



Status epilepticus in sub-Saharan Africa: some new findings

Charles RJC Newton

Centre for Geographical Medicine (Coast), Kenya Medical Research Institute, Kilifi, Kenya Muhimbili University of Health and Allied Sciences, Dar-es-Salaam, Tanzania Institute of Child Health, University College London, UK Department of Psychiatry, University of Oxford, UK







Problems with Definition

- International League against Epilepsy
 - A seizure or series of seizures that last for 30 minutes or more without regaining consciousness between the seizures
- But in Resource Poor Countries
 - Duration is rarely documented
 - Most patients arrive in convulsing at health facility without any adequate documentation of duration

Definitions of Status Epilepticus

- Confirmed (ILAE Definition)
 - any seizure lasting for 30 minutes or longer,
 - 3 or more intermittent seizures from which the patient does not regain consciousness between the seizures

Probable

- Convulsing on arrival to hospital
- Unconscious on arrival with
 - <u>definite</u> Hx of >1 prolonged seizure lasting > 30 mins
 - >10 convulsions in previous 24hrs
- Use of phenobarbital or phenytoin to stop seizures

New ILAE Definition

- A new conceptual definition of status epilepticus with two operational dimensions (t1 and t2) is proposed
- Time point t1 indicates when treatment should be initiated
- Time point t2 indicates when long-term consequences may appear

SPECIAL REPORT

A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus

*†‡Eugen Trinka, §Hannah Cock, ¶Dale Hesdorffer, #Andrea O. Rossetti, **Ingrid E. Scheffer, ††Shlomo Shinnar, ‡‡Simon Shorvon, and §§Daniel H. Lowenstein

Epilepsia, **(*):1-9, 2015 doi: 10.1111/epi.13121

SUMMARY



Eugen Trinka is professor and chairman of Department of Neurology, Paracelsus Medical University Salzburg Austria.

The Commission on Classification and Terminology and the Commission on Epidemiology of the International League Against Epilepsy (ILAE) have charged a Task Force to revise concepts, definition, and classification of status epilepticus (SE). The proposed new definition of SE is as follows: Status epilepticus 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 t.). It is a condition, which can have long-term consequences (after time point t_2), including neuronal death, neuronal injury, and alteration o euronal networks, depending on the type and duration of seizures. This definition is concep tual, with two operational dimensions: the first is the length of the seizure and the time point (t₁) beyond which the seizure should be regarded as "continuous seizure activity." The second time point (t2) is the time of ongoing seizure activity after which there is a risk of long-term consequences. In the case of convulsive (tonic-clonic) SE, both time points (t₁ at 5 min and t2 at 30 min) are based on animal experiments and clinical research. This evidence is incomplete, and there is furthermore considerable variation, so these time points should be considered as the best estimates currently available. Data are not yet available for other forms of SE, but as knowledge and understanding increase, time points can be defined for specific forms of SE based on scientific evidence and incorporated into the definition, without changing the underlying concepts. A new diagnostic classification system of SE is proposed, which will provide a framework for clinical diagnosis, investigation, and therapeutic approaches for each patient. There are four axes: (1) semiology; (2) etiology; (3) electroencephalography (EEG) correlates; and (4) age. Axis I (semiology) lists different forms of SE divided into those with prominent motor systems, those without prominent motor systems, and currently indeterminate conditions (such as acute confusional states with epileptiform EEG patterns). Axis 2 (etiology) is divided into subcategories of known and unknown causes. Axis 3 (EEG correlates) adopts the latest recommendations by consensus panels to use the following descriptors for the EEG: name of pattern, morphology, location, time-related features, modulation, and effect of intervention. Finally, axis 4 divides age groups into neonatal, infancy, childhood, adolescent and adulthood, and elderly. KEY WORDS: Status epilepticus, Seizure, Definition, Classification, Seizure duration.

Table 1. Operational dimensions with t_1 indicating the time that emergency treatment of SE should be started and indicating the time at which long-term consequences may be expected					
Operational dimension I Time (t _I), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t ₂), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)				
5 min 10 min	30 min >60 min Unknown				
	Operational dimension I Time (t ₁), when a seizure is likely to be prolonged leading to continuous seizure activity 5 min				

Classification of Status Epilepticus

Four Axis

- Semiology
 - Motor (convulsive)
 - No motor manifestations
- Aetiology
- EEG correlates
- Age

Table 2. Axis I: Classification of status epilepticus (SE)

(A) With prominent motor symptoms

A.I Convulsive SE (CSE, synonym: tonic-clonic SE)

A. I.a. Generalized convulsive

A. I.b. Focal onset evolving into bilateral convulsive SE

A. I.c. Unknown whether focal or generalized

A.2 Myoclonic SE (prominent epileptic myoclonic jerks)

A.2.a. With coma

A.2.b. Without coma

A.3 Focal motor

A.3.a. Repeated focal motor seizures (Jacksonian)

A.3.b. Epilepsia partialis continua (EPC)

A.3.c. Adversive status

A.3.d. Oculoclonic status

A.3.e. Ictal paresis (i.e., focal inhibitory SE)

A.4 Tonic status

A.5 Hyperkinetic SE

(B) Without prominent motor symptoms (i.e., nonconvulsive SE, NCSE)

B. I NCSE with coma (including so-called "subtle" SE)

B.2 NCSE without coma

B.2.a. Generalized

B.2.a.a Typical absence status

B.2.a.b Atypical absence status

B.2.a.c Myoclonic absence status

B.2.b. Focal

B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/ psychic/experiential, or auditory symptoms)

B.2.b.b Aphasic status

B.2.b.c With impaired consciousness

B.2.c Unknown whether focal or generalized

B.2.c.a Autonomic SE

Axis 2: Aetiology

- Acute
- 2. Remote
- 3. Progressive
- 4. Defined electroclinical syndrome
- 5. Unknown

Axis 3: Electroencephalographic correlates

- Location: generalized (including bilateral synchronous patterns), lateralized, bilateral independent, multifocal
- 2. Name of the pattern: Periodic discharges, rhythmic delta activity or spike-and-wave/sharp-and-wave plus subtypes
- 3. Morphology: sharpness, number of phases (e.g., triphasic morphology), absolute and relative amplitude, polarity
- 4. Time-related features: prevalence, frequency, duration, daily pattern duration and index, onset (sudden vs. gradual), and dynamics (evolving, fluctuating, or static)
- 5. Modulation: stimulus-induced vs. spontaneous.
- 6. Effect of intervention (medication) on EEG

Axis 4: Age

- 1. Neonatal (0 to 30 days).
- 1. Infancy (1 month to 2 years)
- 2. Childhood (> 2 to 12 years)
- 3. Adolescence and adulthood (> 12 to 59 years)
- 4. Elderly (≥ 60 years)

Table 4. Etiology of status epilepticus

Known (i.e., symptomatic)

Acute (e.g., stroke, intoxication, malaria, encephalitis, etc.)

Remote (e.g., posttraumatic, postencephalitic, poststroke, etc.)

Progressive (e.g., brain tumor, Lafora's disease and other PMEs, dementias)

SE in defined electroclinical syndromes

Unknown (i.e., cryptogenic)

Table 5. SE in selected electroclinical syndromes according to age

SE occurring in neonatal and infantile-onset epilepsy syndromes Tonic status (e.g., in Ohtahara syndrome or West syndrome)

Myoclonic status in Dravet syndrome

Focal status

Febrile SE

I-3)

SE occurring mainly in childhood and adolescence

Autonomic SE in early-onset benign childhood occipital epilepsy (Panayiotopoulos syndrome)

NCSE in specific childhood epilepsy syndromes and etiologies (e.g., Ring chromosome 20 and other karyotype abnormalities, Angelman syndrome, epilepsy with myoclonic-atonic seizures, other childhood myoclonic encephalopathies; see Appendices

Tonic status in Lennox-Gastaut syndrome

Myoclonic status in progressive myoclonus epilepsies

Electrical status epilepticus in slow wave sleep (ESES)

Aphasic status in Landau-Kleffner syndrome

SE occurring mainly in adolescence and adulthood

Myoclonic status in juvenile myoclonic epilepsy

Absence status in juvenile absence epilepsy

Myoclonic status in Down syndrome

SE occurring mainly in the elderly

Myoclonic status in Alzheimer's disease

Nonconvulsive status epilepticus in Creutzfeldt-Jakob disease

De novo (or relapsing) absence status of later life

These forms of SE may be encountered prevalently in some age groups, but not exclusively.

Status Epilepticus in Africa

- Burden
 - Minimum Incidence in Kenyan children:
 - Confirmed: 35 (28-46)/100,000/yr
 - All: 108 (93-105)/100,000/yr

Sadarangani el al Lancet Neurology 2008; 7: 145

- 2-5 times that of London
- Lack of facilities of care
- Lack of drugs available to treat Status epilepticus

Aetiology Status Epilepticus in children

Study	Number	umber Prolonged Febrile	Symptomatic		Idiopathic or	Unclass	
		seizure	Acute	Acute on Remote	Remote	cryptogenic	
Tunisia	139	41%	40%	7%	8%	8%	-
Kenya	388	30%	5	51%	7%	7%	9%
London	176	32%	17%	16%	16%	12%	7%

Cause of Convulsive Status Epilepticus in Kilifi

- Malaria 57%
- Acute Bacterial Meningitis 9%
- Febrile seizures not malaria 4%
- Undiagnosed encephalopathy 10%
- Epilepsy 6%
- Undetermined 15%

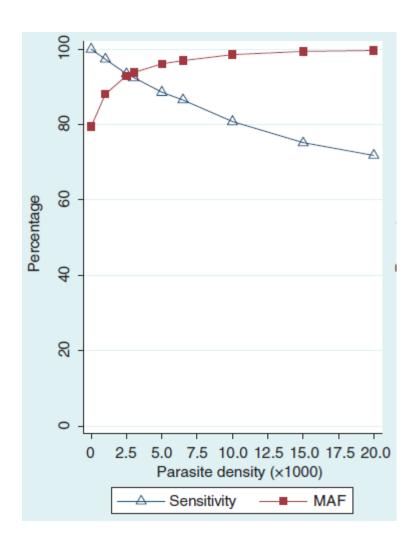
Malaria Attributable Seizures in children admitted to Kilifi District Hospital

 Used a logistic regression model to calculate the Malaria Attributable Fraction (MAF) for convulsive status epilepticus

0.92 (95% CI 0.91—0.93)

Parasitaemia > 2500 parasites/μl





Reduction in Malaria

- Reduction in the incidence of malaria from 2003 – 2008:
- malaria-attributable seizures: declined from 821 to 101 per 100,000/year (88% decrease)
- non-malaria-attributable seizures: 300 to 280 per 100,000/year (6% decrease)

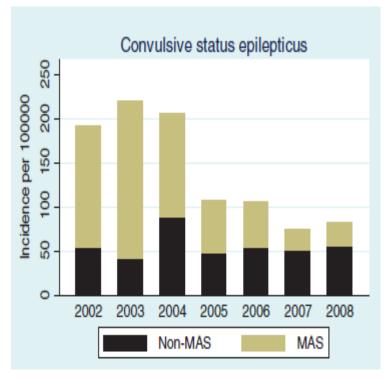


Table 3 The malaria-attributable fractions for seizures, the predicted and the observed decrease in the incidence of seizures and the proportion of the observed decrease that occurred in malaria-associated seizures

Type of seizures	Adjusted malaria- attributable fractions for seizures (95% CI)	Predicted decline in seizures using malaria-attributable fractions/100000/year	Observed decrease in seizures/100 000/year (percentage decrease)	Proportion of the observed decrease that occurred in MAS
All acute symptomatic seizures	92.9% (90.4-95.1%)	794	809 (69.2%)	753/100 000/year (93.1%)
Convulsive status epilepticus	92.9% (89.4-95.5%)	129	111 (57.2%)	111/100 000/year (100%)
Repetitive seizures	93.6% (90.9-95.9%)	404	440 (73.7%)	382/100 000/year (86.8%)
Focal seizures	91.8% (85.6–95.4%)	125	153 (80.5%)	129/100 000/year (84.3%)

Polymorphisms and Malaria Associated Seizures (MAS)

- Polymorphisms with a good fidelity were selected from a list of those genotyped for the malariaGEN consortium
- A logistic regression was used to investigate genetic associations with malariaassociated seizures (MAS) and complex MAS (repetitive, prolonged or focal)
- Samples came from 4 sites:
 - Blantyre, Malawi
 - Kilifi, Kenya
 - Kumasi, Ghana
 - Muheza, Tanzania
- analysis was repeated for four inheritance models (dominant, heterozygous, recessive and additive) adjusting for ethnicity, age, hyperparasitaemia and febrile temperatures to ensure true genotypic effects

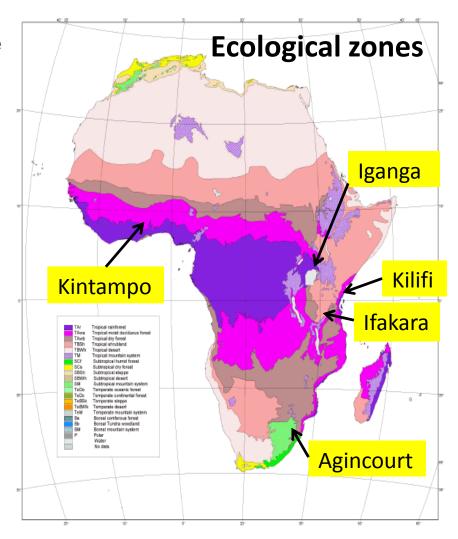
Kariuki et al *Epilepsia* 2013 in press

Polymorphisms associated with prolonged seizures

Site	Blantyre, Malawi	Kilifi, Kenya	Kumasi, Ghana	Muheza, Tanzania	All
Cases:Controls	770:620	900:1148	250:250	175:359	2095:2377
Epidermal growth factor mucin-like hormone receptor (EMRI) 373533	2.32 (0.57-9.42)	1.44 (1.05-1.99)	0.41 (0.23-0.74)	0.19 (0.04-0.95)	
EMRI rs461645	2.61 (0.66-10.33)	1.50 (1.09-2.07)	0.40 (0.28-0.70)	2.88 (0.54-18.36)	
Complement Receptor (CR)-1 rs17047660	0.39 (0.10-1.62)	3.92 (1.71-8.99)	1.51 (0.52-4.42)	3.15 (0.54-18.36)	2.56 (1.41-4.67)
Interleukin (IL)- 17RE rs708567	1.24 (0.49-3.12)	0.55 (0.35-0.86)	1.30 (0.74-2.32)	2.66 (0.59-12.01)	

Studies of Epidemiology of Epilepsy in Demographic Sites (SEEDS)

- Choose to conduct the studies in Health and Demographic Surveillance Systems (INDEPTH):
 - accurate denominators
 - able to identify subjects for follow-up
 - able to measure mortality
- Conducted cross-sectional surveys to detect Active Convulsive Epilepsy (ACE)
 - Most reliably detected
 - Associated with most:
 - Stigma
 - Morbidity e.g. burns
 - Mortality



Ngugi et al Lancet Neurology 2013

Definition of status epilepticus

Definition 1	Seizure lasting 30 or more minutes time by a watch
Definition 2	History of having convulsed all the way to the hospital for a distance of more than a Kilometer
Definition 3	Seizures lasting more than the period of boiling a pot of maize (which takes about 30 minutes)
Definition 4	Seizures lasting more than the news broadcast on radio (which last about 30 minutes)
Definition 5	Seizures lasting more than milking a cow (a process which takes about 30 minutes)

Kariuki et al Neurology 2015

Prevalence of Status Epilepticus

	Agincourt, South Africa	Iganga, Uganda	Kilifi, Kenya
Total population	82,795	64,143	232,176
Number with ACE	245	152	699
Number with SE	181	90	255
Percentage	73.9%	59.2%	36.4%
Prevalence per 1,000 adjusted for sensitivity of survey method	5.293	4.416	2.659

Risk factors of Status Epilepticus in ACE

Risk factor	Agincourt, South Africa	lganga, Uganda	Kilifi, Kenya
SE: non-SE	181: 150	90: 151	254: 512
History of febrile seizures	2.59 (0.27-25.37)	2.60 (1.31-5.17)	0.66 (0.40-1.08)
Acute encephalopathy	0.48 (0.08-2.94)	-	174.99 (62.78-487.80)
Previous hospitalisation	0.77 (0.45-1.32)	1.31 (0.53-3.24)	0.46 (0.33-0.65)
Neurological deficits difficulties	1.88 (1.00-3.52)	1.43 (0.67-3.07)	2.42 (1.62-3.62)
Learning difficulties	1.66 (0.94-2.97)	1.44 (0.67-3.08)	2.62 (1.80-3.81)
Visits traditional healers	1.21 (0.69-2.09)	0.99 (0.50-1.77)	1.75 (1.21-2.55)
Malaria schizont antibodies	1.08 (0.57-2.04)	-	2.92 (1.45-5.87)

are adjusted for age, sex, education and marital status.

SE in Kilifi community

- 832 People with Epilepsy were admitted to Kilifi District Hospital from 2003-2011
 - Status epilepticus reported in
 - 216 (37%) children
 - 127 (51%) adults
- 97/249 (39%) of people with ACE detected in the 2008 survey reported that were admitted to Kilifi District Hospital with Status Epilepticus
 - 30% with malaria
 - 19% with epilepsy
 - 15% febrile seizures
 - 9% burns

Long-term Outcome of children admitted with Status Epilepticus

- 124 children who had been admitted to Kilifi District Hospital were followed up 3-7 years after admission
- 10 died
 - Verbal autopsy:
 - 8 had seizures during the agonal phase (? Status) None were taking anti-epileptic drugs

Prins et al. Epilepsy Research & Treatment 2014

Neurological Deficits

TABLE 3: Neurological deficits on assessment.

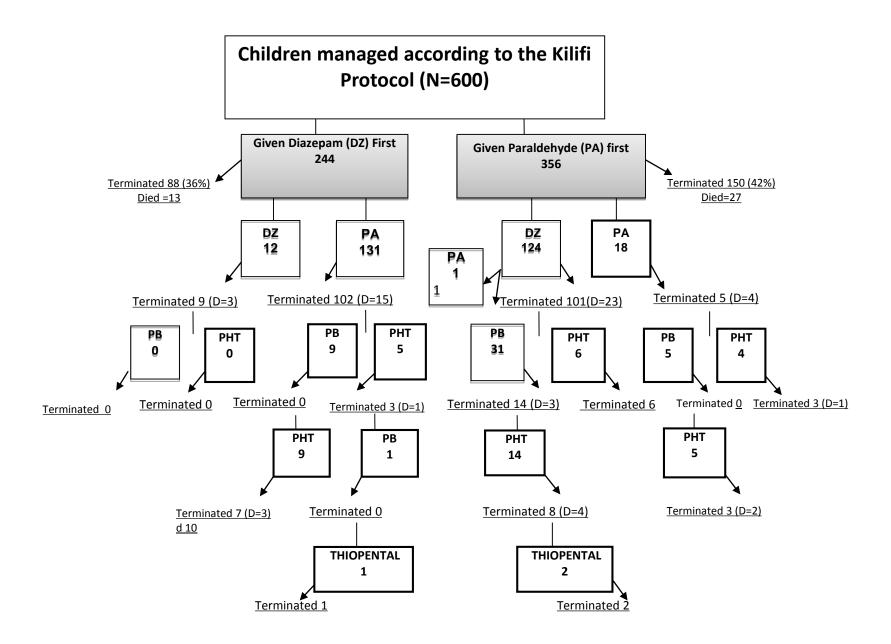
Neurological deficits on assessment	Cases $N = 33$	Controls $N = 10$	P value st
Total screened with TQQ	N = 110	N = 282	
Any neurological deficit, no. (% of total screened with TQQ)	15 (13.6%)	1 (0.4%)	<0.001
Speech impairment	11 (10.0%)	0	< 0.001
Motor impairment	11 (10.0%)	0	< 0.001
Vision impairment	3 (2.7%)	0	0.022
Hearing impairment	1 (0.9%)	0	0.281
Cognitive impairment	1 (0.9%)	1 (0.4%)	0.483
Epilepsy	16 (14.5%)	1 (0.4%)	< 0.001

^{*} Differences between cases and controls with Fisher's exact test.

Treatment and Prevention of Status epilepticus

Protocols for treating acute seizures

Child ha	Child has seizures for >5 mins or 3 seizures lasting <5 mins within 1 hour					
	World Health Organization (WHO) guidelines	Kilifi District Hospital guideline				
1 st line	Rectal Diazepam (0.1ml/kg)	If IV access, Diazepam (0.3 mg/kg)				
	or Paraldehyde (0.4ml/kg PR)	or Paraldehyde (0.4 ml/kg IM)				
	(<i>after 10 mins</i> repeat dose of Diazepam	(If no IV access, rectal (PR) diazepam (0.3				
	(0.25mg/kg PR)	mg/kg)or Paraldehyde (0.4 ml/kg PR))				
	(after 20 mins repeat dose of Diazepam(0.25mg/kg	(either can be given again as a repeat dose				
	PR) or paraldehyde (0.4ml/kg PR))	after 10 mins)				
2 nd line	Or (<i>after 20 mins</i>) Phenobarbital (15 mg/kg IV/IM)	(after 20 mins)				
	Phenobarbital 20mg/kg (0.25mg/kg) in	Phenobarbital (15-18mg/ kg IV) or				
	infants<2wks repeat to half this dose (after 30	Phenytoin (18 mg/kg IV)				
	mins)	(second dose after 30 mins)				
3 rd line		(45-60 min s) Thiopental 4mg/kg then				
		5mg/kg IV infusion over 2hrs with ECG				



Factors associated with the termination of seizures within 15 minutes

	univar	riate analys	sis	multivaria	te analysis
	Total numbers	Odds	95% Conf.	Adjusted	95% Conf.
	(% terminated in	Ratio	interval	Odds Ratio	interval
	15 mins)				
Followed WHO protocol	327 (65.9)	0.44	0.29-0.64	0.52	0.34-0.78
Male	270 (54.4)	1.05	0.75-1.42	1.10	0.78-1.54
Age: < 1 year†	114 (22.9)				
1 - 5 years	323 (65.1)	1.54	1.08-2.21	1.58	1.13-2.53
5-13 years	59 (11.8)	1.65	0.91-2.98	1.27	0.74-2.56
>5 seizures	361 (72.8)	2.23	1.60-3.10	1.89	1.34-2.69
Type of seizure					
generalised†	306 (61.7)				
partial seizures	161 (32.5)	0.76	0.54-1.07	0.78	0.54-1.10
partial-generalised	21 (4.2)	0.69	0.33-1.46	0.64	0.32-1.49
Underlying Condition					
Malaria	244 (49.2)	0.74	0.53-1.01	0.69	0.45-0.99
Meningitis	51 (10.3)	1.16	0.67-199	1.00	0.56-1.79
Encephalopathy	35 (7.1)	1.04	0.55-1.96	0.78	0.37-1.54

Prophylaxis Phenobarbital

- Randomised control trial in Kenyan Children with Cerebral Malaria
- Phenobarbital 20mg IM stat

Crawley et al Lancet 2001; 355:701-6

Seizures	Placebo (n=170)	Phenobarbital (n=170)	
No. lasting > 5 mins	25%	12%	0.42 (0.24-0.76)
Status epilepticus	14%	5%	0.38 (0.17-0.85)
Death	8%	18%	2.49 (1.19-5.23)

Fosphenytoin trial in Kenyan children admitted with an acute encephalopathy to prevent acute seizures and status epilepticus

- Double blind placebo (Normal saline) control randomised trial
- Acute encephalopathy, defined as:
 - unable to localise a painful stimulus for > 4 hours in children > 9 months old
- Given intramuscular injection either
 - Fosphenytoin: 20 Phenytoin Equivalents /Kg
 - Normal Saline: Equivalent amount of fluid for body weight
- Children unventilated
- Clinical seizures recorded by nurses
- 50% of patients had continuous EEG monitoring 72 hours after administration of Fosphenytoin or placebo

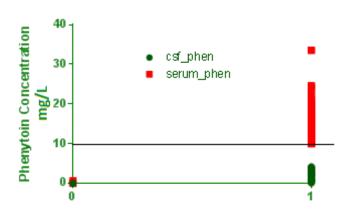
Outcomes

- Primary
 - Reduction in seizures lasting > 5minutes
 - Reduction in status epilepticus (seizure > 30 min)
- Secondary
 - Reduction in the number of seizures
 - Clinical
 - Electrographic
 - Reduction in cognitive impairment as measured by event related potentials

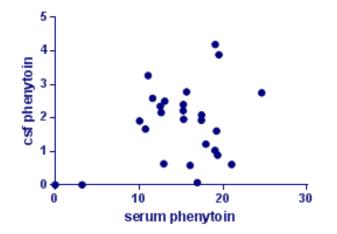
Clinical Characteristics on admission

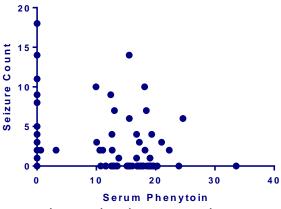
	Fosphenytoin	Placebo
	N= 85	N= 88
Age (Median) years	2.6 (IQR 1.7,3.7)	2.6 (IQR 1.8, 3.5)
Sex		
Male	52	49
Female	33	39
History of Seizures on admission	76	77
Duration of unconsciousness at admission	4 (IQR 2,8)	3 (IQR 2,6)
(Median) hours		
Coma Status; Blantyre Coma Score		
0	16	15
1	30	41
2	39	32
Received 1st line AED prior to study drug	31	35
Received 2 nd line AED prior to study drug	6	8
Diagnosis		
Cerebral Malaria	54	56
Unknown Encephalopathy	27	28
Acute Bacterial Meningitis	4	4

Phenytoin levels

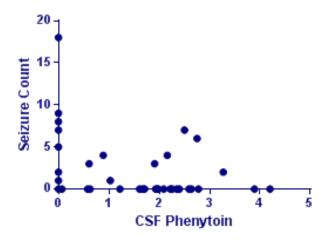


Placebo Fosphenytoin





Relationship between Phenytoin and seizures after administration



Outcome of trail

	Fosphenytoin	Placebo	OR (95% CI)	P-value
	(n=85)	(n=88)		
Number of clinical seizures	33 (38%)	32 (36%)	0.90 (0.48,1.67)	0.73
Number of clinical seizures ≥ 5 mins	17 (20%)	22 (25%)	1.33 (0.65,2.75)	0.43
Number of clinical seizures ≥ 5 mins	11 (13%)	10 (11%)	1.86 (0.82,4.22)	0.13
within 24hrs				
Number of clinical seizures ≥ 30 mins	4 (5%)	5 (6%)	1.23 (0.32,4.79)	0.77
Number of electrographic seizures	6	10	-	0.418
	(7%; n=21)	(4%; n=25)		
Received AED after admin. of study	35 (41%)	33 (38%)	0.86 (0.46,1.58)	0.62
drug				
Received 1st line AED within 24 hrs	20 (24%)	23 (26%)	1.15 (0.57,2.30)	0.69
Received 2 nd line AED within 24 hrs	19 (22%)	16 (18%)	0.77 (0.37,1.63)	0.50

Outcome of trial

	Fosphenytoin (n=85)	Placebo (n=88)	P-value
Outcome at Discharge			
Died	18 (21%)	15 (17%)	0.489
Sequelae	9 (13%; n = 67)	14 (19%; n=73)	0.359†
Time to localize pain (hrs)*	18 (8,28)	14 (6,33)	0.378†
Time to regain full consciousness (hrs)*	21.5(15.5,32.5)	24 (10,48)	0.875
Outcome at 3 months after Discharge			
Lost to follow-up/Withdrew/Not Followed	7 (12%)	11 (18%)	0.415
Neurological deficits	6 (10%)	6 (10%)	0.952

Conclusions

- Status epilepticus very common in Africa
- Difficulties in definition
- Malaria is an important cause
- Genetic polymorphisms in malaria associated seizures to be associated with malaria
- Most not admitted to hospitals
- Appear to resistant to standard anti-epileptic drugs

Acknowledgements

Kilifi, Kenya Institute of Child Health, London, UK

Symon Kariuki Brian Neville

Anthony Ngugi Fenella Kirkham

Bernards Ogutu Helen Cross

Eddie Chengo

Michelle Ikumi Institute of Neurology, London, UK

Richard Idro Ley Sander

Samson Gwer

London School of Tropical Medicine and

Studies of Epidemiology of Epilepsy Hygiene, UK

Albert Akapalu Christian Bottomley

Angelina Kakooza Immo Kleinschmidt

Honrati Masanja
University of Amsterdam

Ryan Wagner Agnes Prins

Kenya Medical Research Institute/Wellcome Trust Supported Collaborative Programme