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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  
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*Department of Emergency Medicine*  
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**Attending Physician  
Emergency Medicine**

*University of Illinois Hospital  
Our Lady of the Resurrection Hospital*

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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
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  - 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***

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- Outcome related to infarct volume

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### **Stroke Volume and Outcome**

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- 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***

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

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### **Limiting Stroke Volume**

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

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### **ED Neuroprotection: *Key Concepts***

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- Aggressively Rx ischemic penumbra

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### **Aggressively Rx Ischemic Penumbra**

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- Maximize cerebral perfusion
- Provide optimal substrates, O<sub>2</sub>
- Avoid cell death
- Maintain intact blood brain barrier

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## Cerebral Perfusion

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

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## Cerebral Perfusion

- $CPP = MAP - ICP$
- $MAP = 2/3 DBP + 1/3 SBP$
- 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

- 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

- 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

- 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

- 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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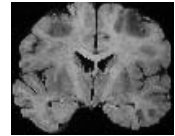


## Watershed Infarct

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

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

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### ED MD: Best Neuroprotectant

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- 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

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- 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

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- 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

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- Manage the airway

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### ED MD Neuroprotection

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- Manage the airway
- ETI, rapid sequence induction

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## ED MD Neuroprotection

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

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## ED MD Neuroprotection

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

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## ED MD Neuroprotection

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

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## ED MD Neuroprotection

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- 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

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- 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

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- 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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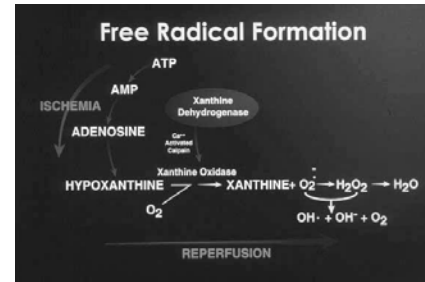
### ED Neuroprotection: Key Concepts

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### Stroke Pathophysiology: Free Radical Formation

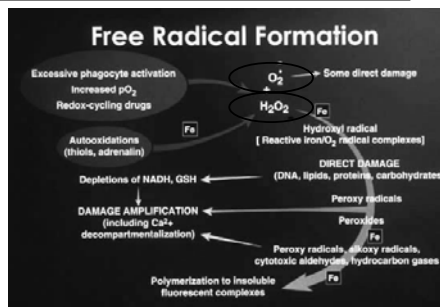


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### Stroke Pathophysiology: Free Radical Formation

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.

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### 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)

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## NXY – 059 Characteristics

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- 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

Lees KR et L. *N Engl J Med* 2006;354(6):588-600.  
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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

Lees KR et L. *N Engl J Med* 2006;354(6):588-600.  
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## SAINT I Primary Outcome Variable:

### Change in Modified Rankin Scale

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**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	

Lees KR et L. *N Engl J Med* 2006;354(6):588-600.  
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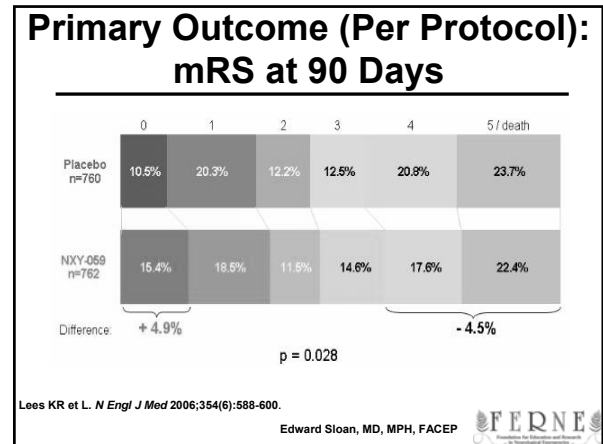
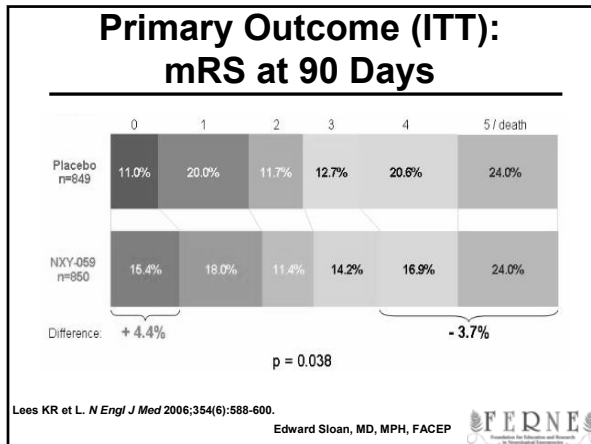
## SAINT I

### Secondary Outcome Variables

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- 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

Lees KR et L. *N Engl J Med* 2006;354(6):588-600.  
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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*  
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### NXY-059 Number Needed to Treat: Benefit Using Outcome Dichotomy

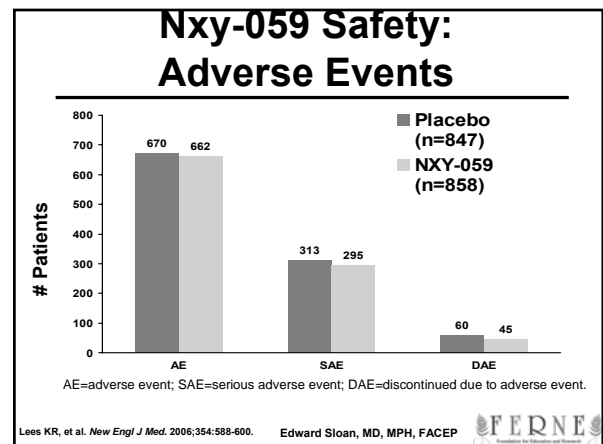
mRS	NNT
0 vs 1-6	23
0-1 vs 2-6	42
0-2 vs 3-6	48
0-3 vs 4-6	28

Saver J. *UCLA Stroke Center*  
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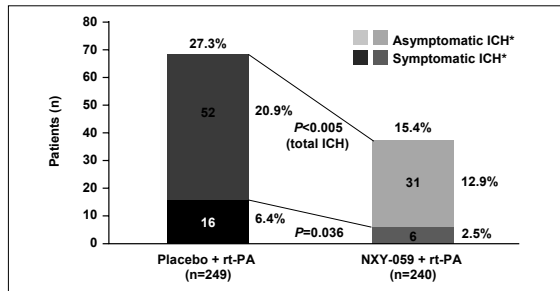
### SAINT I Clinical Endpoints

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)



\*NINDS definition; ICH=intracerebral hemorrhage

Lees KR, et al. *New Engl J Med.* 2006;354:588-600.

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- Specific questions to be addressed

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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  
12/8/2006 5:48 PM

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Overview

## FERNE: *Mission Statement*

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- 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*

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- 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*

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- 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*

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- [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*

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- 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



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


Topic specific abstract searches



Education  
**Handheld Software: HandiStroke Rx**

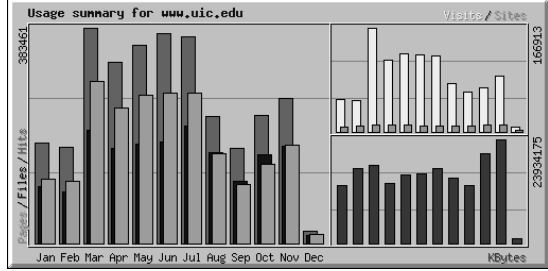
HANDi Stroke Rx  
Available free from [www.ferne.org](http://www.ferne.org)

- 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	5802	2866	10856	23934175	8958	174074	172747	257634	
Oct 2006	7352	5084	4531	2287	11823	20623809	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	8624	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	4384	11740	18026876	166913	287365	200742	383461	
Feb 2006	6114	3297	3976	1775	9587	17155457	49716	111328	82333	171207	
Jan 2006	9779	3249	3684	1701	8241	13365958	62744	114207	100729	179129	
<b>Totals</b>						<b>185291978</b>	<b>1068319</b>	<b>2147416</b>	<b>1748899</b>	<b>3096027</b>	

Education  
**Website Usage: Webalizer**

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