Super-Refractory Status Epilepticus 2014 Pediatric Chula Experience

Definition SE

- Traditional : Prolonged seizure lasting ≥ 30 mins or series of seizure without full recovery to baseline lasting ≥ 30 mins
- Operational : Continuous seizures lasting at least 5 mins or two or more discrete seizures between which there is an incomplete recovery of conciousness
- NCSE : cognitive or behavior change (ranging from mild confusion to coma) coupled with EEG evidence of seizure

Definition SE

Stage of SE	Duration (min)	
Premonitory	0-5	>90% seizure end spontaneously within 4 min
Early	5-30	Seizure lasting over 5min have over 90% probability to last over 30 min
Established	30-60	Criteria used in epidemiology
Refractory	>60	Persistent seizure activity despite 1st and 2nd line Tx

Epidemiology CSE

- Incidence of CSE : 10-38/100000 per year
- Bimodal distribution
  - highest in children (age 0-4years)
  - elderly
- Most common occurred in children less than 1 years
- Associated with poor socioeconomic

Classification of SE

- Generalized convulsive SE
  - Tonic
  - Tonic-clonic
  - Myoclonic
- Generalized nonconvulsive SE
  - Complex partial status
  - Absence status
- Focal SE
  - Epilepsia partialis continua (EPC)

Recommendation of Diagnostic evaluation of a child presenting in SE

New onset SE	Known Epilepsy Patients
Always recommended - Electrolyte - EEG - CT/MRI	Always recommended - AED level
Clinical suspicion - Urine toxicology - Genetic/ Metabolic testing - LP	Consider - Electrolyte - EEG - CT/MRI
Add if Febrile - CBC / Hemoculture - LP	Consider if febrile - CBC /Hemoculture - LP
Refractory/Persistent encephalopathy - Video EEG monitoring	Refractory/Persistent encephalopathy - Video EEG monitoring

Semin Pediatr Neurol 17:144-149

New onset SE : Imaging ??

- CT/MRI

  Imaging abnormality 13% to 32%

  - MRI greater sensitivity for cerebral dysgenesis and other cerebral malformation

  - CT scanning may be used in an emergency setting.

Semin Pediatr Neurol 17:144-149

New onset SE : EEG ??

- EEG
  - Characterize status : Focality
    Epileptiform discharge
    Generalise slow
  - Identify : NCSE
- NCSE

  After CSE were found to be in NCSE 22%

  Subclinical seizure 4%

Semin Pediatr Neurol 17:144-149

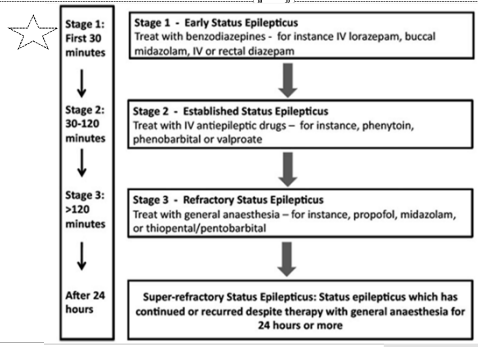
Treatment

- Termination of seizure
- Prevention of seizure recurrence
- Management of precipitating causes
- Management of complication

Treatment : Stabilize patient

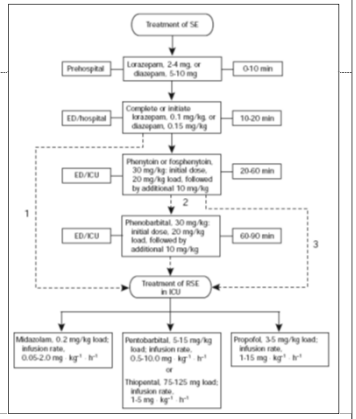
- ABCDE
  - Maintain Airway
  - Breathing : Oxygen / Intubation
  - Circulation : IV access
  - Dextrose
  - Electrolyte : Na Ca Mg PO_4 and AED level

Stage of treatment SE



Brain 2011: 134; 2802–2818

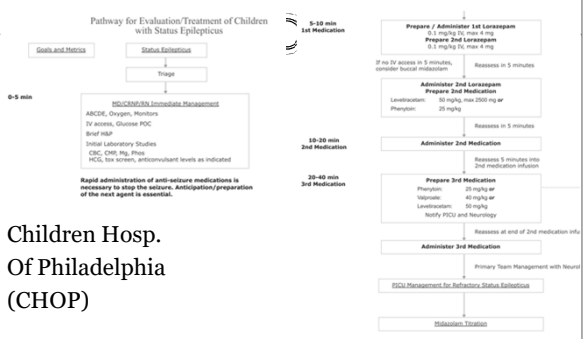
Mayo Clinic



Boston Children's hospital

5 minutes:	Lorazepam, 0.1 mg/kg (usual maximum dose 4 mg/dose); if no IV access, diazepam, 0.5 mg/kg/dose (maximum 20 mg/dose) per rectum
10-15 minutes:	Lorazepam, 0.1 mg/kg/dose and start fosphenytoin, 20 mg PE/kg/dose If fosphenytoin is not available, use phenytoin 20 mg/kg
15-20 minutes:	If seizures persist, phenobarbital 20 mg/kg dose
20-30 minutes:	If seizures persist, fosphenytoin, 10 mg PE/kg

Consider pyridoxine (Vitamin B_6) for infants and children, especially with underlying epilepsy.



Children Hosp.
Of Philadelphia
(CHOP)

Treatment

- 0-5 min : Oxygen, Airway, Position, Vital sign, IV line
  : Investigation
  : IV glucose / Thiamine /Pyridoxine 100 mg
- 6-30 min : Diazepam 0.3-0.5 mg/kg/dose
  Phenytoin 20 mg/kg/dose
  Phenobarbital 20 mg/kg/dose
  Sodium Valproate 20 mg/kg/dose
  Levetiracetam 20 mg/kg/dose
- 30+ min : Add PHT/ PB / VPA
- 60+ min : Midazolam 200 mcg/kg/dose bolus

(Epilepsy Society of Thailand 2011)

Termination of seizure

Drug	Dose&Route	Onset	Duration
Diazepam	0.3 mg/kg IV in 2-5 min 0.5 mg/kg Rectal Max 10 mg	1-3 min Highly lipid soluble	15-30 min
Midazolam	0.2 mg/kg IM/ IV 0.5 mg/kg Buccal / IN Max 10 mg	Fast acting water soluble 3-5 min	2-6 hr
Lorazepam	0.1 mg/kg IV Max 4 mg	6-10 min	12-24 hr

Transmucosal pharmacological therapy

- Intranasal midazolam as effective as intravenous diazepam
- Buccal midazolam as effective as rectal diazepam.
- Intravenous formulations of midazolam (given buccal or intranasal routes) are relatively inexpensive.
- Caregivers prefer intranasal midazolam to rectal diazepam.

Appleton R et al Cochrane Database Syst Rev 2008 Jul 16;(3)

Prevention of recurrence seizure

Drug	Dosage&Route	Rate of infusion	Precaution
Phenytoin	20 mg/kg IV	1 mg/kg/min (50 mg/min) Dilute **NSS** Only	Phlebitis (pH 11-12) Hypotension Arrhythmia
Phenobarbital	20 mg/kg IV	3 mg/kg/min	Sedation Apnea Hypotension
Valproate	20 mg/kg IV	3-6 mg/kg/min	Liver disease Thrombocytopenia Hyperammonemia
Levetiracetam	20 mg/kg IV	Rapid infusion	
Fosphenytoin	20 mg/kg IV/IM	3 mg/kg/min	Prodrug of PHT pH 8-9

Treatment SE

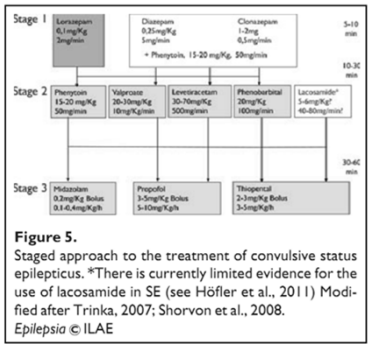


Figure 5.
Staged approach to the treatment of convulsive status epilepticus. *There is currently limited evidence for the use of lacosamide in SE (see Höfler et al., 2011) Modified after Trinka, 2007; Shorvon et al., 2008.
Epilepsia © ILAE

Epilepsia, 53(Suppl. 4):127–138, 2012
doi: 10.1111/j.1528-1167.2012.03622.x

Purple Glove syndrome

Treatment of refractory SE

- No prospective randomised trials comparing the effects of anesthetics in the treatment of RSE.
  - Safety data lacking.

Options:

- Barbiturate anesthetics: Pentobarbital (US) Thiopental (Europe Aus)
- Propofol
- Midazolam.

- Evidence based medicine: No recommendations on data available.
- Even in a large survey of neurologists in USA – little consensus for 3rd / 4th line intervention (*J Neurol Sci 2003*)

Rosenow et al;Epileptic Disord 2002

Midazolam

- Standard dosage Midazolam
  - Loading dose 0.2 mg/kg (200 mcg/kg/dose)
  - maintained at 0.1 to 0.6 mg/kg/hr.

(2 mcg/kg/min titrate every 15 min to 10 mcg/kg/min)

- Half-life of 6 to 40 h after prolonged infusion.
- Main drug interactions : None.
- Main side effects : Sedation
  Respiratory depression
  Hypotension→ Inotropic drug

Brain 2011: 134; 2802–2818

Midazolam infusion

- Requires a syringe driver
- Greater risk of airway suppression (especially following previous Benzo boluses)
- Takes long time to gain control (range 15 mins – 4.5 hours)
- Potential for children left with prolonged seizures and irreversible neuronal cell death in centres without high care facilities
- NOTE: Excluded from APLS guidelines

Rivera et al; CCM 1993
Lal Koul et al; ARCH 1997
Ozdemir et al; Seizure 2005

Thiopentone

- Poor anticonvulsant
- Marked haemodynamic effects
- Prolonged drug effects if infusion used
- Local ICU capacity limited

- Staffing
- Monitoring
- Anaesthetic experience

Very-high-dose Phenobarbitone

- Both barbiturates and benzodiazepines exert a primary effect on the GABA receptor complex.
- No antiepileptic ceiling effect ! No maximum dose beyond which further doses are likely to be ineffective >200 mg/kg!

Complications:

- Sedative and respiratory-depressant properties more likely in combination with benzodiazepines.
- Hypotension unusual and related to the highest Phenobarbitone levels and easily controllable.
- Complications usually related to underlying aetiology

Crawford et al; Neurol 1988

Intravenous Sodium Valproate

- FDA approved 1996.
- Not in APLS guidelines
- No reports of respiratory depression or hypotension.
- Caution in children with underlying liver disease or suspected mitochondrial disorder.
  - Potential hepatic encephalopathy
- Comparative studies:
  - Intravenous Sodium Valproate vs Diazepam infusion
  - Intravenous Sodium Valproate vs Phenytoin.
- No large studies measuring efficacy
- Larger paediatric focused studies are needed
- Still need syringe driver
- Very expensive
- Drug of choice: Absence status

Limdi et al; Neurology 2005
Rossetti & Bromfield; Neurology 2005
Limdi N et al Epilepsia 2007;48(3):478-483
Morton L et al Pediatr Neurol 2007;36:81-83
Metha V et al J Child Neuro 2007; 22:1191

IV Levetiracetam

- FDA approved adults over 16 yrs since 2006
- Limited data in children (most retrospective case reviews – n=10 and n=32)
- Loaded with 25-50mg/kg at level 3
- Effective
- Safe
- Larger comparison studies needed

Kirmani et al Ped Neurol 2009
Abend et al Pediatr Crit Care Med 2009
Gamez-Leyva et al CND Drugs 2009

Why is IV phenobarbitone so good for resource poor countries?

- Highly effective at controlling status
- Safe
- Cheap
- It can be given by rapid IV bolus
- It can be repeated
- It can be given by IM route
- No need for syringe driver
- If control not attained at 1 hour time to arrange transfer to tertiary unit – exceptional situation

Crawford et al; Neurol 1988;
Wilmshurst & Newton; DMCN 2005
Lee et al;Pediatr Neurol 2005

Lacosamide

- Adult :Bolus dose 400 mg (range 200–400 mg), Rate 40–80 mg/min
  - Success Rate 1st/2nd AED: 3/5, 3rd AED: 11/19, >= 4th AED :3/15 Failed in 5 subjects, No serious adverse events
  - 2008-2016 review: 522 SE (486 adults /36 children); overall LCM efficacy 57%; comparable in nonconvulsive and generalized-convulsive (57%/61%);
  - Better in focal motor SE (92%; p = 0.013; p < 0.001).
  - If LCM used as later AED: Eff drop from 100% ->20%.
  - AE : dizziness, abnormal vision, diplopia, and ataxia.
- Pediatric: Bolus 8.7 mg/kg(up to 10 mg/kg), Total first 24 hour 13.8 mg/kg
  - Success 77.8%(7/9), Sz free 44.4 (4/9), failed 2/9
  - 30% to 50% of children experienced at least a 50% reduction in seizure frequency, similar to results obtained in clinical trials in adults. Children with focal onset seizures were most likely to benefit from treatment

Kellinghaus et al; Acta Neurol Scand 2010;
Strzelczyk et al; Epilepsia 2017;
Poddar et al; j.pediatrneurol.2016.

Outcome and Prognosis SE

- Factor determine risk of mortality and morbidity
  - Certain etiology
  - Age
  - Long duration of SE
- Mortality rates
  - Short term during the first 30-60 days after SE mortality rate 7-25%
  - unprovoked or febrile CSE 0.2%
  - acute symptomatic CSE 12.5-16%

Neurologic sequelae

- Secondary epilepsy
- Cognitive deterioration
- Behavioral problems
- Focal neurologic deficit

doi:10.1093/brain/aws091 Brain 2012: 135; 2314–2328 | 2314

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy

Simon Shorvon and Monica Ferlisi

Table 1 **The published literature on treatment outcomes**

Therapy	Number of published papers reporting outcome data	Number of published cases in which outcome data are provided
Pentobarbital/thiopental	23	192
Propofol	24	143
Midazolam	20	585
Ketamine	7	17
Inhalational anaesthetics	7	27
Hypothermia	4	9
Magnesium	2	3
Pyridoxine	2	2
Immunotherapy	8	21
Ketogenic diet	4	14
Vagal nerve stimulation	4	4
Deep brain stimulation	1	1
ECT	6	8
Emergency neurosurgery	15	36
CSF drainage	1	2
Topiramate	10	60
Levetiracetam	8	35
Pregabalin	1	2
Lacosamide	2	10

Table 2 **Overall outcome of anaesthetic therapy**

Outcome	Thiopental/pentobarbital ($n = 192$)	Midazolam ($n = 585$)	Propofol ($n = 143$)
Control	64% (123/192)	78% (458/585)	68% (97/143)
No control ever achieved[a]	5% (9/192)	16% (93/585)	11% (16/143)
Breakthrough seizures	0% (0/192)	3% (19/585)	1% (2/143)
Withdrawal seizures	9% (18/192)	<1% (2/585)	6% (8/143)
Therapy failure because of side-effects	3% (5/192)	<1% (1/585)	6% (8/143)
Death during therapy	19% (37/192)	2% (12/585)	8% (12/143)

[a]Excluding those who died without control who are included in the 'death during therapy' category, and those who switched because of side-effects who are included in the 'therapy failure because of side-effects' category.

Table 3 **Long-term outcome**

Outcome[a]	$n = 596$
Deaths	207 (35%)
Severe neurological deficit	79 (13%)
Mild neurological deficit	80 (13%)
Undefined neurological deficit	22 (4%)
Recovery to baseline	208 (35%)

[a]In the reports of 596 cases (51% of the total of 1168), the long-term outcome was recorded. In the other 575 cases, no long-term outcome data were provided.

Refractory SE ??

- Review diagnosis : True seizure ??
  - Abnormal movement
  - Psychogenic nonepileptic seizures
- Review Treatment : Adequate ??

Differential diagnosis of CSE

- Tonic extensor spasm
  - tentorial herniation
  - acute brainstem dysfunction
- Acute dystonic reaction
- Chorea
- Paroxysmal dyskinesia
- Psychogenic status epilepticus

Clinical features of epileptic seizures versus psychogenic nonepileptic seizures

Clinical feature	Epileptic seizures	Psychogenic nonepileptic seizures
Eye closed	Uncommon	Very common
Stereotyped Sz semiology	Common	Less common
Sz duration > 2 mins	Uncommon	common
Sz onset at sleep	Common	Uncommon
Enuresis	Common	Uncommon
Injury	Common	Uncommon
Medial tongue bite	Common	Uncommon (Tip of tongue)

C.E. Elger, D. Schmidt / Epilepsy & Behavior 12 (2008) 501–539

Refractory SE

- Consult : neurologist
- EEG Monitoring
- Look for treatable cause : autoimmune encephalitis
- Refer

Brain Monitoring

- Continuous
- Non-invasive
- Highly sensitive to a variety of brain insults
- Reasonably specific
- User friendly
- Not too expensive!

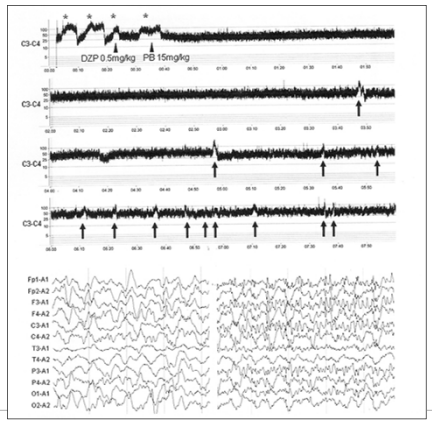
Kurtz et al Curr Opin Crit Care 2009

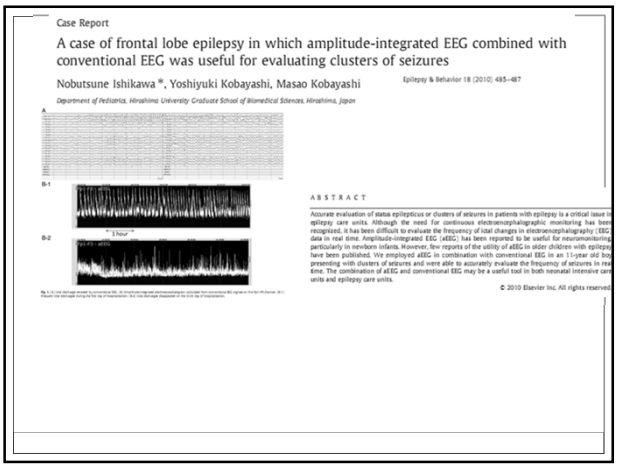
Monitoring

cEEG (continuous EEG – full head montage)
- The Gold standard – not viable in most SA settings
- Non-convulsive seizures
- Ischaemia

aEEG (Amplitude-integrated EEG)
- Assessing if burst suppression attained
- Non-convulsive seizures
- Potential artefact

- Need to remember overall underlying cause usually the defining feature for the outcome of the child.





Case Report

A case of frontal lobe epilepsy in which amplitude-integrated EEG combined with conventional EEG was useful for evaluating clusters of seizures

Nobutsune Ishikawa *, Yoshiyuki Kobayashi, Masao Kobayashi

Department of Pediatrics, Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, Japan

Epilepsy & Behavior 18 (2010) 485–487

ABSTRACT

Accurate evaluation of status epilepticus or clusters of seizures in patients with epilepsy is a critical issue in epilepsy care units. Although the need for continuous electroencephalographic monitoring has been recognized, it has been difficult to evaluate the frequency of ictal changes in electroencephalography (EEG) data in real time. Amplitude-integrated EEG (aEEG) has been reported to be useful for neuromonitoring, particularly in newborn infants. However, few reports of the utility of aEEG in older children with epilepsy have been published. We employed aEEG in combination with conventional EEG in an 11-year old boy presenting with clusters of seizures and were able to accurately evaluate the frequency of seizures in real time. The combination of aEEG and conventional EEG may be a useful tool in both neonatal intensive care units and epilepsy care units.

Non Pharmacological Rx : SRSE

- Ketogenic Diet
- IV Methyl Prednisolone (In specific cases)
- IVIG
- Surgical Resection
- VNS
- (Case to be presented during the meeting)