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## **STATUS EPILEPTICUS: ASPECTS OF EMERGENCY CRITICAL CARE**

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### **Objectives and Goals**

- Review current concepts, epidemiology, and pathophysiology of major motor SE (adults)
- Aspects important to critical care
- Diagnostic and treatment algorithms based on potential etiology and patient condition
- ED disposition of patients with SE
- Goal is to help improve care and outcomes

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### **Disclosure and Support**

- NETT (NIH-NINDS)
- RAMPART (NIH-NINDS)
- ALIAS 2 (NIH-NINDS)
- Currently, no industry funded support but will be involved with evaluation of biomarkers of brain injury (DOD and industry) and a brain injury clinical trial (DOD and industry)

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### What is Status Epilepticus?

- Continuous seizure or not regaining consciousness between seizures:
  - 30 minutes – Epilepsy Foundation of America
  - 10 – 20 minutes – Veteran’s Affairs SE Cooperation Study
  - 5 minutes – newest definition (proposed 1999) not universally accepted
- Symptom of underlying disease or problem!!!

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### Proposed Definitions

- Early or Impending SE – continuous or intermittent seizure lasting more than 5 min. without full recovery in between
- Established SE – lasting > 30 min. without recovery
- Probably is really a continuum (more on this later)

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### Why the Confusion/New Definition?

- 40% of seizures lasting 10-29 min. stop spontaneously (mortality - 2.6%)
- Seizures > 30 min. mortality is 19%
- Mean duration of generalized seizure is 52.9 to 62.2 seconds (motor) and 59.9 sec. (EEG)
  - No seizure lasted > 2 min.
  - 5 minutes is > - 18 standard deviations
- No good reason to defer treatment if seizing 5 min.

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### Other Considerations

- Subtle Status Epilepticus
  - Usually with prolonged status
  - Motor and EEG manifestations can be less florid
  - Still requires aggressive therapy
- Partially Treated Status
  - Overt clinical signs stop
  - Subtle symptoms
  - EEG still shows seizure
  - About 10% of treated cases

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### Non-Convulsive SE

- Personality changes, lethargy, agitation, confusion blinking, automatism, etc.
- Up to 13% of neuro ICU patients
- 16% severe head trauma
- In one study of continuous EEG monitoring (570 patients) – 92% (101) of 110 with seizures had non-convulsive seizures
- Difficult to Diagnose!!!

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### Myoclonic Status

- Usually post anoxia
- Extremely poor prognosis
- Often not treated as aggressively

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### Literature Applicability

- Studies are inpatients and outpatients
- Inpatient SE (by new definition) probably worse outcomes than those in ED only
- Data from NHAMCS

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### EPIDEMIOLOGY

- Richmond, VA study: 41 per 100,000/year
  - Overall mortality 22%
  - 27 per 100,000/year if young (15 – 59 years)
    - Mortality 14%
  - 86 per 100,000/year for elderly ( $\geq$  60 years)
    - Mortality 38%
- “These numbers show that available treatments for SE are not effective enough...”

Delorenzo, et al. Neurology 1996

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### EPIDEMIOLOGY (cont.)

- NEJM Review
  - In U.S. 102,000 to 152,000 cases/year
  - 42,000 to 55,000 deaths (30% - 50% mortality???)
- Other Data
  - Swiss - 10.3/100,000/year
  - Germany – 17.1/100,000/yr
  - Rochester, MN – 18.1/100,000/yr
- Average – 20 episodes /100,000/year for Caucasians

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### ETIOLOGIES - Adults

- Low blood concentrations of AEDs (34%)
- "Remote Symptomatic Causes" (i.e. old neurological problems - 24%)
- CVA (22%)
- Anoxia/hypoxia (~13%)
- Metabolic abnormalities (~15%)
- Alcohol and drug related (~13%)

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### ETIOLOGIES - Pediatrics

- Fever (52%)
- "Remote symptomatic" (39%)
- Low AED levels (21%)
- Other (< 10%)

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### Outcomes

- Mortality for adults ~ 20% (from NEJM review that quotes a 1994 textbook - seems high for my population and for new definition)
- Those with first episode of SE are at future risk for SE and chronic epilepsy
- PREDOMINANT FACTOR ASSOCIATED WITH OUTCOME IS CAUSE (age)

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### Outcomes

- Based on etiology:
  - Low mortality – hx epilepsy with precipitating factors (low AED levels, sleep deprivation)
  - High mortality – anoxia, multiple medical problems
- Age (elderly)
- Prolonged or refractory
- Remember two above often associated with other issues!!!

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### Breaking SE

- Acute processes often difficult to treat
  - Electrolyte abnormalities (i.e. hyponatremia)
  - Renal failure
  - Infections (CNS or sepsis)
  - Acute stroke or head trauma
  - Other
- Chronic or established process often easier to break
  - Chronic seizures
  - Known chronic CNS disease
  - Alcohol withdrawal

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Minimal Discussion of Requisite  
“Physiology” and “Cell” and  
“Molecular” Stuff

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### Changes in Physiology

- Fever
  - Look for other causes
  - Correlates with severity of cerebral injury
- Cardiovascular
  - Elevated BP (later can fall)
  - Tachycardia and cardiac arrhythmia
  - Elevated Pulmonary Artery pressures
- Blood and Fluids
  - Acidosis, hyperkalemia, CK, leukocytosis, etc
  - Abnormal CSF (WBC, protein)

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### Basic Mechanism of SE

- Appears that SE can become self-sustaining
  - Animal models (chemical or electrical) of SE
  - Human observations (no real "proof")
- Initiation of SE can be stopped by drugs that increase inhibition or reduce excitation
- Self-sustaining SE:
  - Easily stopped only by drugs that directly or indirectly inhibit glutamatergic neurotransmission
  - GABAergic and barbituates loose potency

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### Self-Sustaining SE

- Seconds to minutes
  - Existing receptors move from synaptic membrane to endosomes
  - Can move from storage to synaptic membranes
- Minutes to hours
  - Increase in proconvulsive neuropeptides
  - Depletion of inhibitory neuropeptides
- Hours to days
  - Change in gene expression
  - Neuronal death

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## Neuronal Cell Death

- This is what we want to prevent – “Time is brain”
- Can occur even in the absence of convulsive activity (animal and experimental models)
- Anecdotal in humans but probably occurs

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## Neuronal Loss After SE

- 1970's pointed to cerebral ischemia as the cause (loss in temporal lobe, Cortex, and particularly Hippocampus)
- Later models suggested enhanced neuronal activity (“excitotoxicity”)
  - Increased blood flow in rodent model more than compensated for increased cell activity
  - Calcium accumulation in mitochondria following prolonged NMDA receptor activity
    - altered mitochondrial function
    - necrotic or apoptotic cell death
    - supported by the neuro-protective effect of NMDA receptor antagonists

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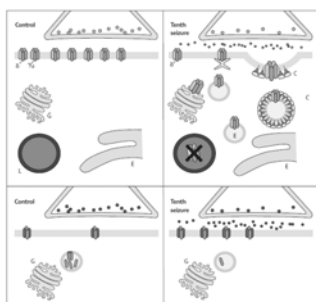


Figure 1. Model of one hypothesis of receptor trafficking in transition of single neurons to status epilepticus. Top: after repeated seizures, the synaptic membrane of GABA<sub>A</sub> receptors forms clusters (C), which internalize as clathrin-coated vesicles (E), inactivating the receptors because they are no longer within reach of the neurotransmitter. These vesicles develop into endosomes (E), which can deliver the receptors to lysosomes (L) where they are destroyed, or to the Golgi apparatus (G) from where they are recycled to the membrane. Bottom: by contrast, in NMDA synapses, subunits are trafficked by the synaptic membrane and assemble into additional receptors. As a result of this trafficking, the number of functional NMDA receptors per synapse increases whereas the number of functional GABA<sub>A</sub> receptors decreases.

Chen JWY, Wasterlain CG, Lancet Neurol. 2006; 5:246-256

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### Pharmacoresistance

- Time-dependant resistance to benzodiazepines and others well documented in animal models
- In humans – early treatment more effective implying resistance is one possible explanation

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This is a “Critical Care”  
Conference

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### Special Conditions in Critically Ill Patients

- More Difficult to treat
- Diagnosis can be difficult (sedation/paralysis)
- Causes different based on conditions:
  - Infections/sepsis
  - Liver Failure
  - Renal Disease
  - Transplant Patients
  - Metabolic Encephalopathy
  - Antibiotics

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### Need for ICU Care

- In S.F. 55% of ED patients were admitted to ICU
  - Complications of SE (i.e. respiratory insufficiency)
  - Treat the underlying cause of SE
- University of Virginia
  - Most common reason for ICU was need for mechanical ventilation and weaning after successful termination
  - This was a change (over a 15 year period) from the need to terminate SE
    - Use of lorazepam, faster therapy, airway skill in ED

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### Liver Failure

- Incidence 2% - 33% have seizures
- Pathophysiology
  - Ammonia
  - Toxins
  - Other associated abnormalities (sodium, etc)
- Pharmacokinetics
  - Albumin (Phenytoin and Valproic Acid)
  - Metabolism (poor liver clearance)
  - Consider using non-protein bound renal clearance meds for long-term therapy

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### Renal Disease

- 2% - 10% have seizures
  - Uremia
  - Metabolic disorders
  - Dysequilibrium from dialysis
- Protein-bound drugs not effectively dialyzed
- Renal metabolism (gabapentin, pregabalin, ethosuxamide, levetiracetam, phenobarbital, topiramate)
  - Serum concentrations decreased by 50%
  - Require replacement after dialysis

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## Organ Transplant

- Liver (25% - 30%)
  - Immunosuppressant agent toxicity (most commonly cited)
    - Cyclosporin
    - Tacrolimus
  - Metabolic abnormalities
  - Infections
  - Usually post-op day 4 - 6 (Benzo withdrawal ???)
  - Treatment usually phenytoin (short-term)
- Kidney (1% - 5%)
- Heart (2% - 6.5%)
- Lung (22% - 27%)
- Pancreas (13%)

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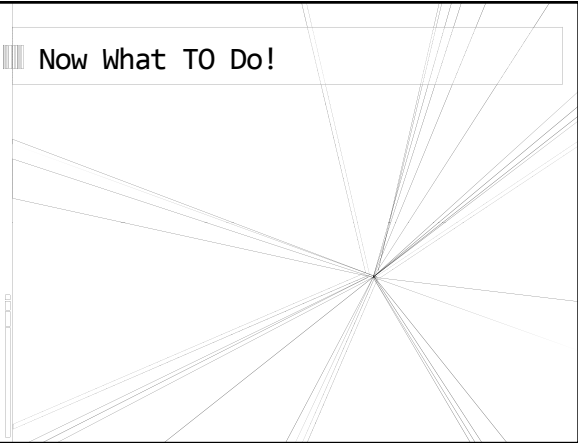
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## Now What TO Do!



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## Evaluation

- ABCs
- Quick physical exam (primary survey)
- "Treat before diagnose"
- Begin thinking about root cause
- History ASAP
- RE-EVALUATE (secondary survey)!!!

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### “Time is Brain” Treatment Principles

- Time dependant loss of GABA receptors means decreasing responsiveness to benzodiazepines
- Tight timetable for treatment protocols
  - One treatment fails proceed to next (conventional)
  - Compressed algorithm (Silbergleit)
- Diagnostic strategy is important but should not delay treatment

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### Diagnostic Studies

- Because of new definition diagnostic workup needs are variable:
  - Little as H & P, glucose, and anticonvulsant levels
  - May be as much as a “jumbo” work-up
    - Multiple labs
    - CT or MRI
    - LP
- Re-evaluate!

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### Treatment and Protocols

- ✓ Pre-hospital
- ✓ Traditional vs. proposed “accelerated” protocols (new thoughts)
- ✓ At DRH (and many other institutions) many have used the new the proposed “accelerated” protocol for years

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## Pre-Hospital Tx

- PHTSE trial showed that pre-hospital treatment is effective
    - Seizure > 5 minutes
    - Randomized placebo controlled
      - Lorazepam
      - Diazepam
      - Placebo
- Lewinstein DH, Alldredge BK. NEJM. 1998;338:970-976
- Outcome
    - Mortality 30% (placebo) vs. 23% (Tx, not sig)
    - ICU admissions lower if stopped seizing by ED arrival (32%) than if still seizing (73%;  $p < 0.001$ )

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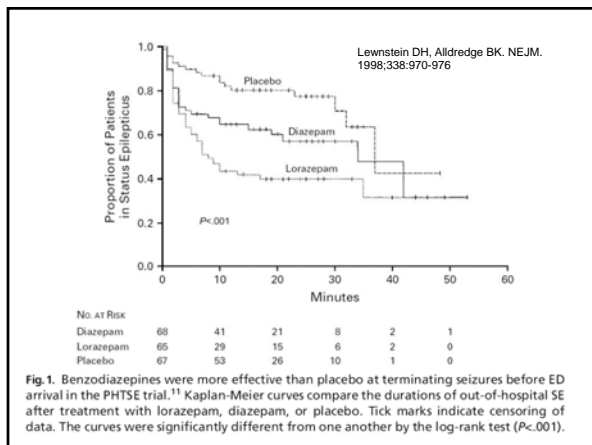
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## What Else Does This Mean

- The "Time" is pre-hospital – Patients were "censored if:
  - Arrived in the ED and still seizing
  - Given "open-label" (standard?) therapy
- Some patients are in the field a long time and do not receive treatment
- Lorazepam is heat labile
- We need easier to give effective therapies

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## Potential EMS Practices

- IV Diazepam
- Rectal Diazepam
- IM Midazolam (not FDA approved but may be used by up to 30% of ambulances)
- RAMPART
  - RCT
  - IV lorazepam vs IM midazolam in pre-hospital setting

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## Treatment Protocols




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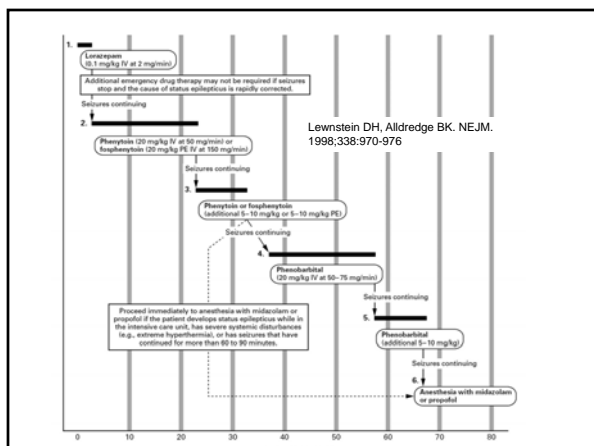
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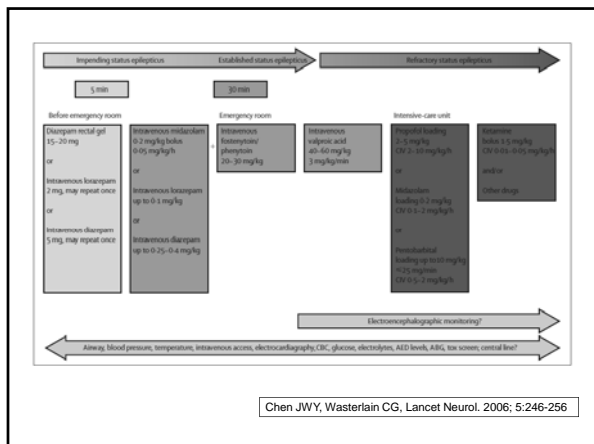
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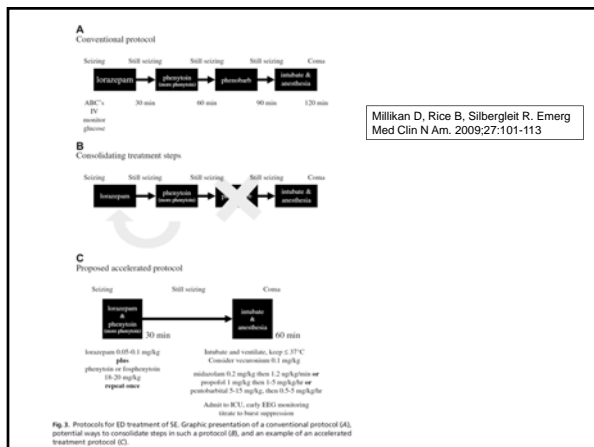
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- ### Drugs
- **Standard Protocol**
  - **Lorazepam** 0.1 mg/kg (max 4 mg)
  - **Diazepam** 0.3 mg/kg (max 10 mg)
  - **Midazolam** 0.2 mg/kg (max 10 mg)
  - **Phenytoin or Fosphenytoin** 15-20 mg/kg (up to 30 mg/kg) (I start 1/2 dose immediately)
  - **Propofol** 1-2 mg/kg load then 2-10 mg/kg/hr (ranges as high as 2-5 mg/kg load have been used) (not for kids)
  - **Pentobarbital** 10-15 mg/kg bolus then 0.5-1 mg/kg/hr
  - **Midazolam drip** 0.05-2.0 mg/kg/hr
  - **Others**
  - **Valproic Acid** 20-30 mg/kg (in Europe up to 40-60 mg/kg) at 3mg/kg/min (faster rates fro SE). It is approved for SE in (Norway and Germany ??? Others now) . Avoid if severe liver disease or mitochondrial disease.
  - **Levetiracetam (Keppra)** dose not standard but up 2-4 grams over 15 minutes administered to volunteers. Not approved for SE but may have advantages for critically ill liver disease patient (renal metabolism)
  - **Lidocaine** really old school but Japan

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Thanks to:  
MCEP  
WSU  
Robert Sherwin, MD

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1. Abou Khaled KJ, Hirsch LJ. Advances in the management of seizures and status epilepticus in critically ill patients. *Crit Care Clin.* Oct 2006;22(4):637-659; abstract viii.
2. Abou Khaled KJ, Hirsch LJ. Updates in the management of seizures and status epilepticus in critically ill patients. *Neurol Clin.* May 2008;26(2):385-408, viii.
3. Agarwal P, Kumar N, Chandra R, et al. Randomized study of intravenous valproate and phenytoin in status epilepticus. *Seizure.* Sep 2007;16(6):527-532.
4. Appleton R, Macleod S, Martland T. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. *Cochrane Database Syst Rev.* 2008(3):CD001905.
5. Arif H, Hirsch LJ. Treatment of status epilepticus. *Semin Neurol.* Jul 2008;28(3):342-354.
6. Bleck TP. Intensive care unit management of patients with status epilepticus. *Epilepsia.* 2007;48 Suppl 8:59-60.
7. Chen JW, Naylor DE, Wasterlain CG. Advances in the pathophysiology of status epilepticus. *Acta Neurol Scand.* Apr 2007;115(4 Suppl):7-15.
8. Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. *Lancet Neurol.* Mar 2006;5(3):246-256.
9. Chen L, Feng P, Wang J, et al. Intravenous sodium valproate in mainland China for the treatment of diazepam refractory convulsive status epilepticus. *J Clin Neurosci.* Apr 2009;16(4):524-526.
10. Costello DJ, Cole AJ. Treatment of acute seizures and status epilepticus. *J Intensive Care Med.* Nov-Dec 2007;22(6):319-347.
11. Dhar R, Mirsattari SM. Current approach to the diagnosis and treatment of refractory status epilepticus. *Adv Neurol.* 2006;97:245-254.
12. Drislane FW, Lopez MR, Blum AS, et al. Detection and treatment of refractory status epilepticus in the intensive care unit. *J Clin Neurophysiol.* Aug 2008;25(4):181-186.
13. Garcia Penas JJ, Molins A, Salas Puig J. Status epilepticus: evidence and controversy. *Neurologist.* Nov 2007;13(6 Suppl 1):S62-73.
14. Gilad R, Izkovitz N, Dabby R, et al. Treatment of status epilepticus and acute repetitive seizures with i.v. valproic acid vs phenytoin. *Acta Neurol Scand.* Nov 2008;118(5):296-300.
15. Kinirons P, Doherty CP. Status epilepticus: a modern approach to management. *Eur J Emerg Med.* Aug 2008;15(4):187-195.
16. Lhatoo SD, Alexopoulos AV. The surgical treatment of status epilepticus. *Epilepsia.* 2007;48 Suppl 8:61-65.
17. Limdi NA, Shimpi AV, Faught E, et al. Efficacy of rapid IV administration of valproic acid for status epilepticus. *Neurology.* Jan 25 2005;64(2):353-355.
18. Logroscino G, Hesdorffer DC, Cascino G, et al. Mortality after a first episode of status epilepticus in the United States and Europe. *Epilepsia.* 2005;46 Suppl 11:46-48.
19. Loscher W. Mechanisms of drug resistance in status epilepticus. *Epilepsia.* 2007;48 Suppl 8:74-77.
20. Lowenstein DH. Treatment options for status epilepticus. *Curr Opin Pharmacol.* Jun 2005;5(3):334-339.

21. Lowenstein DH. The management of refractory status epilepticus: an update. *Epilepsia*. 2006;47 Suppl 1:35-40.
22. Lowenstein DH, Cloyd J. Out-of-hospital treatment of status epilepticus and prolonged seizures. *Epilepsia*. 2007;48 Suppl 8:96-98.
23. Manno EM. Safety issues and concerns for the neurological patient in the emergency department. *Neurocrit Care*. 2008;9(2):259-264.
24. Mehta V, Singhi P, Singhi S. Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children: a randomized controlled trial. *J Child Neurol*. Oct 2007;22(10):1191-1197.
25. Meldrum B. Status epilepticus: the past and the future. *Epilepsia*. 2007;48 Suppl 8:33-34.
26. Miller LC, Drislane FW. Treatment of status epilepticus. *Expert Rev Neurother*. Dec 2008;8(12):1817-1827.
27. Millikan D, Rice B, Silbergleit R. Emergency treatment of status epilepticus: current thinking. *Emerg Med Clin North Am*. Feb 2009;27(1):101-113, ix.
28. Mirski MA, Varelas PN. Seizures and status epilepticus in the critically ill. *Crit Care Clin*. Jan 2008;24(1):115-147, ix.
29. Novorol CL, Chin RF, Scott RC. Outcome of convulsive status epilepticus: a review. *Arch Dis Child*. Nov 2007;92(11):948-951.
30. Parviainen I, Kalviainen R, Ruokonen E. Propofol and barbiturates for the anesthesia of refractory convulsive status epilepticus: pros and cons. *Neurol Res*. Oct 2007;29(7):667-671.
31. Rosenow F, Hamer HM, Knake S. The epidemiology of convulsive and nonconvulsive status epilepticus. *Epilepsia*. 2007;48 Suppl 8:82-84.
32. Rossetti AO. Which anesthetic should be used in the treatment of refractory status epilepticus? *Epilepsia*. 2007;48 Suppl 8:52-55.
33. Selvitelli M, Drislane FW. Recent developments in the diagnosis and treatment of status epilepticus. *Curr Neurol Neurosci Rep*. Nov 2007;7(6):529-535.
34. Towne AR. Epidemiology and outcomes of status epilepticus in the elderly. *Int Rev Neurobiol*. 2007;81:111-127.
35. Trinka E. The use of valproate and new antiepileptic drugs in status epilepticus. *Epilepsia*. 2007;48 Suppl 8:49-51.
36. Uges JW, van Huizen MD, Engelsman J, et al. Safety and pharmacokinetics of intravenous levetiracetam infusion as add-on in status epilepticus. *Epilepsia*. Mar 2009;50(3):415-421.
37. van Rijckevorsel K, Boon P, Hauman H, et al. Standards of care for adults with convulsive status epilepticus: Belgian consensus recommendations. *Acta Neurol Belg*. Sep 2005;105(3):111-118.
38. Walker M. Status epilepticus: an evidence based guide. *BMJ*. Sep 24 2005;331(7518):673-677.
39. Young GB. Status epilepticus and refractory status epilepticus: introductory and summary statements. *Adv Neurol*. 2006;97:183-185.
40. Ziai WC, Kaplan PW. Seizures and status epilepticus in the intensive care unit. *Semin Neurol*. Nov 2008;28(5):668-681.