% Evaluations good or excellent
- 5000+ EM professionals
- 7800+ contact hours over 9 years

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Education

**Web-based Learning: Video Slideshows**

- Audio, video and slide content
- Able to access individual slides for specific content
- MS Producer, viewable with Windows Media Player



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Education

**Web-based Content: Guidelines**

- [www.guidelines.gov](http://www.guidelines.gov)
- [www.acep.org](http://www.acep.org)
- PDFs of the guidelines summarized and the actual publication, when available
- Materials can be printed, shared

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Education

**Web-based Content: Journal Clubs**


- Neurological emergencies
- TIA, AIS, tPA use, ICH, TBI
- PDFs of the actual publications
- Organized based on ability to increase understanding of content area
- Materials can be printed, shared

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Education  
**Web-based Learning: EMedHome.com**

- FERNE generated content
- CME can be obtained via the EMedHome website
- Slides and audio



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Education  
**Web-based Learning: Abstract Search**

Topic specific abstract searches



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Education  
**Handheld Software: HandiStroke Rx**

HANDi Stroke Rx  
 Available free from  
[www.ferne.org](http://www.ferne.org)

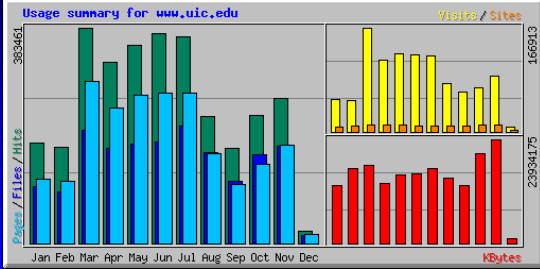
- Written at Mount Sinai, New York
- Funded by a FERNE grant
- NIH Stroke Scale
- tPA Inclusion/Exclusion criteria
- tPA dosage calculator
- Continuation of care orders



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Education  
**Website Usage: Webalizer**



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| Summary by Month |           |       |       |        |       |                  |                |                |                |                |
|------------------|-----------|-------|-------|--------|-------|------------------|----------------|----------------|----------------|----------------|
| Month            | Daily Avg |       |       |        |       | Monthly Totals   |                |                |                |                |
|                  | Hits      | Files | Pages | Visits | Sites | KBytes           | Visits         | Pages          | Files          | Hits           |
| Dec 2006         | 8927      | 5003  | 5156  | 2496   | 1826  | 1168771          | 7489           | 15469          | 15009          | 20781          |
| Nov 2006         | 8587      | 5758  | 5902  | 2966   | 10956 | 23934175         | 8958           | 174074         | 172747         | 257634         |
| Oct 2006         | 7352      | 5084  | 4531  | 2287   | 11823 | 20623909         | 70300          | 140465         | 157629         | 227935         |
| Sep 2006         | 8607      | 3679  | 3524  | 2123   | 8936  | 13268612         | 63715          | 105733         | 110394         | 166214         |
| Aug 2006         | 7301      | 5231  | 5122  | 2524   | 8602  | 15000507         | 78263          | 158802         | 162164         | 226343         |
| Jul 2006         | 11856     | 6744  | 6624  | 3947   | 9198  | 17275874         | 122376         | 267365         | 209077         | 367544         |
| Jun 2006         | 12445     | 5992  | 8929  | 4125   | 9067  | 15965474         | 123756         | 267883         | 179769         | 373367         |
| May 2006         | 11353     | 5707  | 8929  | 4064   | 10332 | 15681861         | 126005         | 264419         | 176921         | 351967         |
| Apr 2006         | 10765     | 5646  | 8010  | 3815   | 10760 | 13824602         | 114455         | 240308         | 169385         | 322965         |
| Mar 2006         | 12369     | 6475  | 9269  | 6384   | 11740 | 18026878         | 166913         | 287365         | 200742         | 383461         |
| Feb 2006         | 8114      | 3297  | 3976  | 1775   | 9587  | 17155457         | 49716          | 111328         | 82333          | 171207         |
| Jan 2006         | 8778      | 3249  | 3684  | 1701   | 8241  | 13368958         | 62744          | 114207         | 100729         | 179129         |
| <b>Totals</b>    |           |       |       |        |       | <b>185291978</b> | <b>1068319</b> | <b>2147416</b> | <b>1746889</b> | <b>3096027</b> |

Education  
**Website Usage: Webalizer**

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