The Neurological Institute of New York

Columbia University College of Physicians and Surgeons

Treatment of Status Epilepticus

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Status Epilepticus

- **Definition: GCSE vs NCSE**
- **Epidemiology**
- **Clinical presentation**
- **Approach**
  - **Diagnostic workup**
  - **Therapy**
  - **RSE**
- **Outcome and pathophysiology**

Definition: Status Epilepticus

5 min or more of (a) continuous seizure activity or (b) recurrent seizure activity without return to baseline

- GCSE: convulsions that are a/w rhythmic jerking of the extremities
  - Focal motor status epilepticus and epilepsia partialis continua not included in this definition
- NCSE (aka subtle SE): seizures on EEG without convulsions typically in acutely ill patients with severely impaired mental status +/- subtle motor movements
  - To be differentiated from the ‘‘wandering confused’’ patient with a relatively good prognosis

GCSE

Epidemiology

Seizure related ER visits:

- 1 Million annually
- 1% of all ER visits
- Most self-limited

Pallin, 2008 #2;Farhidvash, 2009 #10;Pitts, 2008 #1

Convulsive SE:

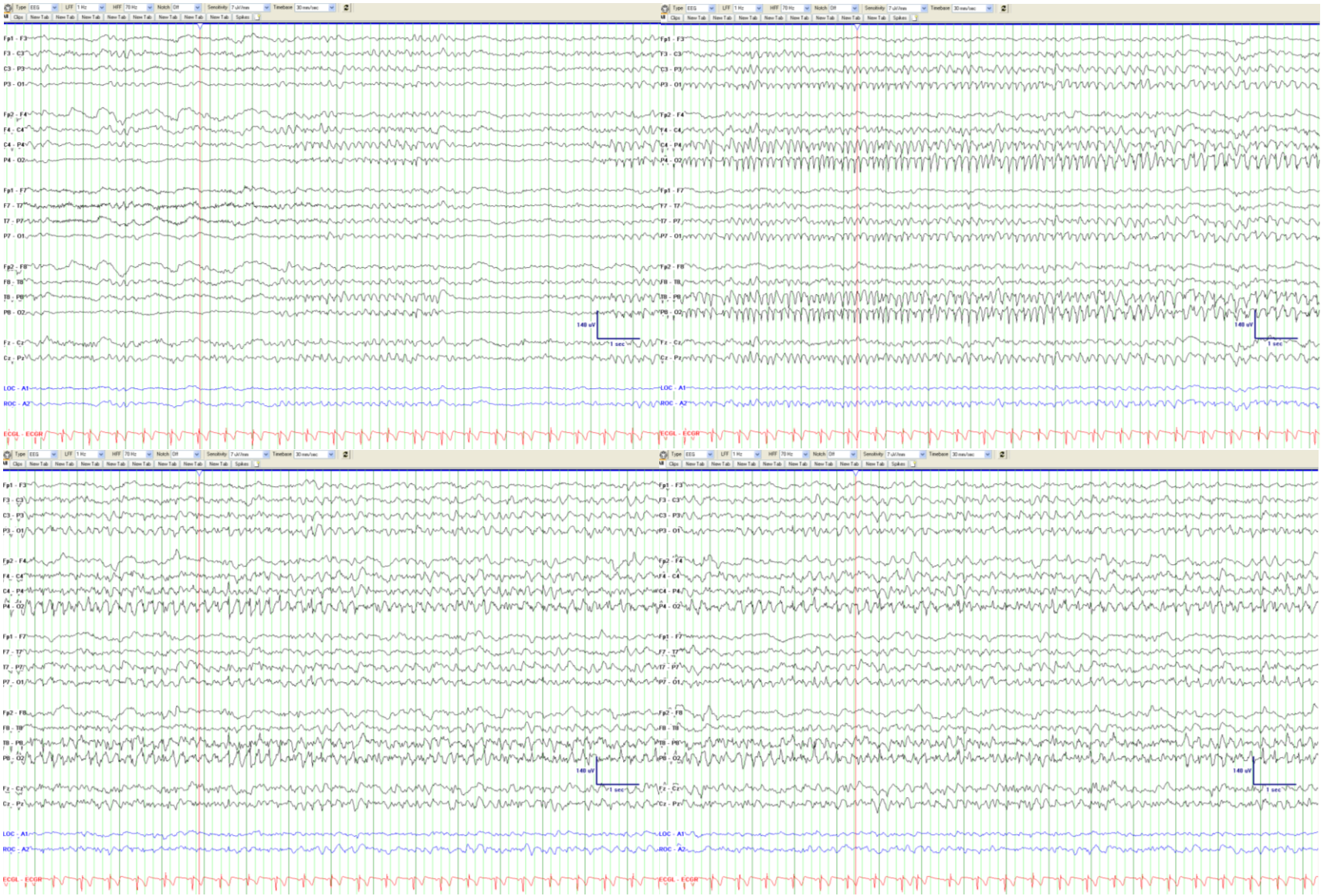
- 18-28 cases / 100000 persons
- ~ 200.000 annually

Shorvon 2000

Clinical presentation

- Generalized tonic-clonic movements or rhythmic jerking of the extremities
- Mental status impaired (coma, lethargy, confusion)
- May have post ictal focal neuro deficits (e.g., Todd's paralysis,)

65 yo man with amyloid angiopathy p/w change in mental status



Epidemiology: NCSz/NCSE

Unknown.

No population based studies!

- Neuro ICU prevalence:
  - –NCSz 18% to 34%
  - –NCSE 10%

  Jordan JCN 1993; Pandian ArchNeurol 2004; Claassen Neurol 2004

- ER: 37% of 198 patients undergoing urgent EEG for altered MS

  Privitera EpilRes 1994

DIAGNOSIS (N=570)	NCS	NCSE
CNS infection	9%	17%
Toxic-metabolic encephalopathy	13%	8%
Epilepsy-related seizures	11%	20%
Brain tumor	11%	12%
Post neurosurgery	15%	8%
SAH	5%	13%
TBI	10%	8%
ICH	4%	9%
Unexplained decrease in LOC	10%	5%
AIS	2%	7%

Claassen et al Neurol 04/07, NCC 2006

NCSz/NCSE

Clinically controlled GCSE

- EEG: 48% NCSz; 14% NCSE
- Mortality: 51% NCSE vs. 32% EDs vs. 13% none (controlled for age & etiol) DeLorenzo Epil 1998

MICU

- NCSE in 8-10% of comatose patients w/ no clinical evidence of seizures

Towne et al Neurol 00, Oddo et al CCM 2009

Sepsis

- 31% NCSz/PEDs
- Independently a/w mort and morb

Oddo et al CCM 2009

Hypoxia

- NCSz 10-40% during hypothermie/rewarming
- Independently a/w outcome

Zanderberg et al Neurol 06, Rossetti et al Neurol 07

Predictors

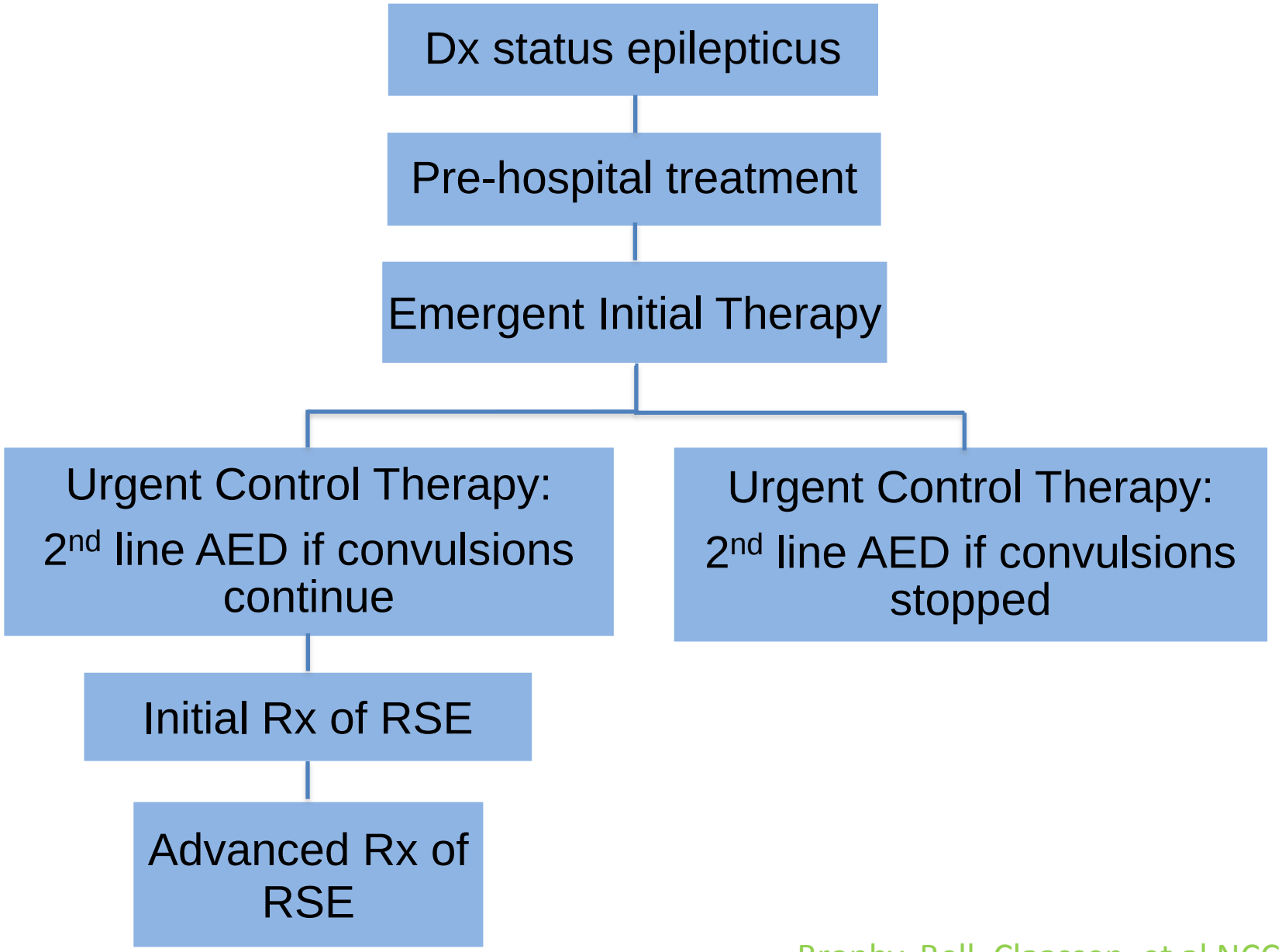
1. **Coma**: 56% of comatose pts vs. 12%
2. **Young** age: 36% of pts <18 yo vs. 17% of pts > 18.
3. **Epilepsy** in the past medical history: 41% vs. 16%, or remote risk factors for szs
4. **Convulsive seizures** prior to monitoring: 43% of pts with vs. 12%
5. **Periodic discharges** (PLEDs or GPEDs) or Suppression-burst
6. Oculomotor abnl's: nystag, hippus or eye deviation
7. Cardiac or respiratory arrest
8. Sepsis

Varelas Neurol 2003; Husain JNNP 2003, Claassen Neurol 2004; Oddo CCM 2009

Management concepts

- ABCs
- Control seizures asap
- Don’t undertreat
- Determine the underlying cause of seizures and address this if necessary
- Once convulsions have ceased consider NCSz
- No evidence based recs for NCSE but most would treat similar to convulsive SE
- Do not approach above sequentially but simultaneously

Status epilepticus: management overview



Brophy, Bell, Claassen, et al NCC 2012

Initial management approach

- Assess/manage airway, breathing, and circulation: IV access, O2, secure the airway
- Seizure abortive meds
- Screen for the underlying cause
- Immediate Rx of life-threatening causes of SE

Acute processes
• Metabolic disturbances: Elytes, Renal failure
• Sepsis
• CNS infection: meningitis, encephalitis, abscess
• Stroke: ischemic stroke, ICH, SAH
• TBI
• Drugs (toxicity, withdrawal from opioid, benzos, barbiturate, or ETOH, AEDs non-compliance)
• Hypoxia, cardiac arrest
• Hypertensive encephalopathy, PRES
• Autoimmune encephalitis, paraneoplastic
Chronic processes
• Epilepsy: breakthrough seizures
• Chronic ETOH abuse (intoxication or withdrawal)
• CNS tumors
• Remote CNS pathology (e.g., stroke, abscess)

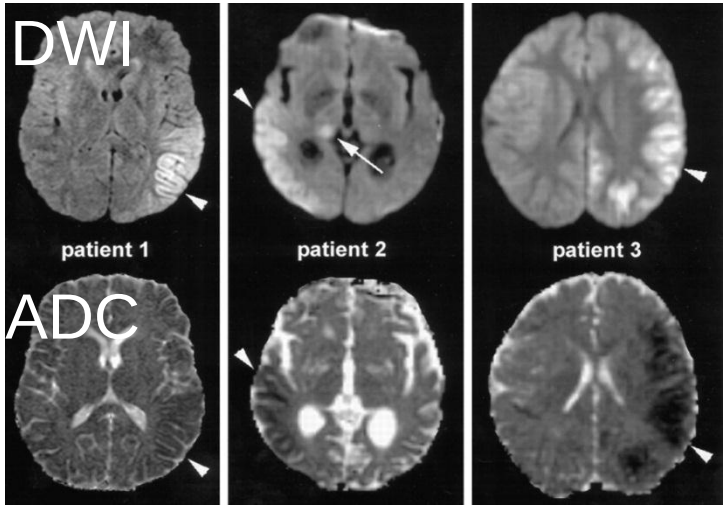
Brophy, Bell, Claassen, et al NCC 2012

Approach: Diagnostic workup

All patients
• FS glucose
• Monitor vital signs.
• Head CT (appropriate for most cases)
• Labs: blood glucose, CBC, BMP, Ca, Mg
• cEEG monitoring
Consider based on clinical presentation
• Brain MRI
• Lumbar puncture
• Toxicology panel (i.e. isoniazid, TCAs, theophylline, cocaine, sympathomimetics, ETOH, organophosphates, cyclosporine)
• Other Labs: LFT, troponin, T&H, coags, ABG, AED levels, tox screen (urine/blood), inborn errors of metabolism

Brophy, Bell, Claassen, et al NCC 2012

MRI changes from SE



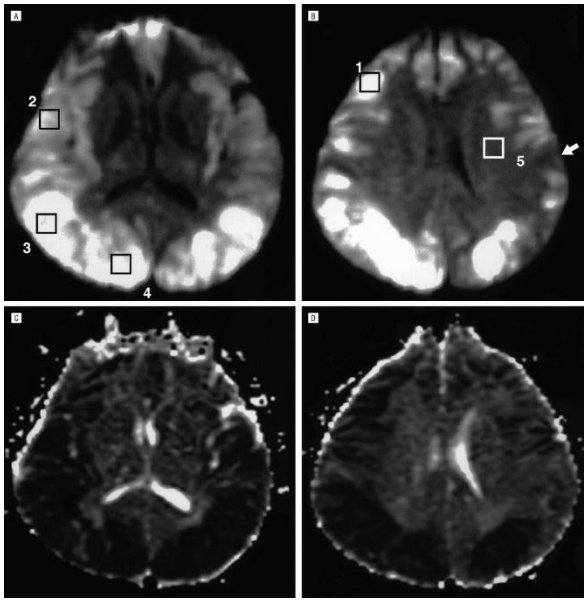
Decrease ADC/increased DWI after CPSE & seizures

- Hippocampal formation
- Cortical areas adjacent to the primary pathology
- Posterior part/pulvinar of the thalamus

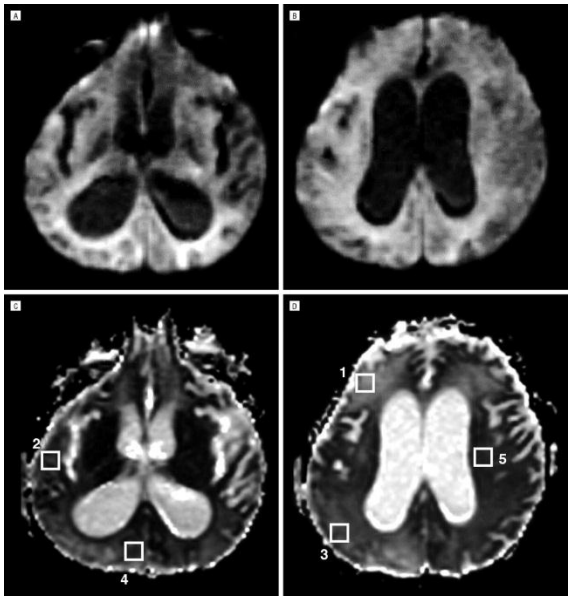
Szabo 2005, Kim 2001, Farina 2004

MR perfusion: increased perfusion in region of decreased diffusion Szabo 2005

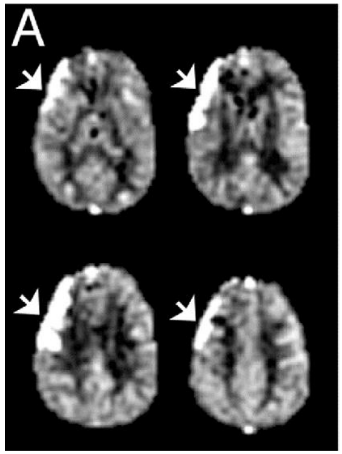
Initial DWI shows diffuse, gyriform cortical hyperintensities



5 months later diffuse low signal intensities



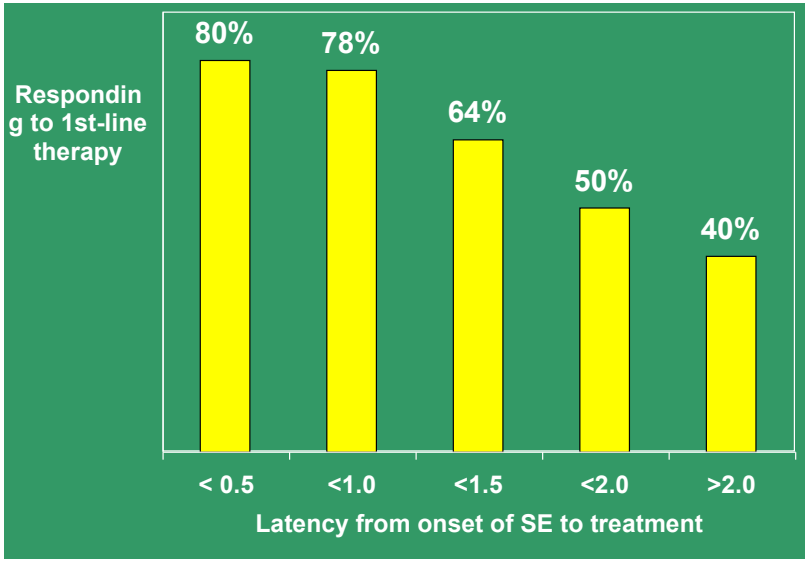
ASL



Detre 1996

Chu 01

Seizure Rx: Emergent initial therapy (1st line)



Lowenstein Neurology 1993

Pre-hospital LRZ vs DZP vs PLB

- No seizures on ER arrival: 59% LRZ vs 43% DZP vs 21% PLB
- Respiratory complications: 23% PLB 10-11% with LRZ/ZP

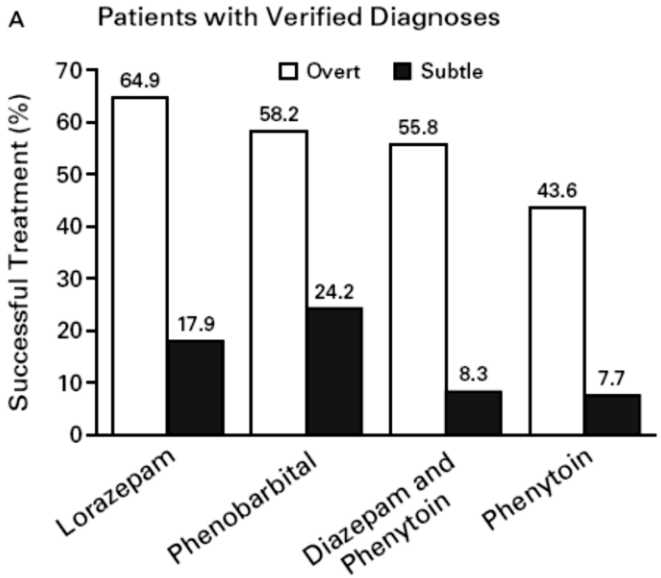
Alldredge NEJM 2001

RAMPART: 10 mg IM MDZ for pre-hospital SE

- Safe and effective alternative to IV lorazepam

Silbergleit et al, NEJM 2012

AED	Success	hypovent	hypoten	arrhyth
LRZ	65%	14%	28%	12%
PB	58%	13%	34%	3%
DZ+ PHT	56%	19%	33%	2%
PHT	44%	11%	29%	9%
mean	55%			



Treiman et al. NEJM1998

Emergent initial therapy (1st line)

	Dosing
Recommended	
Lorazepam	**4 mg IV, may repeat in 5-10 minutes**
Alternatives	
Diazepam	0.15 mg/kg IV (max 10 mg/dose, may repeat in 5 min)
Midazolam	**0.2 mg/kg IM (max 10 mg)**
Others	
Phenytoin	20 mg PE/kg IV (IM), may give additional 5 mg/kg
Phenobarb	20 mg/kg IV (may give additional 5-10 mg/kg)
VPA	20-40 mg/kg IV (may give additional 20 mg/kg)
Levetiracetam	1-3 g IV

Brophy, Bell, Claassen, et al NCC 2012

Urgent control therapy (2nd line)

AEDs following administration of short acting benzos required for all who p/w SE

- No consensus which AED best
- Should it depend if seizures stopped after first AED

Drug	GTC Success
Mean 1st line	56%
Mean 2nd line	7%

Treiman et al. NEJM 1998

Similar efficacy for IV VPA vs IV DPH

Agarwal P, et al. Seizure 2007

Urgent control therapy (2nd line)

	Dosing
Recommended	
VPA	**20-40 mg/kg IV (may give additional 20 mg/kg)**
Phenytoin	**20 mg PE/kg IV (or IM), may give additional 5 mg/kg**
Alternatives	
cIV Midazolam	Initial 0.2 mg/kg; maintenance 0.05–2 mg/kg/hr
Others	
Phenobarb	20 mg/kg IV (may give additional 5-10 mg/kg)
Levetiracetam	1-3 g IV

Brophy, Bell, Claassen, et al NCC 2012

Refractory status epilepticus (RSE)

Def: Patients that do not respond to the standard SE

- Often benzo followed by acceptable second AED

Bleck Arch Neurol 2005

Epidemiology RSE: 38% of overt SE; 82% of subtle SE

Treiman et al 1998

Predictors of RSE

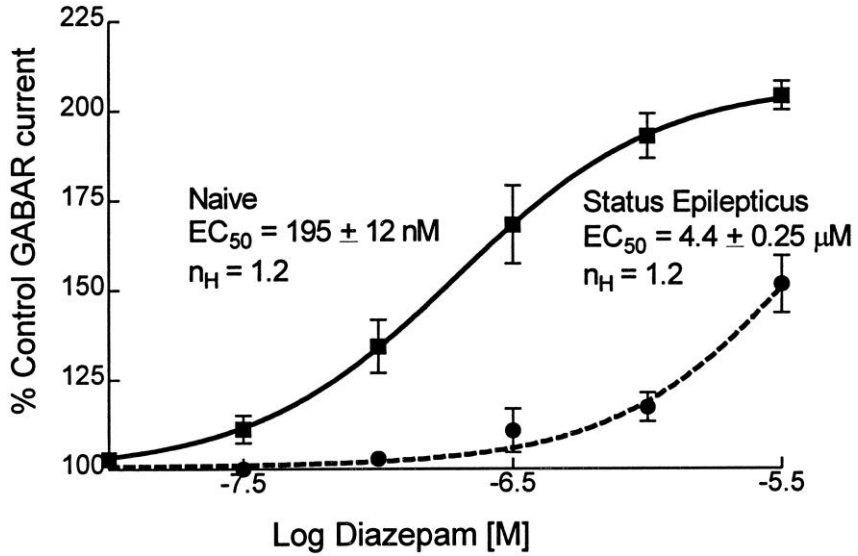
- Non-structural cause (HIE, tox/metab, CNS infection)
- Hyponatremia in first 34 hrs
- Delayed diagnosis/treatment
- Subtle or NCSE
- Focal motor seizures at onset
- Young age

Lowenstein et al 1993, Young 1996,Mayer et al 2002, Holtkamp et al 2005

Reasons for refractoriness

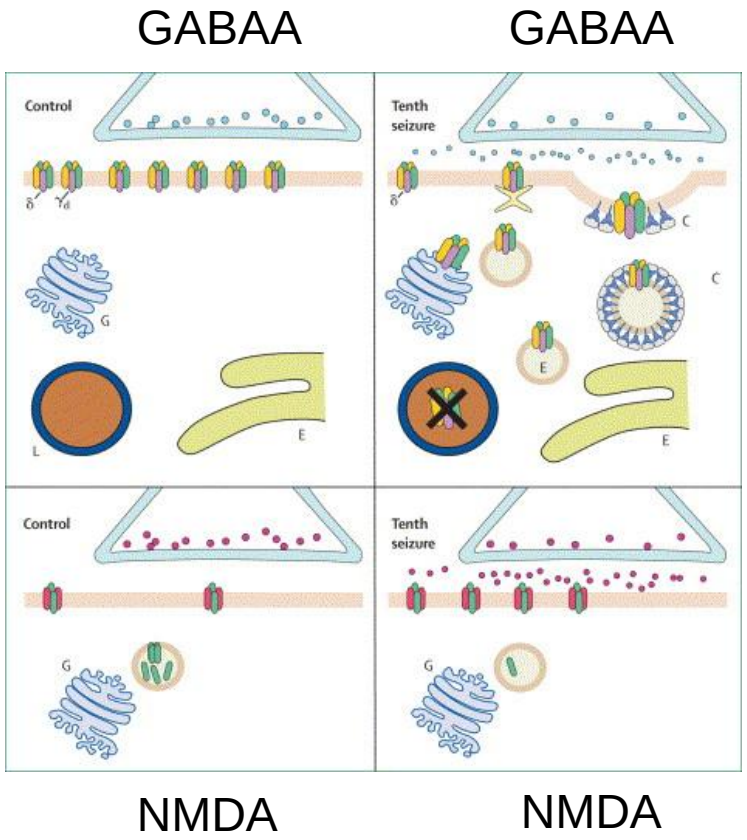
- Reduced sensitivity of GABAA receptors in the hippocampal dentate granule cell to AEDs (e.g. diazepam)
- Reduced surface expression of GABAA receptors (e.g. trafficking) & upregulation of NMDA receptors
- Overexpression of drug efflux transporters

Kapur J Neurosci. 1997; Mazarati Brain Res 1998, Loscher Epilepsia 2007, Chen Lancet Neurol 2006



Kapur J. Neurosci. 1997

GABAA receptors are destroyed in lysosomes



NMDA receptors are mobilized

Clinical characteristics of RSE

- Primarily clinically subtle electrographic or NCSz
- Clinical findings
  - "nystagmus, eye blinking, and/or mild motor movements
  - marked impairment of consciousness
  - continuous or nearly continuous, usually bilateral, ictal discharges on EEG

Treiman Epil 1984, ILAE Epil 2006

"I do not believe that one can treat refractory status epilepticus without continuous EEG monitoring any more than one would treat complex cardiac arrhythmias without electrocardiographic monitoring."

Bleck ArchNeurol 2002

Treatment of RSE

- Most cases should be treated with a cont IV AED: MDZ, PRO, PTB
- Alternatives (if not used already, NCSE): VPA, DPH, LEV

	Dosing
Recommended	
cIV MDZ	**Initial 0.2 mg/kg; maintenance 0.05 – 2 mg/kg/hr**
Alternatives	
cIV PRO	20 mcg/kg/min, maintenance 30-200 mcg/kg/min
cIV PTB	5–15 mg/kg, maintenance 0.5–5 mg/kg/hr
VPA	20-40 mg/kg IV (may give additional 20 mg/kg)

Brophy, Bell, Claassen, et al NCC 2012

Treatment of RSE

	MDZ (N=55)	PRO (N=35)	PTB (N=106)
Breakthrough szs	49%	20%	12%
Withdrawal seizures	63%	47%	40%
Hypotension requiring pressors	31%	38%	68%
Mortality	46%	52%	48%

Claassen Epilepsia 2001

RCT comparing cIV PRO vs cIV PTB:

- terminated early after enrolling 23 patients due to insufficient recruitment (150 needed)
- Similar fct outcome and complications
- Barbiturate group with longer days of MV

Rossetti NCC 2011

Treatment of RSE

PRO major concerns:

- Propofol infusion syndrome (PRIS)
  - prolonged high dose infusion
  - refractory bradycardia with metabolic acidosis, rhabdomyolysis, hyperlipidemia and enlarged or fatty liver
  - rare in RSE case series but may be underreported

Iyer CCM 2009, Power Epilepsy Res 2011, Rossetti Epil 2004

PTB concerns:

- hypotension requiring pressors
- prolonged mechanical ventilation
- Cardiac dysfunction
- Propylene glykol

Rossetti NCC 2011, Yaffe Neurol 1993

Other options for refractory SE

- Levetiracetam
- Lacosamide
- Ketamine
- Other barbiturates (e.g. thiopental)
- Other benzo drips (e.g. LRZ)
- Inhalation anesthetics (e.g. isoflurane)
- Lidocaine
- Verapamil
- Paraldehyde
- Acetazolamide
- Ketogenic Diet
- Steroids
- IVIG
- Plasmapheresis
- ACTH
- Vagus nerve stimulation
- Electroconvulsive therapy
- Deep brain stimulation
- Transcranial magnetic stimulation
- Hypothermia

Ketamine

- NMDA receptor antagonist; barbs/benzos work well early in SE, not late; Ketamine is opposite
- **Loading dose:** 1-2 mg/kg IV/1 min
- **Maintenance dose**: 0.01-0.03 mg/kg/min cIV (adjust with liver failure)
- **Principle**: use only with benzos
- **Theoretical advantage**: neuroprotective, hemodynamic stability
- **Disadvantage**: prolonged use anecdotally linked to brain atrophy consistent with animal models of NMDA antagonist-mediated neurotoxicity, may cause hypertension
- **Caution with:**
  - intracranial mass, TBI, globe injuries, hydro, elevated ICP
  - hypertension, chronic CHF, tachyarrhythmias, MI
  - ETOH history

Borris 2000; Mazarati 1998, 1999; Mewasingh 2003

So far a few anecdotal case reports of using ketamine mostly with benzos

Hsieh et al Clin Neuropharm 2010, Yeh Seizure 2011, Pruss &Holtkamp Epil Res 2008

Pharmacologic Alternatives

Levetiracetam (1-3 g, at 2-5 mg/kg/min IV)

- 70% of patients resolution of SE within 48 hrs after failing at least one AED (retrosp 36 pts)

Moddel et al JNNP 2009

Lacosamide (200-400 mg IV, at 200 mg IV/15 min)

- Effective in small series of focal SE
- Effective as add on therapy in brain TU pts

Albers et al Seizure 2011, Swisher et al NCC 2011

Ketogenic diet: annecdotal experience

Kossoff Epil Curr 2011

Inhaled anesthetics: usually SE recurs when discontinuing inhaled anesthetics

Kofke Anesth 1989, Mirsattari Arch Neurol 2004, Fugate AnAnal 2011

Non-pharmacologic Alternatives

Hypothermia:

- Small case series (N=4), some efficacy suggested

Corry NCC 2008

ECT

- Small case series (N=3), unclear efficacy

Kamel NCC 2010

Surgery

- For focal pathology
- Vagal nerve stimulation
- bilateral deep brain stimulation (centromedian thalamic nuclei)

Lhatoo et al Epil 2007, O'Neill et al Neurosurg 2011, Patwardhan et al Surg Neurol. 2005, Valentin et al Brain Stim 2011

Treatment intensity
Seizure suppression vs burst suppression vs EEG suppression?

RSE treated with PRO or PTB (+/- MDZ): 61% to suppression-burst (N=49)

- Conclusion: neither agent nor the extent of EEG suppression correlated with outcome
- “The lack of demonstrated advantage of treatment to burst suppression may argue against the routine administration of such aggressive treatment”

Rossetti AO ‘05

Duration of PTB Treatment

	>96 hrs	<96 hrs	P
Sz free	89% (8/9)	74% (23/31)	.12
Survive	78% (7/9)	35% (11/31)	.03

No obvious differences in etiology, severity (N=40)

Krishnamurthy KB '96

Many experts continue cIV AED therapy for 24-48 hrs of complete seizure control before gradually withdrawing cIV AED therapy

ICU Management of SE

Cor: cardiac arrhythmias, contraction band necrosis (presumably 2/2 massive catecholamine release, inflamatory component?), MI Manno 2005

- Cardiovascular monitoring, follow Troponin/EKG

Lungs: hypoxia; pulm edema; aspiration

- Most need to be intubated, chest Xray, CT-Angio

ID: fever (may have infection causing SE or aspiration PNA)

- LP, Blood/Urine cultures, chest Xray, antibiotics as clinically indicated

Elytes: changes in GLC, K, Na, pH, and WBC (may have elyte imbalance causing SE or Elyte imbalance and leukocytosis from SE)

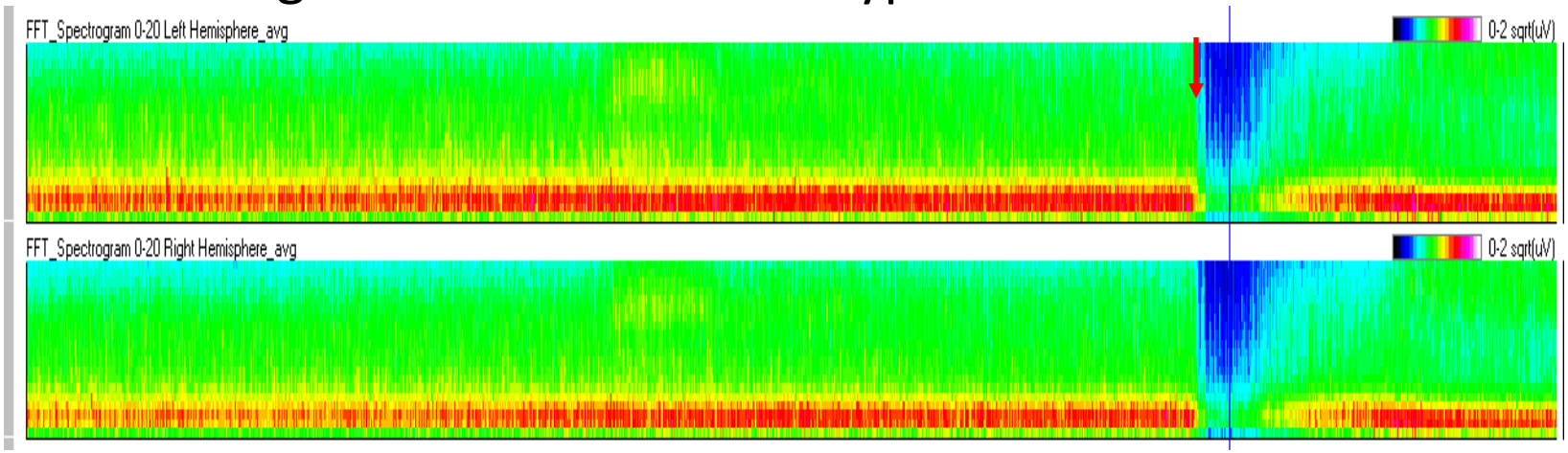
- Check and replete lytes PRN

Renal: rhabdomyolysis, myoglobinuria, ATN

- Analyze urine, trend Chem 7

Titrate medication using cEEG

25 yo M with TBI with refractory ICP crises, CSA with pentobarbital bolus 100 mg and the initiation of hypothermia.



RSE	Continuous IV medication			
	Midazolam (N=55)	Propofol (N=35)	Pentobarbital (N=106)	Total (N=196)
Breakthrough seizures	49%	20%	12%	24%
Withdrawal seizures	63%	47%	40%	47%

Claassen Epil 2001

Conclusion, SE treatment

- SE frequent , in ICU mostly NCSE
- Occurs with or without acute brain injury
- Management approach:
  - Control seizures asap
  - Don’t undertreat
  - Simultaneously give 1st and 2nd line therapy with ABCs and diagnosing underlying etiol
  - AEDs: 1st lorazepam and VPA/phenytoin (straight to cIV AED is option)
- Once convulsions have ceased consider NCSz
- RSE therapy controversial mostly cIV AED, need cEEG