5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 5

Refractory status epilepticus: What to do and how dangerous is it to the brain? (Level 2)

Which AED to choose when first line SE treatment fails?

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Atkinson Morley Regional Neuroscience centre

St George's University Hospitals NHS
NHS Foundation Trust

Which AED to choose when first line SE treatment fails?

Hannah Cock
Professor of Epilepsy & Medical Education
Consultant Neurologist

International Epilepsy Congress, Bangkok June 2019

Declaration

I have received

NIH National Institute of Neurological Disorders and Stroke

–Funding for ESETT

– U01NS073476, U01NS088034, U01NS088023, U01NS056975, U01NS059041, and R01NS099653

– Hospitality from all major AED manufacturers

– Invited talks & honoraria for UCB Pharma, Janssen-Cilag, Sanofi-Synthelabo, GSK, Eisai, Novartis

– Site PI for GWPharma, Novartis, Bial

– Unrestricted Research Grants from UCB Pharma, Johnson&Johnson & Pfizer

MANY DRUGS COVERED IN THIS PRESENTATION ARE NOT LICENSED FOR USE IN SE

http://www.whopaysthisdoctor.org/

Outline

- Definitions & timing
- Considerations before the 2nd line AED
- 2nd line AED options - background
  - (fos)Phenytoin
  - Valproate
  - Levetiracetam
- Recent randomized controlled trials
- Current guidelines
- Other types of SE

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STATUS EPILEPTICUS DEFINITION

- SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to **abnormally prolonged seizures** (after time point 1, **t1**).
- It is a condition that **can have long-term consequences** (after time point 2, **t2**) including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.

⇉ **t1** **initiate treatment**
⇉ **t2** **aim for control**

ILAE Task Force on Classification of SE. Trinka, Cock et al., Epilepsia, 2015

t1 and t2 in different SE Types

SE Type	T 1 : likely to be prolonged/ lead to continuous sz	T2 : may cause long term consequences
Tonic Clonic SE	5 minutes	30 minutes
Focal SE with Imp.Conscious.	10 minutes	> 60 minutes
Absence SE	10-15 minutes*	unknown

*Evidence currently limited, future data may modify

Classification 1: Semiology

- Presence/absence prominent motor features
- Degree of impaired consciousness

A: Convulsive	B: Non-Convulsive
1. CSE (TCSE) a. Generalized b. focal onset c. unknown onset	1. With Coma
2. Myoclonic a. with coma b. without coma	2.a Generalized a. typical absence b. atypical absence c. myoclonic absence
3. Focal Motor	2.b Focal a without imp.aware. b aphasic c with imp.aware.
4. Tonic	2c Unknown
5. Hyperkinetic	a Automonic

Does speed really matter?

Prognostic factors, morbidity and mortality in tonic–clonic status epilepticus: A review

A. Neligan, S.D. Shorvon*

- Long duration, Age, Etiology = poor outcome

Study	Population	Duration	Poor outcome* (%)
Towne, USA 1994	n=253, >16y	< > 1 hour	**2.7 vs 32.0, OR 17.9**
Eriksson, Finland 1997	n=65, <18y	< > 2 hours	**32.7 vs 68.8, p<0.025**
Sagduyu, Turkey 1998	n=66, 6-77y	< > 1 hour	**3.0 vs 29.4, OR 2.41**
Gulati, India 2005	n=30, <18y	< > 45 mins	**9.5 vs 100.0, p<0.001**
Drislane, USA 2009	n=119, 24-96y	< > 10 hours	31.0 vs 69.0, p<0.05
Power, Norway, 2016**	n=56, 20-86y	< > 2 hours	**16.7 vs 52.3, OR 6.12**

Bold: multivariate analysis
*death or significant disability
** Refractory cases only, inc 38 NCSE

Neligan & Shorvon Epilepsy Research 2011
Crawshaw & Cock, Seizure 2019 in press

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Are you sure (enough) it's status epilepticus?

Favour Dissociative Seizures	Not useful discriminators
Long (> 5minutes) duration of individual events	Tongue biting[a]
Fluctuating course (waxing and waning)	Incontinence
Asynchronous rhythmic movements[b]	Gradual onset
Pelvic thrusting[b]	Non-stereotyped[c]
Side to side head/body movements in a convulsion	Flailing/thrashing movements
Closed eyes	Opisthotonous
Ictal Crying	History of associated Injuries
Recall of items during event	

[a] except significant lateral. [b]Can be seen in frontal lobe focal seizures. [c]often report being able to hear, but not to respond. Dissociative seizures are often, but not always less stereotyped than epileptic. Features favouring epileptic seizures include prolonged post-event confusion and sterturous breathing.

Cock & Edwards, Clinical Medicine 2019

Most Practical/Useful Test
Home (staff) video

- Expert review, 97% Specific and 95% sensitive Dx DNES

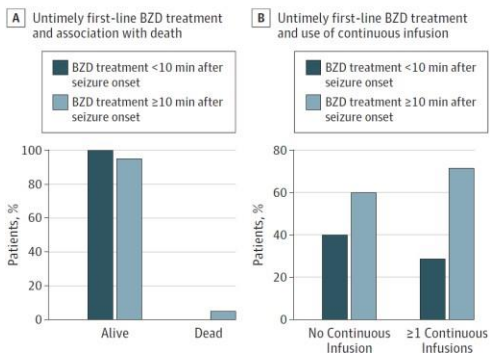
Ramanujan, Seizure 2018

- Secured device
  - Password/face/fingerprint protected
  - NHS systems (as in VEEG)
  - Videos NOT syncing to cloud
- Sufficient footage
  - Whole body, including face
  - At least 1-2 minutes, as much as possible
- Transferred to secure systems asap
  - Encrypted email/webtransfer systems
  - Deleted from host device

Crawshaw & Cock, Seizure 2019 in press

Have they had sufficient benzodiazepines?

Figure 1. Untimely First-line Benzodiazepine (BZD) Treatment and Association With Outcome



Outcome	AOR	95%CI, p
Death	11.0	1.43 - ∞, p=0.02
Cont. infusion	1.8	

- Prospective
- N = 218
- Paediatric RCSE

Delays especially:
- out of hospital
- intermittent sz

Gainza-Lein Jama Neurology 2018
Fernandez Neurology 2018

Benzodiazepine Use (interim)

- 207 subjects, 43 sites (USA)
- 511 administrations
- 82% at least one (first) dose pre-ED

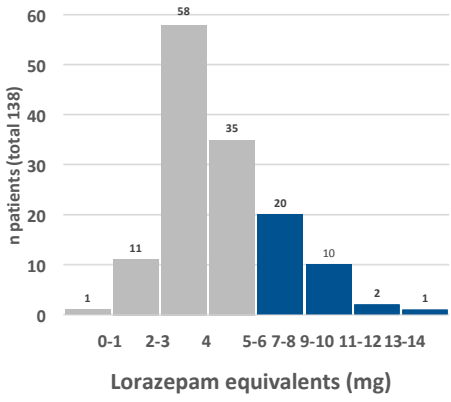
88 (43%) children
95 (46%) 18-65y
24 (12%) >66y

Total Number of Administrations by Setting			
Setting	Diazepam	Midazolam	Lorazepam
Prior to EMS	26 (66%)	9	4
EMS	9	108 (82%)	14
ED	5	42	294 (86%)

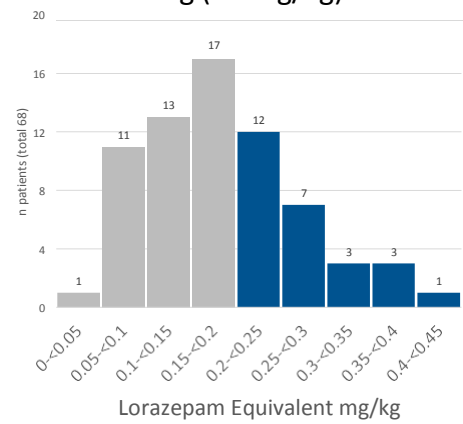
Sathe, Academic Emergency Medicine 2019 in press

Distribution cumulative BZD dose as Lorazepam Equivalents

>32Kg (8mg)



<32Kg (0.2mg/kg)



76% Underdosed

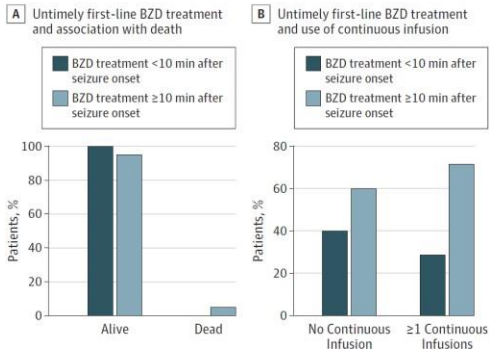
62% Underdosed

Pattern of repeated small doses in EMS and ED

Sathe, Academic Emergency Medicine 2019 in press

Have they had sufficient benzodiazepines?

Figure 1. Untimely First-line Benzodiazepine (BZD) Treatment and Association With Outcome



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Gainza-Lein Jama Neurology 2018
Fernandez Neurology 2018

ESETT Established Status Epilepticus Treatment Trial

>32Kg 76% Underdosed
<32Kg 62% Underdosed
Pattern of repeated small doses in EMS and ED

Sathe, Academic Emergency Medicine 2019 in press

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- **2nd line AED options - background**
  - **(fos)Phenytoin**
  - **Valproate**
  - **Levetiracetam**
- Recent randomized controlled trials
- Current guidelines
- Other types of SE

Background: 2nd line AED in Established[1] SE

Property/AED	(fos)Phenytoin	Levetiracetam[2]	Valproic Acid[2]
US "popularity"	Most commonly used (60-65%)	Used often (20-30%)	Least often
Administration	Slow	Fast	Fast
Speed of action	Slow administration	Slow brain entry, acts slowly	Rapid
Action last long	Yes	Yes	Yes
Efficacious in animal models	Least effective	In combination with diazepam	Very effective
Clinical efficacy	Focal seizures	Focal and generalized	Focal and generalized
Safety	Hypotension, rash, cardiac arrhythmia	Safe	Safe for acute use

[1]benzodiazepine refractory
[2]unlicensed use

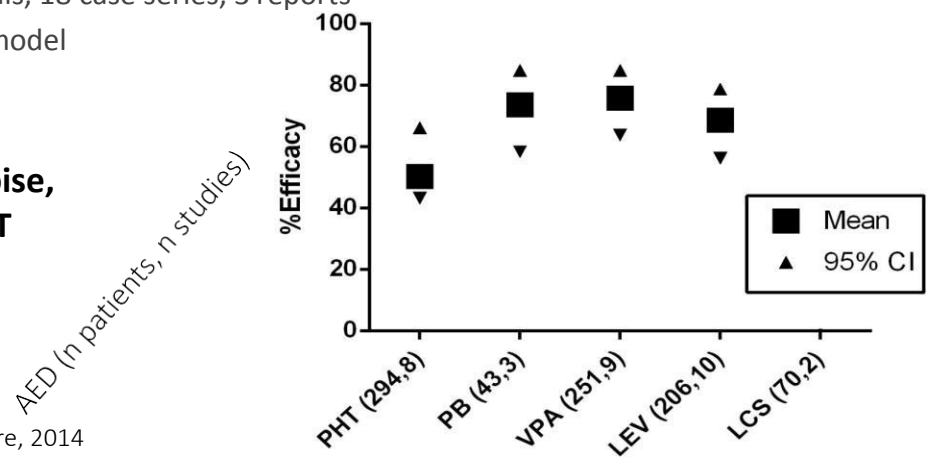
Clinical Equipoise, Pending RCT

Crawshaw & Cock, Seizure 2019 In press

Meta-analysis, Established SE

- 2652 papers - 27 data extracted
  - Post BZD, included CSE, Sz cessation
  - 1 RCT, 5 open trials, 18 case series, 3 reports
  - Random effects model

Clinical Equipoise, Pending RCT



Yasiry & Shorvon, Seizure, 2014

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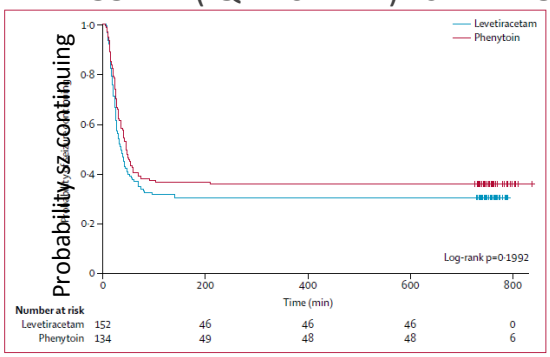
  - –(fos)Phenytoin
  - –Valproate
  - –Levetiracetam
- **Recent randomized controlled trials**
- Current guidelines
- Non-convulsive Status epilepticus

Open RCT LEV vs Phenytoin (Paediatrics)

- **EcLIPSE** eclipse-study.org.uk
  - –Age **6m-18y**, n= 286, (152 LEV,134 PHT; 42% Febrile), 30 sites
  - –LEV 40mg/kg@5min vs PHT 20mg/kg@20+min
  - –**Time from randomization to cessation convulsive sz**
  - –LEV 35min (IQR 20 – NA) vs PHT 45min (IQR 24 – NA), Not SIgnificant



Outcome	LEV	PHT
CSE Terminated	70%	64%
Rx additional AED	38%	37%
Rx RSI (anaesthesia)	29%	33%

Lyttle et al, Lancet 2019

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  - LEV 40mg/kg@5min vs PHT 20mg/kg@20+min
  - **Time from randomization to cessation convulsive sz**
  - LEV 35min vs PHT 45min (NS);

SAFETY

1 death (LEV then PHT)
- Massive ceberal oedema

2 Serious Adverse Reactions (PHT)
- Life-threatening HypoBP
- worsened sz/reduced LoC (? SUSAR)

Lyttle et al, Lancet 2019

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  - LEV 40mg/kg@5min vs PHT 20mg/kg@20+min
  - **Time from randomization to cessation convulsive sz**
  - LEV 35min vs PHT 45min (NS); 1 death, 2 (1 participant) SAR (PHT)

- **NS any outcome**
- **Not superior, ? Safer**
- **LEV "could be 1st choice"**
  - Ease & speed of administration
  - Lack of interactions
  - Easy conversion to oral maintenance

Lyttle et al, Lancet 2019

Open RCT LEV vs Phenytoin (Paediatrics)

- **ConSEPT** predict.org.au
  - Age **3m-16y**, n=233 (119LEV vs 114 PHT, **72% Febrile**), 13 sites
  - LEV 40mg/kg@5min vs PHT 20mg/kg@20min
  - **Sz cessation 5 mins after completed infusion**

Methodological advantages:
- Site and age stratification
- Video (67%) and blinded adjudication outcome
- Pre-specified subgroups (age, Febrile)
- Sz control maintained 2h

Dalziel et al, Lancet 2019

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  - LEV 40mg/kg@5min vs PHT 20mg/kg@20min
  - **Sz cessation 5 mins after completed infusion**
  - Success LEV 60% vs 50% PHT (NS),
  - Maintained at 2h both 70%

Outcome	LEV	PHT
Allergy <2h	0	4%
Purple Glove < 2h	0	1%

Safety
- 1 death (PHT)
- Haem.Encephalitis day 27)
- No SAR

Dalziel et al, Lancet 2019

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  - –**Sz cessation 5 mins after completed infusion**
  - –Success LEV 60% vs 50% PHT (NS),1 death (PHT) no SAR

- **NS any outcome**
- **Not superior, ? Safer**
- **Consider sequential** - adds only 10-20mins
- - save ~10% RSI

Dalziel et al, Lancet 2019

ESETT

Established Status Epilepticus Treatment Trial

ESETT LEADERSHIP TEAM

Jaideep Kapur

https://nett.umich.edu/clinical-trials/esett


Bleck


Cock


Chamberlain


Cloyd


Elm


Fountain


Fureman


Lowenstein


Shinnar


Silbergleit


Treiman


Trinka

58 USA Sites

NETT: **N**eurological **E**mergencies **T**reatment **T**rial

PECARN: **P**ediatric **E**mergency **C**are and **A**pplied **R**esearch **N**etwork

Primary CCC/NETT SDMC PECARN Pharmacology Phenomonology NINDS

Established Status Epilepticus Treatment Trial

A multicenter, randomized, **double blind**, comparative effectiveness study of fosphenytoin, valproic acid, or levetiracetam in the emergency department treatment of patients with benzodiazepine-refractory convulsive status epilepticus.

Nov 2015-Jan2019
Children and adults
Bayesian adaptive randomization
Seizure control at 60mins without other AED (including RSI)

Cock et al, Ep & Behav 2019 in press
Silbergleit et al, in preparation

Study Drug	Dose Mg/kg (max)
Fosphenytoin	20[1](1500)
Valproate[2]	40 (3000)
Levetiracetam[2]	60 (4500)

[1]PE mg phenytoin equivalents [2]unlicensed

Established Status Epilepticus Treatment Trial

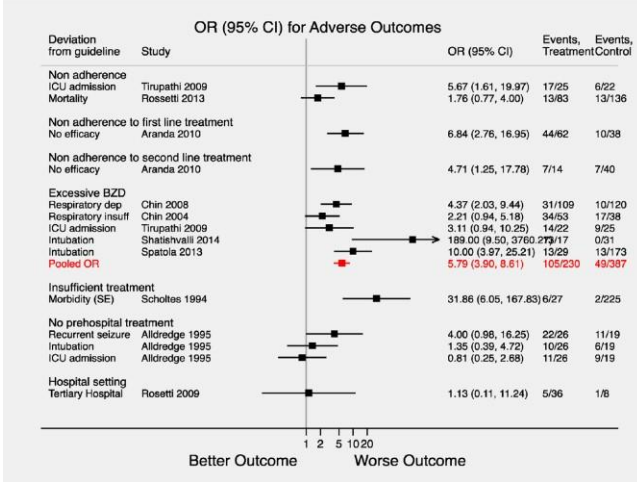
Results

Imminent
n=478
Age 2y and above (94)

Study Drug	Dose Mg/kg (max)
Fosphenytoin	20[1](1500)
Valproate[2]	40 (3000)
Levetiracetam[2]	60 (4500)

FDA IND approved doses, no major safety concerns

Deviation from Guidelines



Non-Adherence
OR Adv. Outcome
5.79 (2.9-8.61)

More likely to
- continue seizing
- have ↓ respiration
- need intubation
- need ICU
- (die)

Uppal *Seizure* 2018
St George's Local Audit

Give it promptly, give ENOUGH
(and not too much)

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St George's University Hospital London Guidelines

Drug	Dose; Rate (Maximum)	May be preferable	Contraindications & Cautions
(fos)Phenytoin	**20mg/kg;** 50mg/min (2000mg)	• Already taking Phenytoin, suspected poor adherence • Alternatives contra-indicated or previously ineffective	• Significant hypotension • Bradycardia, Heart block • Porphyria • Generalized epilepsy • Overdose of recreational drugs or antidepressants
Valproate	**40mg/kg;** 10mg/kg/min (3000mg)	• Already taking Valproate, suspected poor adherence • Generalized epilepsy • Comorbid migraine, mood disorder • Alternatives contra-indicated or previously Ineffective	• Women of childbearing age[1] • Pre-existing liver disease or pancreatitis • Known metabolic disorder predisposing to hepatotoxicity • Caution in acute stroke (risk of thrombocytopenia)
Levetiracetam	**60mg/kg**; 6mg/kg/min (4500mg)	• Already taking Levetiracetam, suspected poor adherence • Need for minimal drug interactions • Alternatives contra-indicated or previously ineffective	May not be best choice in: • acute or prior brain injury • known mood/behaviour disorder (may exacerbate) • Reduce dose in renal impairment

[1]Relative contraindication.

CSE: Stop the seizures

- Premonitory & Initial SE (Inc out of hospital)
  - –**Benzodiazepines** (**10mg** Buc MDZ, **4mg** iv LZP)
  - –Max X 2 doses (including prehospital)
- Established SE
  - – **Phenytoin** (Fos-Phenytoin) **20mg/kg**
  - – **Valproate 40mg/kg**
  - – **Levetiracetam 60mg/kg**
- Refractory SE
  - –Anaesthesia/ ITU management

5-20 minutes

20-40 minutes

40-60 minutes

Glauser, Epilepsy Curents 2016 AES guidelines

Speed & Adequacy of Treatment more important than choice of drug

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- **Other types of SE**

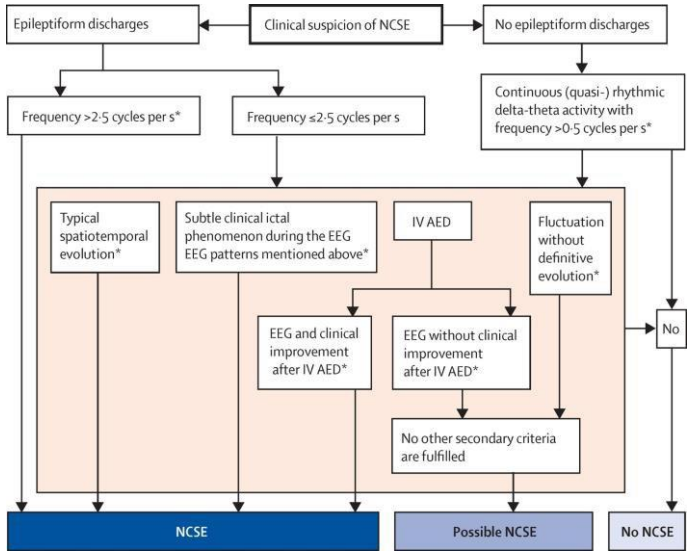
Other types of SE

- In IGE (Absence/Myoclonic SE)
  - Should be Treated, with EEG if possible.
  - Oral BZD (community) or iv Lorazepam + Valproate (or Levetiracetam)
- De Novo Absence SE later life
  - 1mg LZP with resus equipment
- Focal SE (including non-convulsive)
  - Diagnosis sometimes challenging
  - ALL cases →neurologist, clinical & EEG confirmation
  - Serial iv AEDs, try to avoid ICU in most
  - Phenobarbitone 15mg/kg iv

Hocker, Epilepsia 2018

Non-convulsive SE

- Electro-clinical diagnosis, often difficult
  - EEG (Salzburg criteria) and clinical (neurology) review



MUST have
- video
- full electode array

ICU Esp. Challenging

SCORE software
https://www.holbergeeg.com

Beniczky, Epilepsia 2013
Leitinger, Lancet Neurol 2016

Non Convulsive SE

- Management individualised
- Key Questions
  - Comatose?
  - Known Epilepsy?
  - Good general state?

van Rijckevorsel, Acta Neurol Belg 2006

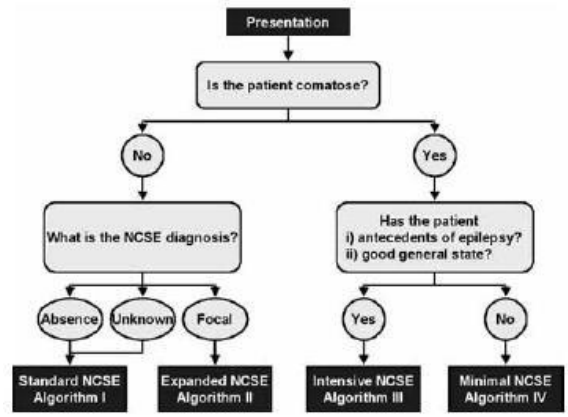


FIG. 1. — Choosing the appropriate treatment algorithm for non-convulsive status epilepticus.

- Initial Benzo for all
- Expert (neurology) clinical review & EEG Monitoring
- Serial iv AEDs, try to avoid ICU unless Y to all above
  - Phenobarbitone 15mg/kg iv
  - Drug resistant epileptic encephalopathies, ? time limited trial

Hocker, Epilepsia 2018

Conclusions

- Be as sure as you can that it is Status Epilepticus
- Ensure timely adequate initial benzodiazepines
- For established CSE, recent trials support
  - –Levetiracetam 60mg/kg or Valproate 40mg/kg

  may

  be preferable to Phenytoin 20mg/kg
- Speed and adequacy of treatment early on (<1-2h) key
  - –Widely available and accepted guidelines
  - –v. variable service provision & implementation

8th London-Innsbruck
SE Colloquim
April 2021
www.statusepilepticus.eu

THANKYOU

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