

Emergency Management of Convulsive Status Epilepticus

What you hope for, what you
settle for, what you get.

Presenters

- Sandy Hopper
- Stuart Lewena
- David Krieser
- Mark Mackay

Convulsive Status Epilepticus

- Format of Session
 - Introduction
 - Background on PEMS and PREDICT
 - Why CSE?
 - Outline 2 PREDICT seizure studies
 - Case History
 - PREDICT Studies
 - Open discussion and questions

PREDICT

- Paediatric Research in Emergency Departments International CollaboraTive
- Major Australian and New Zealand Children's Hospitals and large mixed EDs with high paediatric census
- Multi-site research network convened in December 2004 to facilitate Paediatric Emergency Medicine Research

PEMS

- The **Paediatric Emergency Medicine Society of Australia and New Zealand (PEMS)** is an organisation of medical professionals with an interest in promoting the emergency medical care of children.

Why CSE?

- Common potentially life threatening paediatric emergency
- Requires aggressive, time critical management

Status Epilepticus-Acute Morbidity

- Acute physiological changes
 - Hypertension, tachycardia, increased cardiac output
 - Catecholamine release, increased CBF, hyperthermia
- After 30-60 mins progression to decompensated S.E.
 - Hypotension, acidosis, hypoxia, hyponatraemia / kalaemia
 - Rhabdomyolysis, DIC, leucocytosis
 - Associated with irreversible neuronal injury
- Systemic disturbance including hypoglycemia and fever exacerbate neuronal injury

Status Epilepticus-Acute Morbidity

- CSE in children has a lower mortality compared to adults **but**
- Neurological sequelae are age dependent
 - Occur in 29% of children <1 y.o* cf 6 % of >6 y.o.
- Mortality / morbidity dependent on
 - Duration of S.E., secondary systemic effects
 - Underlying aetiology
 - Interval between onset of S.E. and initiation of treatment

*Maytal et al Pediatrics 1989

Status Epilepticus-Long term sequelae

- Difficult to determine whether S.E. per se causes cognitive problems b/c S.E. often seen in the context of an acute cerebral insult
- Cognitive impairment more likely a result of the underlying aetiology that causes the S.E.

The PREDICT studies

The Acute Management of Seizures in Children

- Survey current practice and guidelines among clinicians at PREDICT sites regarding acute seizure management in children
- Determine direction of future research

CSE PREDICT Study

- 5 yr retrospective study of the presentations and management of children with CSE to EDs in Australia and NZ
- 8 sites within PREDICT

The case

We will present a “typical case” in order to highlight some of the controversies in management of this presentation

Felicity

- A 3 year old child arrives at your ED with ongoing seizure activity. The ambulance service gave her 1.5 mg of IM midazolam 4 minutes prior to arrival.
- She is still fitting.
- Is this status epilepticus?

Definitions

- Physiological definition
 - Recurrent Seizures w/o complete normalisation of neurochemical and physiological homeostasis
- The most widely accepted definition
 - a seizure >30 minutes duration or recurrent seizures over a 30 minute period without return of consciousness in between*
- A more pragmatic definition
 - a seizure of greater than 10 minutes duration (e.g. on arrival at hospital)

*EFA working group on status epilepticus JAMA 1993

She is still fitting

What do you do?

Immediate actions

- A (posture, suction, airway adjuncts)
- B (O₂ by mask, beware BVM with spontaneous ventilation)
- C (IV access, fluids if hypoperfusion)
- DEFG (don't ever forget glucose)

- And now ?

More Benzos?

- What route? (what if there is no IV access?)
- What drug? (midaz vs diaz)
- What dose? (titrated, or larger initial dose)
- How long do you wait?

You get an IV in

- Take some bloods (BSL is 7.2)
- Give some IV midazolam
- She is still fitting

- What is your next step?

Second Line agents

Phenytoin

Phenobarb

Paraldehyde

Midazolam (infusion)

Second Line agents

- When should you start them?
- What should you do whilst you are waiting for them to work?

You start phenytoin

- She stops convulsing, but remains obtunded. She withdraws to pain (GCS= 6)
- She maintains her airway and is pink and well perfused.
- What now?

History

- Felicity is previously well, developing normally, and family history is unremarkable.
- She has had a snotty nose for 2/7, and felt a little hot this morning.
- She was discovered fitting on the floor of the living room by her mother who was preparing lunch and who heard noises coming from the living room.
- Her mother called an ambulance, who arrived within 10 minutes, and treated her along standard lines

Examination

- Felicity is morphologically normal, well grown
- Her airway is clear, She is breathing spontaneously, rate of 24.
- She is normotensive, pulse rate of 138, warm hands
- She groans to painful stimuli, her pupils are 4/4 R/R, and reflexes are symmetrically normal.
- Skin is normal

Investigations

- What tests would you do?

Her breathing becomes shallow and laboured

- You see intermittent left sided posturing
- Accompanied by nystagmoid eye movements
- Is this subtle convulsive activity?

What are the Third Line options

And how do you choose?

Third Line options

- Wait for phenytoin to work
- Midazolam (bolus, infusion)
- Thiopentone/ Suxamethonium/ ETT
- Paraldehyde
- Phenobarbitone
- Valproate

RSI and status epilepticus

When do YOU intubate?

Before you decide, she sighs,
rolls over and goes to sleep.

She is breathing and localises to
pain

Over the next 60 minutes her
mental status improves, there is
no further seizure activity

The Neurologist arrives

The PREDICT Studies

The Acute Management of Seizures in Children

A PREDICT Survey of Emergency Department Practice in Australia and New Zealand

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PREDICT

- Paediatric Research in Emergency Departments International CollaboraTive
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Objective of Seizure Management Study

- Survey current practice regarding acute seizure management in children
 - Senior clinicians at PREDICT sites
- Determine direction of future research
- Determine common ground for future guideline development

Practice Guidelines

- Guidelines for the management of acute seizures and status epilepticus are widely available
- Many clinicians are unaware of or do not follow guidelines
- Guideline driven practice may not improve outcomes

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Methods

1. Compilation of CPGs from PREDICT sites via site representatives
2. Standardised survey of senior clinicians (EM and/or PEM) at PREDICT sites facilitated by site representatives
 - Questionnaire
 - Clinical scenarios
 - MCQs
 - Open responses
 - Data analysis
 - EpiData
 - Descriptive statistics performed with STATA
 - Ethics approval as audit

Results

- 11 PREDICT sites participated
- 78/83 (94%) senior physicians returned surveys (50% male)
 - 40 (51%) FRACP
 - 28 (36%) FACEM
 - 10 (13%) both
- 10 sites utilised 7 CPGs
 - 1 site had no CPG for acute seizure
- Status Epilepticus (SE)
 - Defined
 - 1 site as seizure lasting 15 minutes
 - 4 sites as 30 minutes or recurrent seizures without recovery

Results

Status Epilepticus: First Line Management

CPG Recommendations

- benzodiazepine in 10 CPGs
- With IV access
 - 4 CPGs diazepam only
 - 1 CPG midazolam only
 - 5 CPGs either diazepam or midazolam
- Without IV access
 - 8 of 10 CPGs offered options
 - midazolam IM, IN, buccal
 - diazepam PR

Physician Responses

- With IV access
 - Midazolam 50%
 - Range 0.1-0.2mg/kg (100% of respondents)
 - Diazepam 44%
 - Range 0.1-0.25mg/kg (60.6%)
- Without IV access
 - Rectal diazepam 49%
 - 0.3-0.5mg/kg (68.6%)
 - IM midazolam 41%

Results

- Second Line CPG recommendations
 - Phenytoin (10 CPGs)
 - Phenobarbitone (10)
 - Emphasis on infants
 - Thiopentone (9)
 - Paraldehyde (6)
 - Midazolam infusion (4)
 - Lignocaine (1)
 - Pyridoxine (8 CPGs in children <18 or 24 months)

Physician Responses

- **Second Line SE treatment**
 - Phenytoin 89%
 - Dose 15-20mg/kg (100% of respondents)
- **Third line**
 - Phenobarbitone 33%
 - Dose 15-20mg/kg (82.1%)
 - Thiopentone with RSI 32%
 - Paraldehyde PR 22%
- **Fourth Line**
 - Thiopentone with RSI 60%
 - Dose 2-5mg/kg (94.3%)
 - Phenobarbitone 16%
 - Midazolam infusion 13.3%

Results

	Investigation of First Time Seizure	
	Physician Responses % (n = 78)	
	First AFEBRILE Seizure	First FEBRILE Seizure
Routine Testing in ED		
BSL	93.6	60.3
Elec	80.8	20.5
Ca	83.3	15.3
Mg	70.5	12.8
FBE	39.7	35.9
Blood Culture	3.8	32
LP	-	2.6
Urine MCS	26.9	55.1
EEG	5.1	-
CT	10.3	-
MRI	1.3	-
No routine tests	5.1	20.5

Results

Routine Follow up Investigation

First AFEBRILE seizure

- EEG 60.3%
- CT 11.5%
- MRI 1.3%
- None 20.5%
- As per referral physician 24.4%

First FEBRILE seizure

- EEG/CT/MRI 0
- None 93.6%
- As per referral physician 6.4%

First Afebrile Seizure

Utility of Diagnostic Tests

- AAN Practice Parameter-Evidence Based review
- Evaluating a first non febrile seizure in children.
 Hirtz et al. *Neurology* 2000;55(5):616-23
 - Class I: Prospective cohort with adequate sample size.
 - Class II: Retrospective or prospective with inadequate sample size
 - Class III: Small cohort/ case report/ expert opinion
- Standard, Guideline, Option

Laboratory Studies

- FBC, Electrolytes, Urea, Creatinine, Glucose, Calcium, Magnesium, Toxicology
 - Abnormalities rarely found
 - Clinical history usually suggestive
 - In infants <6 months of age where up to 70% may have hyponatraemia (class II)

PRACTICE OPTION

determine on individual clinical basis
e.g. Vomiting, diarrhoea, risk factors

EEG- What's the Evidence

10 Class I studies

- 4 showed abnormal EEG predictive of recurrence
- 54% chance of recurrence if EEG abnormal c.f. 25% chance if normal in one study ($p < 0.001$)
- Activation procedures increase the yield
- Early (<24 hrs) vs. late
 - higher yield if done early? (54% v 34%)
King et al *Lancet* 1998;352:1007-11
 - others believe lack sensitivity (61%) & specificity(71%)
Gilbert et al *Neurology* 2000;54:635-641

CONCLUSION

- STANDARD OF CARE but optimal timing unclear

Role of EEG

- Support the clinical diagnosis of epileptic seizures
- Distinguish focal vs. generalised epilepsies
- Identify specific epilepsy syndromes
- Guides in choice of further investigation
- Predictive of long term outcome

Role of MRI

- Non-idiopathic partial seizure
- Significant focal EEG changes
- Associated neurological abnormalities (cognitive/ motor impairment)
- Suspected cerebral pathology from (abnormal) history/examination

Results

Routine Admission

First AFEBRILE Sz

- 23.1% of ED SMS admit first AFEBRILE seizure

First FEBRILE Sz

- 20.5% of ED SMS admit first FEBRILE seizure

Results

Routine Referral

First AFEBRILE seizure

- ED SMS to Paediatrician **83.3%**
- ED SMS to GP **10.3%**
- ED SMS to Neurologist **6.4%**

First FEBRILE seizure

- ED SMS to Paediatrician **10.3%**
- ED SMS to GP **76.9%**
- ED SMS to Neurologist **0**
- No referral **12.8%**

Limitations

- Nominally anonymous, site coded with collection by site representative may have led to pressure on individuals to follow local CPG.
- Do survey responses correlate to actual practice?
- This is a snapshot at one point in time. Practice parameters evolve.
- Survey of consultant practice. Emergency care is also provided by trainees and their practice may differ.

Conclusions

- The initial management of status epilepticus is broadly similar
- Second line and subsequent management including use of RSI is varied
- Collaborative future research should aim to close evidence gaps and create consistent clinical practice guidelines

Questions



Status Epilepticus in the ED

What we actually do

A PREDICT study of management

Dr Stuart Lewena

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RCH Melbourne

Introduction

- 5 yr study of the presentations and management of children with CSE to EDs in Australia and NZ
- 8 sites within PREDICT
- Standardised case definition
 - Minimum 10 minutes seizure duration
 - Seizure control definitions
 - Excluded head trauma

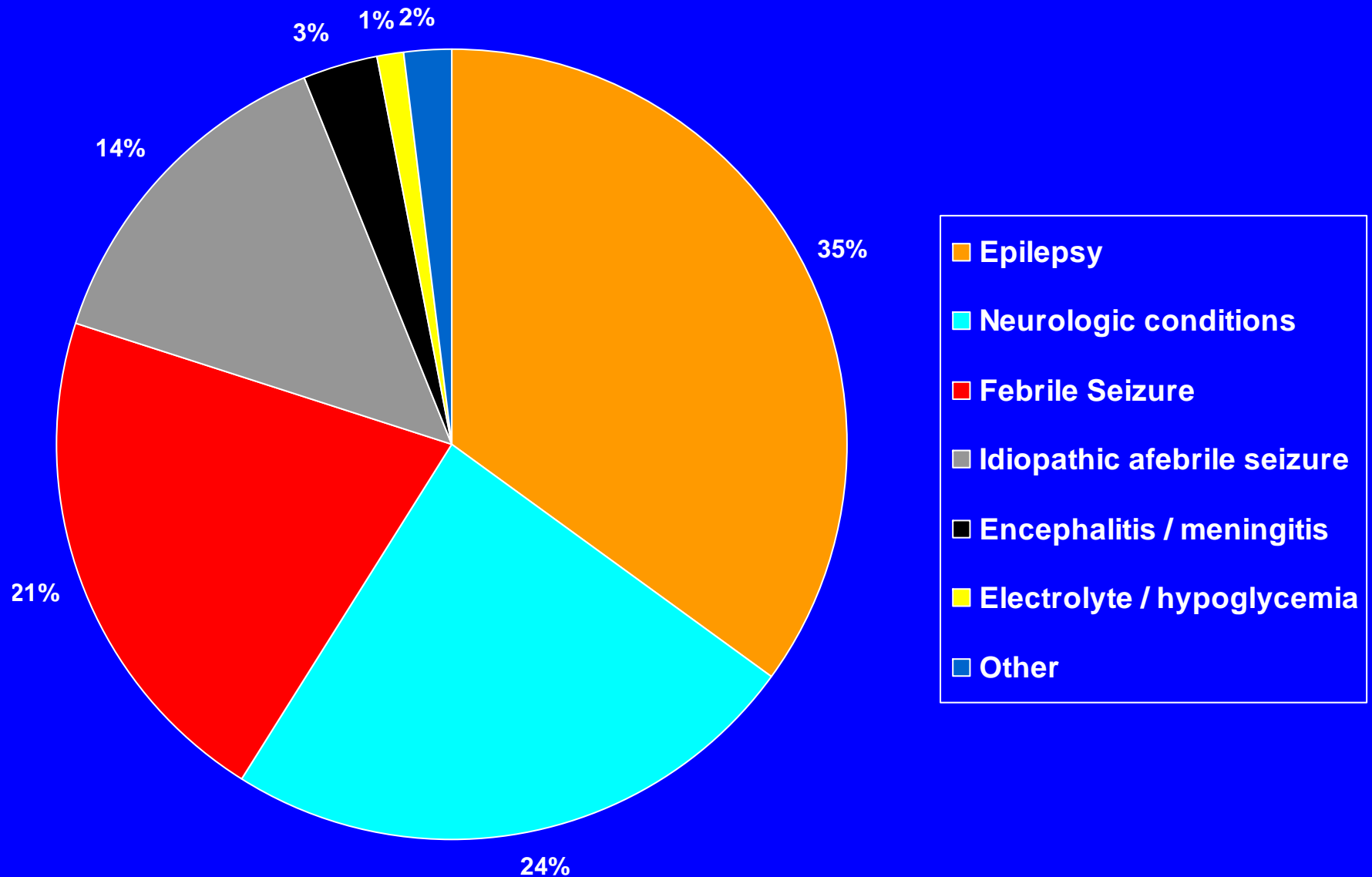
Population

- 542 episodes
- Median age 3 yrs (IQR 1 – 6 yrs)
- Equal sex distribution
- 33% cases of CSE represented children presenting with their first seizure
- 59% known to have epilepsy or other chronic neurological conditions

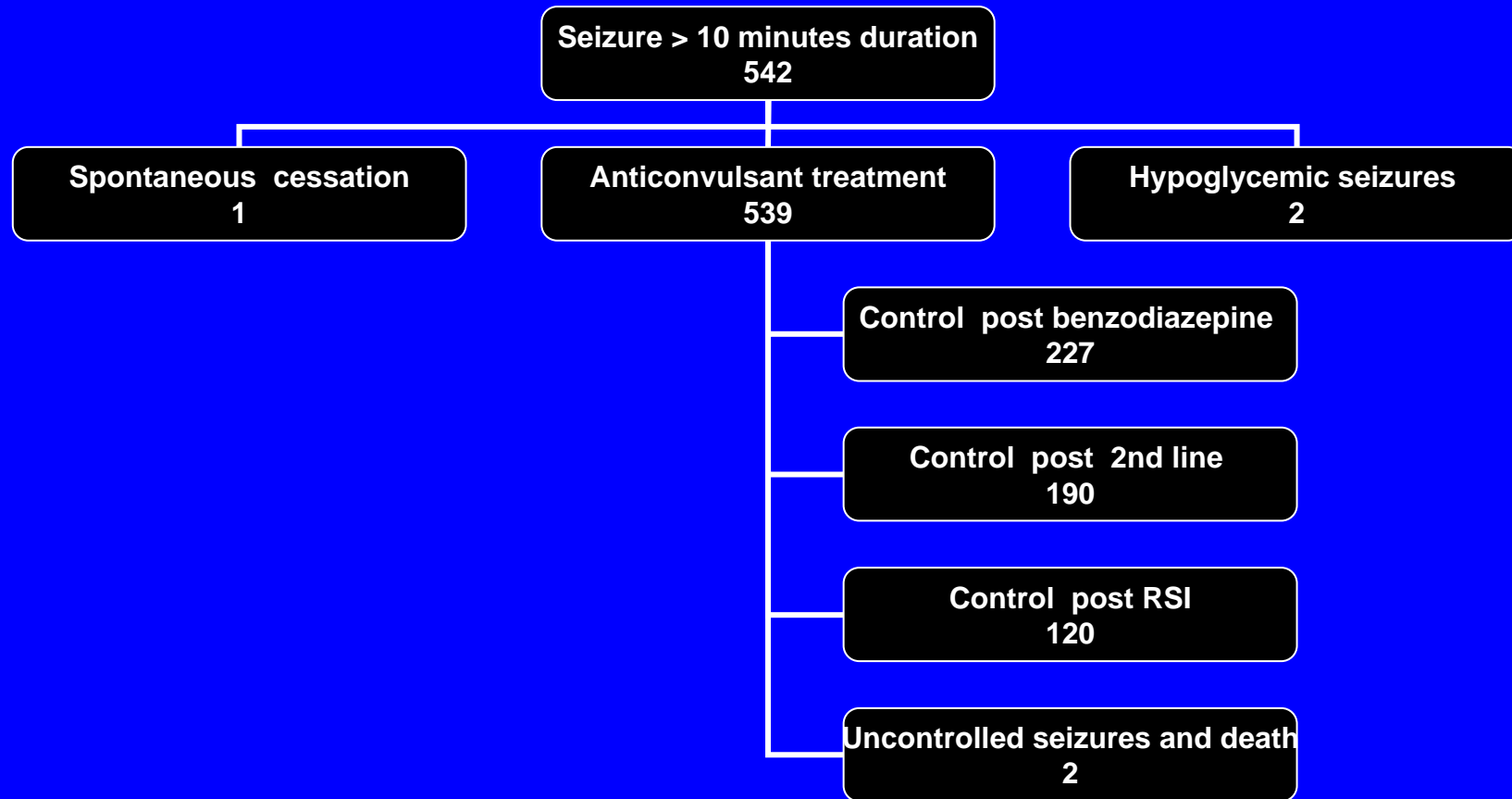
Prehospital Phase

- Median seizure duration at presentation of 45 minutes (IQR 30 – 60)
- Prehospital anticonvulsants in 48%
 - PR diazepam
 - IM midazolam
 - 8% more than 1 dose

Diagnoses



ED Management and Outcome



Anticonvulsant Management

- First line treatment
 - IV diazepam 55% (avg total 0.30 mg/kg)
 - IV midazolam 39% (avg total 0.22 mg/kg)
- Frequently given in repeated smaller than recommended incremental doses rather than 1 or 2 larger doses
 - Concern re adverse effects of recommended dose?

Anticonvulsant Management

- Second line treatment
 - Given to 70% (95% CI 66-74%)
 - Phenytoin most frequent (87%)
 - Phenobarbitone 11%
 - Paraldehyde 2%
 - Combination 14%
 - Median time 24 minutes (IQR 15 – 36)
- Seizure control with standard first and second line therapy in 77% (417/539)

Rapid Sequence Induction /Intubation

- “Failure of anticonvulsant management”
- 25% had RSI performed
 - 122 (23%) with ongoing seizures
 - 14 (2%) post ictal
- Median time to RSI 45 mins (IQR 25 – 68)
- Appears to be a safe ED intervention
- Significant resource implications
- Wide variation in practice

Variation in RSI Use

Site	n	RSI %	95% CI
A	76	16	8 – 26
B	53	9	3 – 21*
C	122	22	15 – 31
D	49	20	10 – 34
E	74	58	46 – 69*
F	24	37	19 – 59
H	89	21	13 – 31
J	55	20	10 – 33
Total	542	25	21 – 29

Seizure Control

- Seizures controlled in all but 2 patients who died
 - 42% after benzodiazepines
 - 35% after second line (mainly phenytoin)
 - 22% after RSI

Time to Control

- Median time to seizure control 30 minutes post ED arrival (IQR 12 – 50 minutes)
- Failure to achieve control within 40 minutes of ED presentation in 33% (95% CI 29 – 37%)
- Total median seizure time 79 mins (IQR 51 – 110)

Impact of Prehospital Duration

- Does a prolonged prehospital phase influence ED treatment?
 - For each doubling of prehospital seizure time
 - 6% reduction in time taken to administer 2nd line drug (95% CI 13% decrease to 1% increase)
 - No impact on time to perform RSI (95 % CI 15% reduction to 16% increase)

Conclusions

- 1st and 2nd line anticonvulsant treatment of children with CSE in PREDICT sites reflects recommended guidelines
- Significant proportion experience a prolonged seizure – both pre hospital (45) and after arrival (30)
- Neglect of prehospital phase?
- Variation between sites in progressing to RSI for seizure control vs waiting and hoping

Questions?

Questions Raised

- How long is too long?
 - Systemic effects / physiological decompensation
 - Neuronal injury
 - Strength of evidence

Questions Raised

- Apply our current treatment more aggressively?
- Search for alternative / more effective early therapies?
- Better detection of subclinical seizure activity?

Recommendations

- Need to play harder AND smarter
- Don't tolerate prolonged refractory seizure activity – intervene
- Do explore early therapeutic interventions.
 - Increased prehospital benzodiazepine administration?
 - More rapid phenytoin?
 - Early midazolam infusion?
 - Others?

We acknowledge the staff and
patients at each PREDICT site
and
Site representatives / coauthors
for reviewing thousands of
medical records

Tips and Tricks

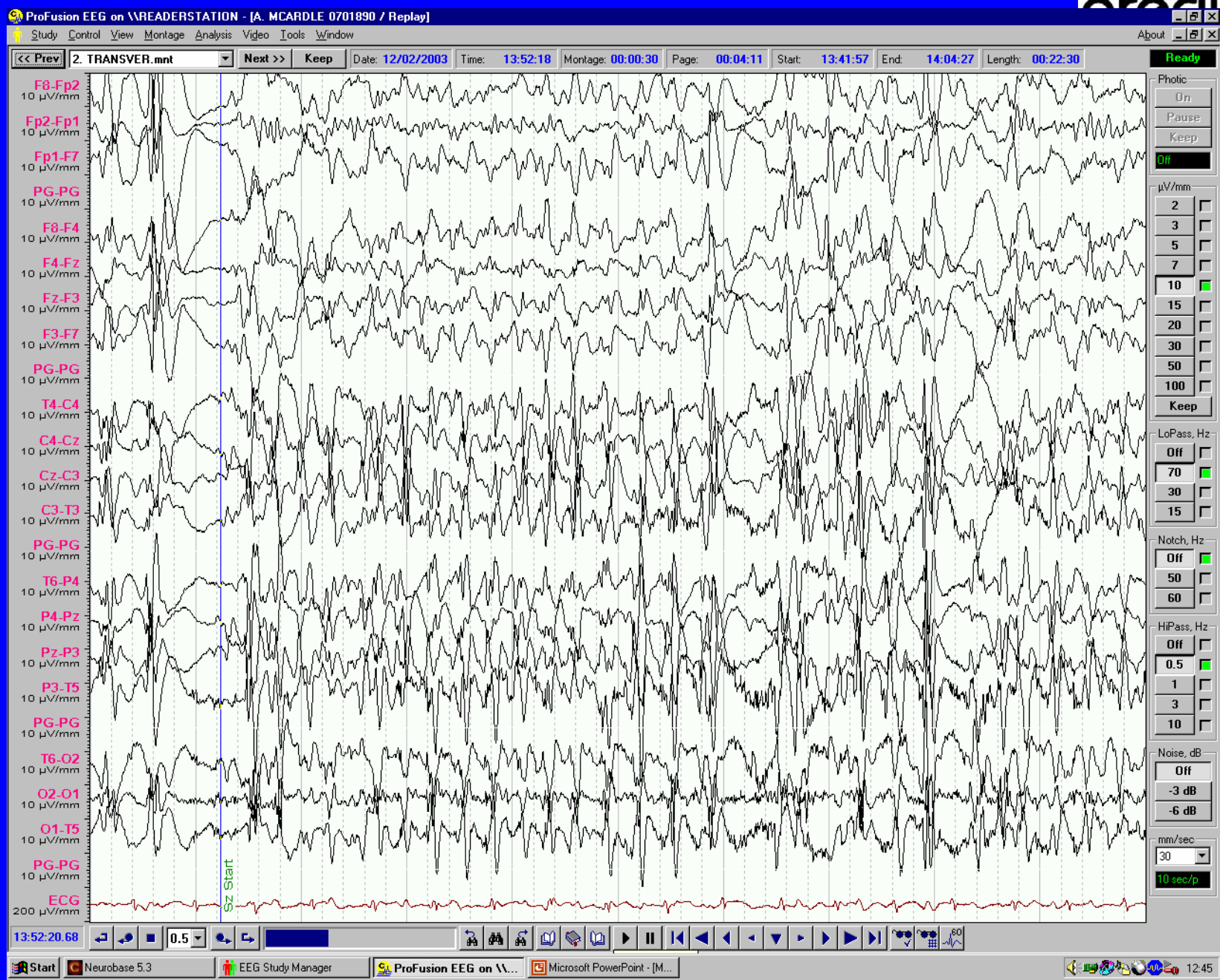
Mark “The Neurologist” Mackay

Absence Status Epilepticus

- Prolonged periods of decreased consciousness and unresponsiveness
- EEG crucial to diagnosis and demonstrates generalised spike wave activity
- May be associated with occasional myoclonic jerks, automatisms and sometimes GTCS
- Can be divided into typical and atypical ASE
- Causes:
 - Carbamazepine in pts with primary generalized epilepsy
 - Benzodiazepine or barbiturate withdrawal
 - Hypocalcaemia, hyponatraemia

Myoclonic status epilepticus

- See erratic or generalised myoclonic jerks associated with clouding of consciousness, stupor, drooling and ataxia
- EEG shows generalised epileptic activity that is closely associated with myoclonic jerks
- See in Lennox Gastaut and myoclonic astatic epilepsy of Doose



Absence and Myoclonic Status Epilepticus

- I.V. benzodiazepines are the drugs of choice
- Clonazepam 0.5-1.0 mg Q 4-6 hrly
- EEG should be obtained prior to and after therapy
- Phenytoin and phenobarbitone can exacerbate ASE
- Prognosis depends on aetiology and subtypes of absence and myoclonic status epilepticus
- Myoclonic status may also respond to

Intravenous Valproate

- Propensity of “standard” medications to exacerbate absence status (PHT, PB, +/- CLB)
- Useful in absence or myoclonic status
- Infuse at a rate of 6mg/kg/min
- Can give btn 20-40mg/kg loading dose followed by infusion of 5mg/kg/hr

- Not currently available in Victoria
- Limited efficacy data

Complex Partial Status Epilepticus

- 33-50% of patients have a past history of epilepsy
- Can be frontal or temporal lobe in origin
- “Epileptic twilight” state.
- Impaired consciousness, confusion, agitation, bizarre, psychotic behaviour
- EEG very important in confirming diagnosis
- Commonest precipitant is change in medications
- Management controversial

Refractory Status Epilepticus

- Several definitions
 - Ongoing seizure activity 60-90 mins following initiation of treatment
 - Failure to respond to combination of benzodiazepine and phenytoin or phenobarbitone
 - Low likelihood of response (<10%) if second line agents fail
- Overall mortality of 32%, higher in symptomatic grps
 - increased by young age, multifocal or generalised abnormalities, acute symptomatic pts
- Response determined by aetiology and duration of SE
 - acute or progressive causes are more likely to be refractory
- Options: Barbituates or Midazolam both bind to GABA_A receptors

Treatment options for Refractory GSE and CPSE

Holtkamp et al J Neurol Neurosurg Psych 2003

- Survey of 63 epileptologists and critical care neurologists in 3 European countries
- 66% initially used another non anaesthetic anticonvulsant agent (mainly Phenobarb)
- Once decision was made to proceed to GA 58% used barbituates, 29% propofol and 13% midazolam
- 70% titrated to burst suppression (most units had continuous monitoring)
- 94% reduced anaesthesia after 48 hrs

RSE-Barbituates

- Thiopentone is the most widely used agent in
- High lipid solubility and slow metabolism
- Slow metabolism, T_{1/2} of 15-60 hrs
- Neuroprotective properties
- Initial bolus of 4-8 mg/kg
- Followed by Infusion of up to 10 mg/kg/hr
- Increase until achieve burst suppression pattern
- Complications include hypotension, myocardial depression and low cardiac output
- Alternatively can use repeated boluses of phenobarbitone 10 mg/kg every 30 minutes

RSE-Midazolam

- Water soluble in acidic solutions
- At physiological pH becomes lipophilic
- Rapid elimination with $t_{1/2}$ of 1-4 hours
- Short elimination half life 1.5-3.5 hrs
- Problems with tachyphylaxis

RSE Meta-analysis in 193 adults

- Midazolam vs. Propofol vs. Pentobarbital
- Overall 48% mortality regardless of Rx choice
- Titration of treatment to burst suppression associated with less breakthrough seizures and better outcome but higher frequency of hypotension
- Compared to other treatments Pentobarbital associated with lower frequency of short term treatment failure, breakthrough seizures and change to an alternative drug but higher frequency of hypotension

RSE Meta analysis in 111 children

- 12 articles, treatments included DZP, MDL, Thiopental, pentobarbital, isoflurane
- All except DZP were 100% efficacious
- Overall Mortality of 16% (20% in symptomatic compared to 4% in idiopathic cases, $p=0.04$).
- No deaths in MDL treated group but highest mortality in isoflurane group
- Conclusion: MDL should be considered as first line therapy in refractory childhood refractory SE