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Seizures and Status Epilepticus

Lindsey Morgan

April 30, 2019

A 10 month old presents with focal right arm shaking that is non-suppressible. Parents note it has been occurring for the last 3 hours, and he has been quite irritable and will not feed. His vitals on presentation are: 37.6, 145, 76/58, 96% on RA. You notice rhythmic tonic-clonic movements of the right arm, as well as subtle right face rhythmic synchronous twitching. While asking the nurse to draw up IN midazolam for you, what is the test you want to order STAT to help determine seizure etiology?

a. CBC with differential
b. EEG
c. Electrolytes
d. Head CT
e. Lumbar puncture

Objectives

- Review epidemiology and outcomes of pediatric status epilepticus
- Discuss treatments for status epilepticus
- Discuss rationale for EEG and cEEG in high risk patients
- Review existing pathways and their use in the PICU
- Discuss outcomes and become familiar with SUDEP

Epidemiology - Epilepsy

- Worldwide, about 50 million people have epilepsy
- The average incidence of epilepsy each year in the U.S ~150,000 or 48 for every 100,000 people
- Prevalence in US: 5-11.5/1,000
- In 2015: 1.2% US population had active epilepsy (3.4 million)
  - Alaska: 7,200 (1,100 children, 6,100 adults)
- 1 in 26-70 people will develop epilepsy in their lifetime

CDC Epilepsy Data and Statistics

Provoked seizures are not epilepsy

- Small risk of a seizure in the absence of precipitating factor

- Febrile seizures (ages 6mo – 6 years)
- Alcohol-withdrawal seizures
- Metabolic seizures (sodium, calcium, magnesium, glucose, oxygen)
- Toxic seizures (drug reactions or withdrawal, renal failure)
- Convulsive syncope
- Acute concussive convulsion
- Seizures within first week after brain trauma, infection or stroke

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Epidemiology – Seizures/Status

- Seizures: ~2% of all visits to children's hospital ED
  - ~3.1 million pediatric ED visits/year for seizures. 6-7% of these have SE
  - Incidence of SE 10.3-41/100,000
- Pediatric refractory SE (RSE): 10-25% of patients w acute seizures; 4% of all admissions to PICU
  - RSE higher in acute symptomatic vs unprovoked seizure
- Status Epilepticus
  - Mortality rate associated with seizures lasting >30 minutes as high as 19%
  - Short and long term neurologic morbidities: including recurrent SE, cognitive deficits, neurodevelopmental delays

Tasker RC, Wainwright MS et al. 2016; Chen JWY et al. 2006; Fernandez I, et al. 2014; Brophy GM, et al. 2012; DeLorenzo et al. 1996; Chin RFM et al 2006.

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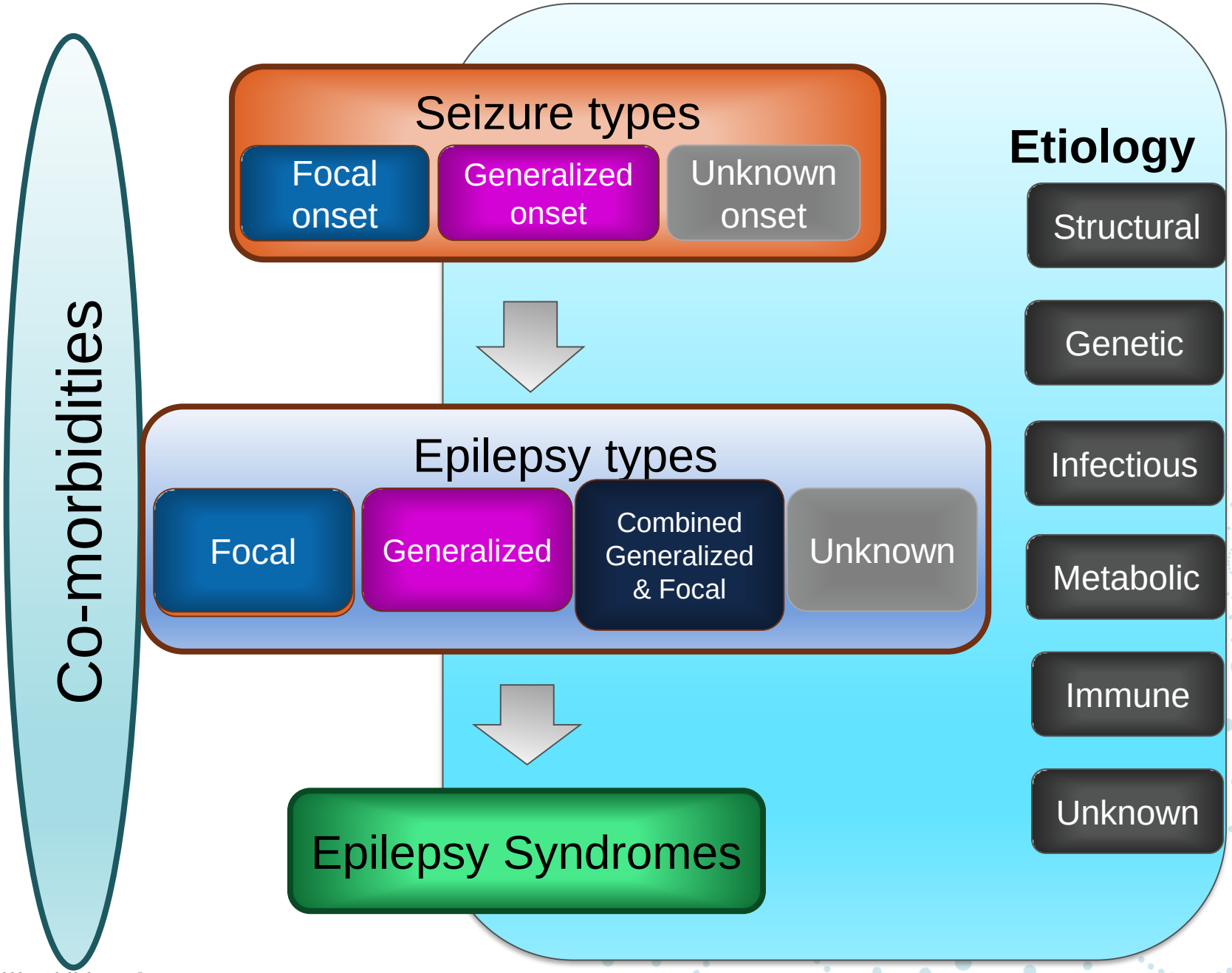
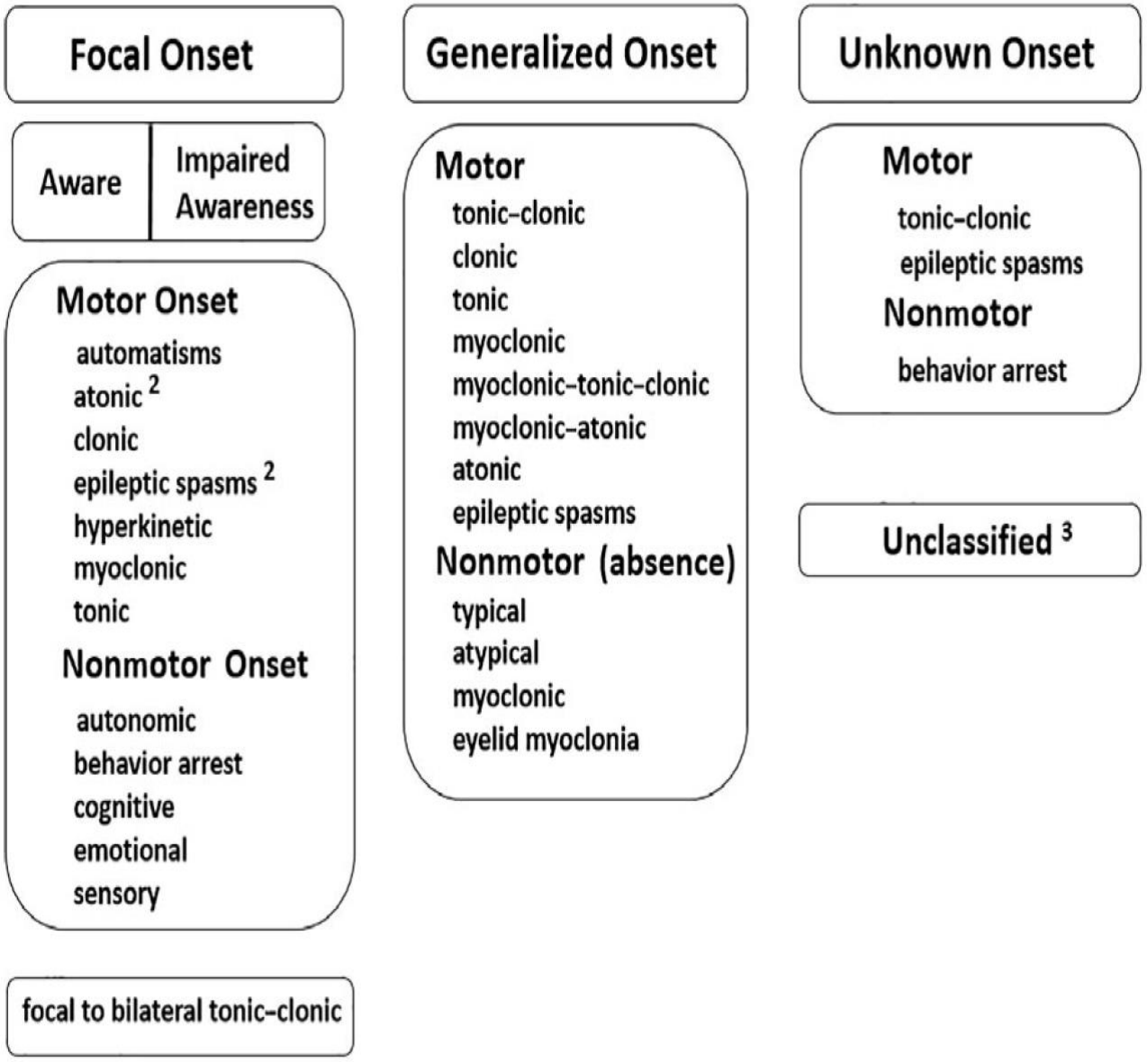
Seizure Types and Definitions

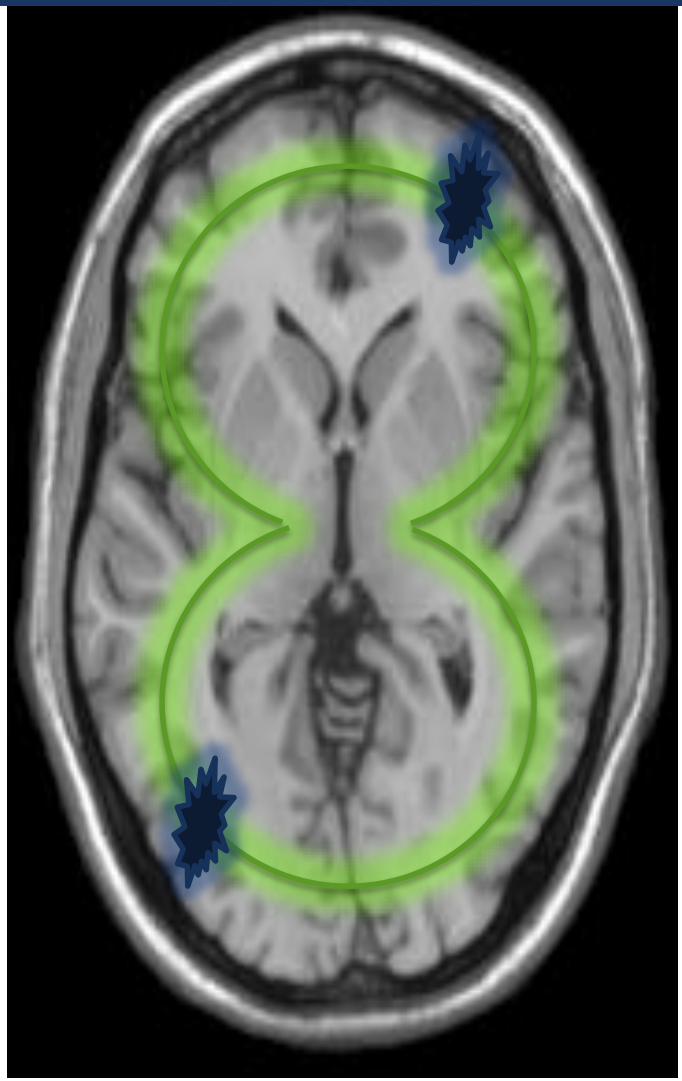

Co-morbidities
Seizure types
Focal onset
Generalized onset
Unknown onset
Epilepsy types
Focal
Generalized
Combined Generalized & Focal
Unknown
Epilepsy Syndromes
Etiology
Structural
Genetic
Infectious
Metabolic
Immune
Unknown

ILAE 2017 Classification of Seizure Types Expanded Version [1]



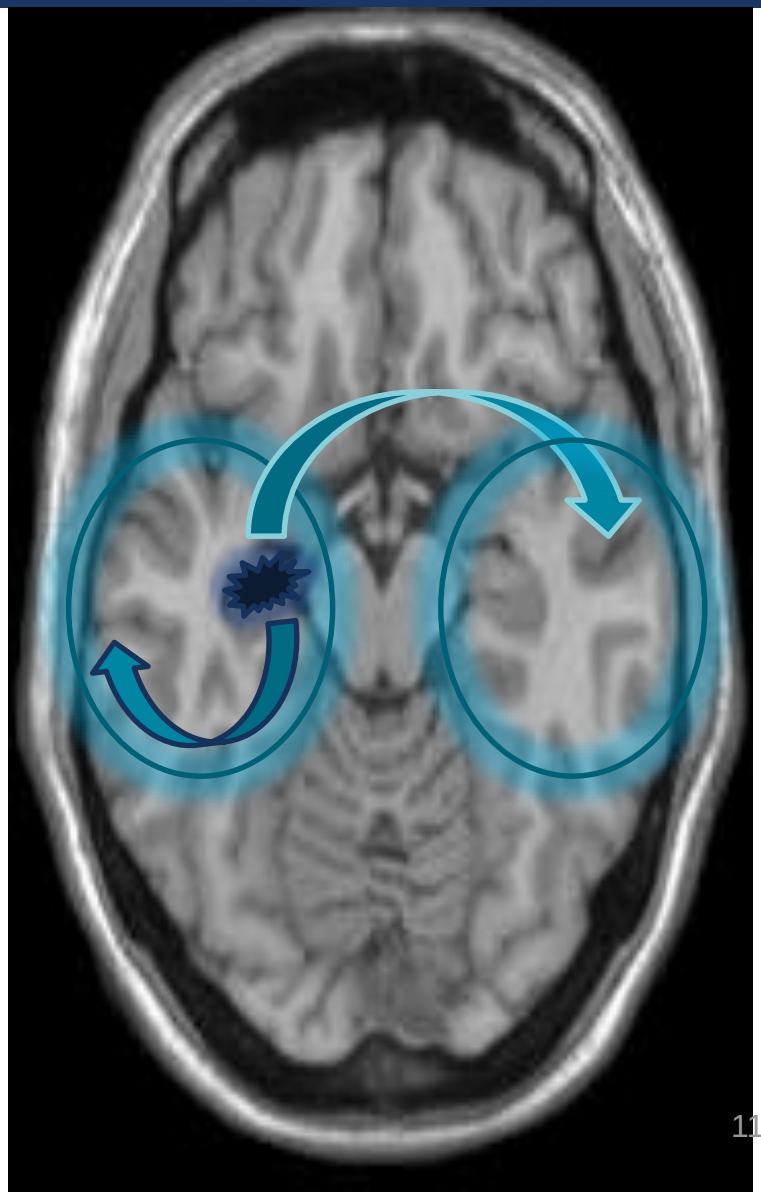
Generalized Seizure

- Originate at some point within and rapidly engage bilaterally distributed networks
- Can include cortical and subcortical structures but not necessarily the entire cortex



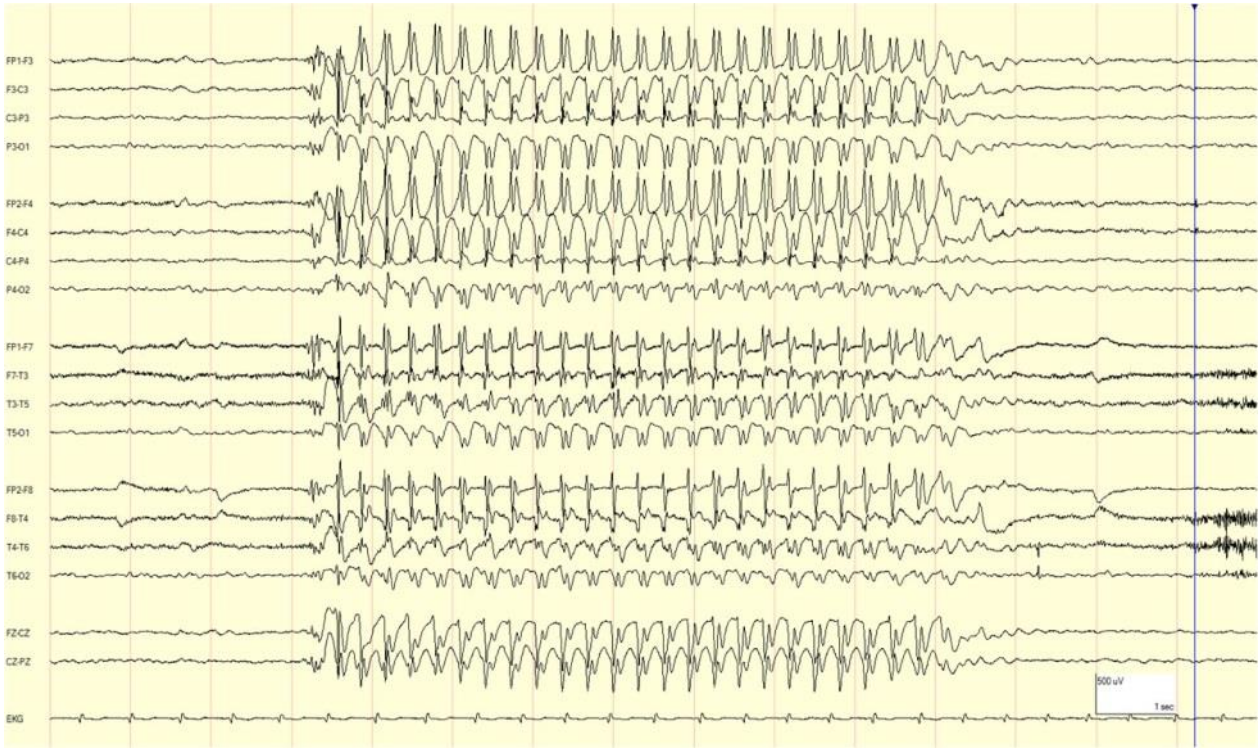
Focal Seizure

- Originate within networks limited to one hemisphere
- May be discretely localized or more widely distributed….



Further Seizure Definitions

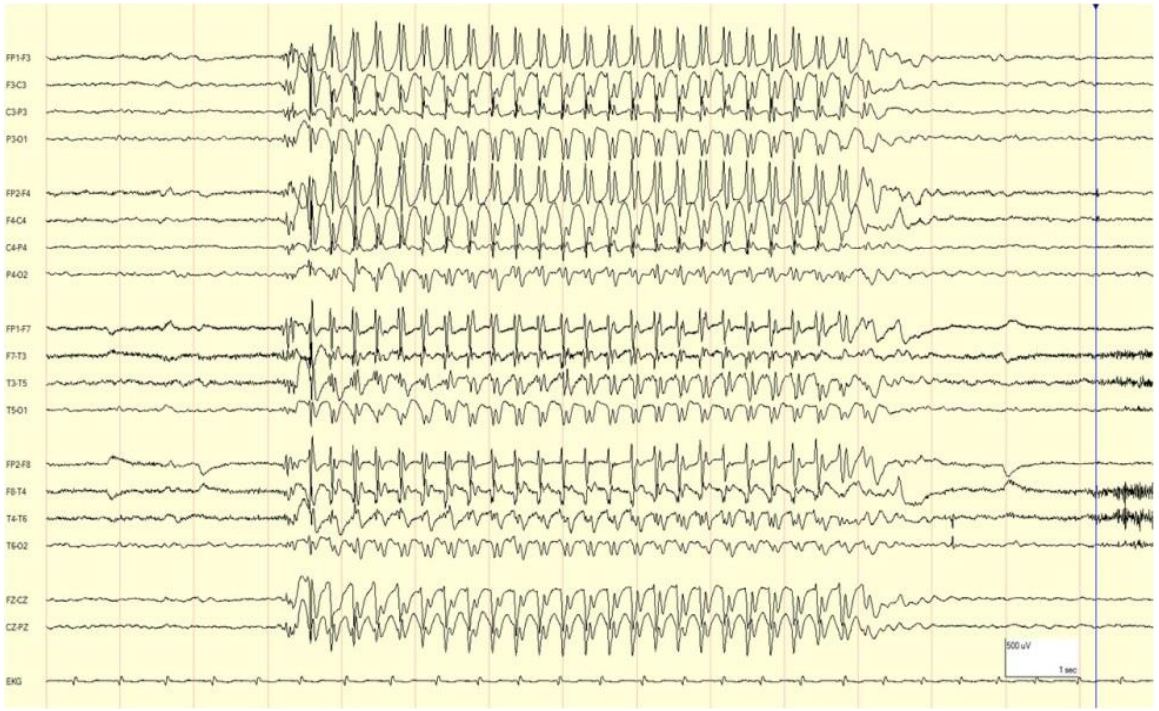
- Seizure
- Status Epilepticus (SE)
  - Tonic-clonic (>5 min)
  - Focal SE with impaired consciousness (>10 min)
  - Absence SE (>10-15 min)



Trinka E, et al. Epilepsia, 2015

Seizure Definitions

- Refractory Status Epilepticus (RSE)
- Subclinical seizure/ Electrographic seizure
- Nonconvulsive Status Epilepticus (NCSE)/ Electrographic Status Epilepticus (ESE)



Trinka E, et al. Epilepsia, 2015

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Status Epilepticus

CASE

- 4 year old with no PMHx heard by his parents to be grunting and thrashing in his bedroom
- Parents noted him to have his eyes open, labored breathing, arms and legs rhythmic synchronous shaking
- EMS called, and he's still shaking on their arrival 8 minutes later
- IM midazolam given and shaking stops
- In ED he's talking appropriately but is observed to have no movement of his left arm, minimal of his right leg
- Diagnosis?
- Immediate next Steps?

CASE continued

- Diagnosis
  - Status Epilepticus
  - Potential Causes?

- Immediate next steps?
  - CT Head

- CT head normal. He likely had what type of seizure?
- What phenomenon is he experiencing?

Time is Brain: Status Epilepticus

- Prior definition of convulsive SE was >30 minutes of continuous activity or intermittent activity without return to baseline in between for >30 min

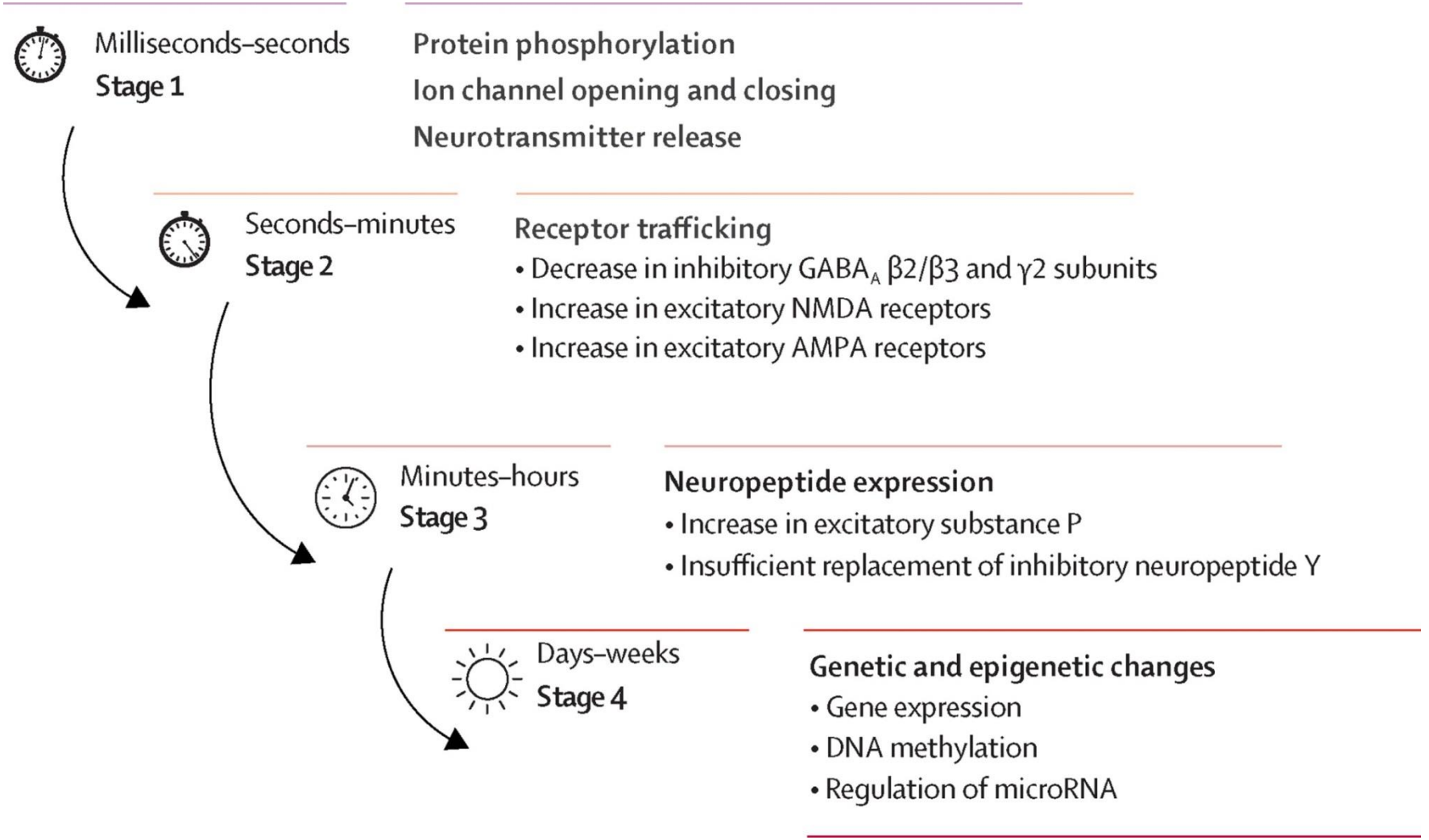
- New definition is >5 minutes
  - Animal models suggest permanent neuronal injury much earlier
  - Pharmacoresistance occurs well before 30 minutes

- Mortality in children with convulsive SE 3-11%

- Meta-analysis of children with RSE shows mortality rate of 20% in symptomatic SE, and 4% in idiopathic SE

Brophy GM, et al. 2012
Chen JYW, et al. 2006
Mazarati AM, et al. 1998

Timing of cellular changes



Betjemann *Lancet Neurology* 2015

Physiologic changes during status epilepticus

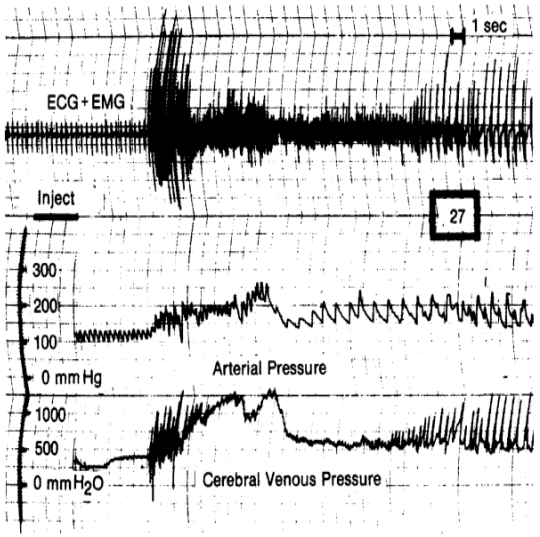
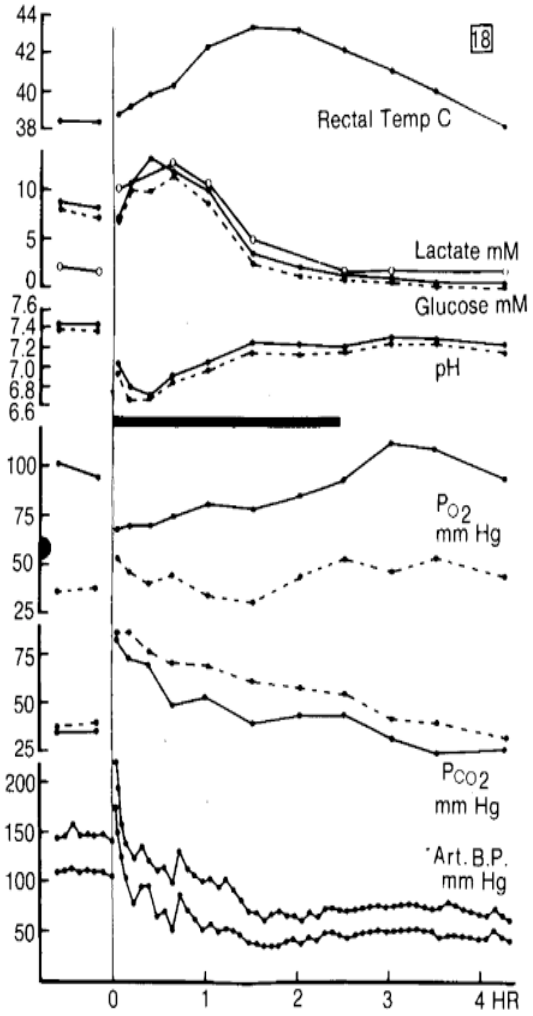
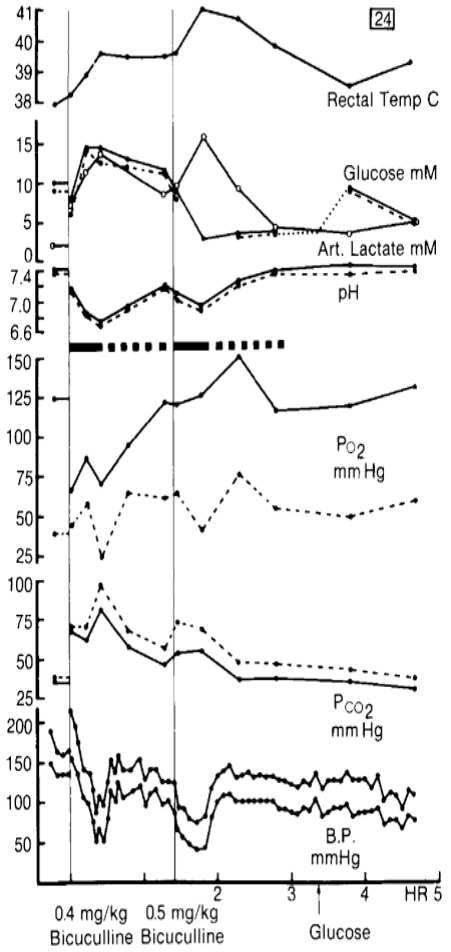


Fig 2.—Polygraph records showing rise in arterial and cerebral venous pressure at onset of seizure in baboon 27. "EKG + EMG" is recorded between electrodes in left arm and chest wall. Intravenous injection of bicuculline (0.4 mg/kg) is indicated by horizontal bar ("inject"). After 3 sec of irregular generalized jerks, tonic flexor spasm developed. Highest mean arterial and cerebral venous pressures occurred during first 6 sec of this spasm. Subsequently, bradycardia developed and was associated with widening of pulse pressure.

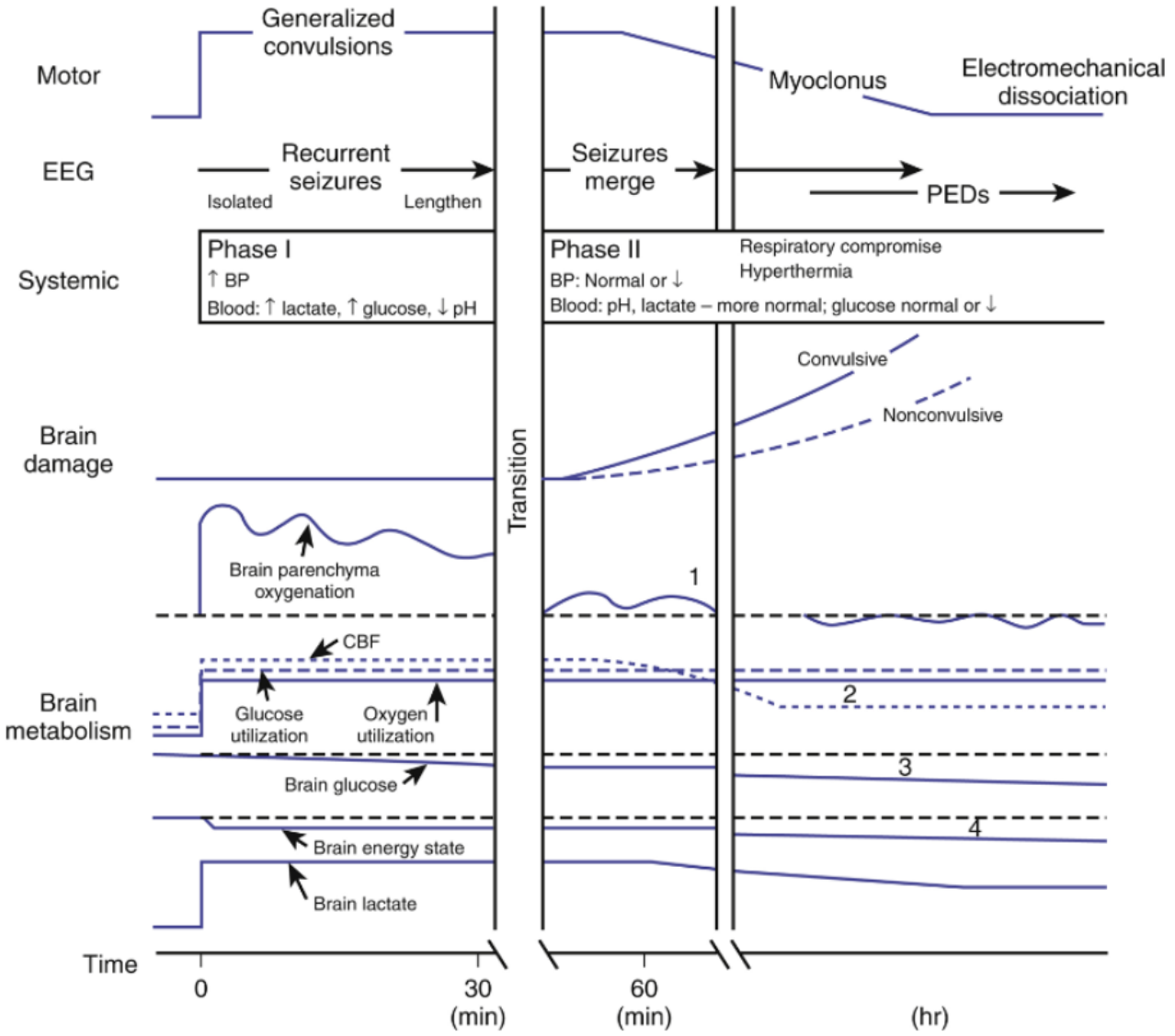
"Deaths (both those occurring suddenly and those threatened and then forestalled by perfusion-fixation) were primarily due to cardiovascular malfunction"





Meldrum and Horton (1973) Arch Neurol 28:1-9

Physiologic changes over time



Fuhrman & Zimmerman *Pediatric Critical Care*

Treatment Delay

- Delay of treatment >30min associated with delayed seizure control
- 1st and 2nd line meds effective in terminating SE 86% if seizure <20min, but only 15% if seizure >30 min

BUT WE ARE DELAYED IN TREATMENT

- 1st dose BZD given at median 30min (6-70); 2nd dose 40 min (20-95)
  - In hospital 5min (4.5-80) vs out of hospital 30min (12-60min)
- 1st non-BZD at 69min (40-120min); 2nd dose 120min (75-296)
- Continuous infusion started at 180min (120-645)

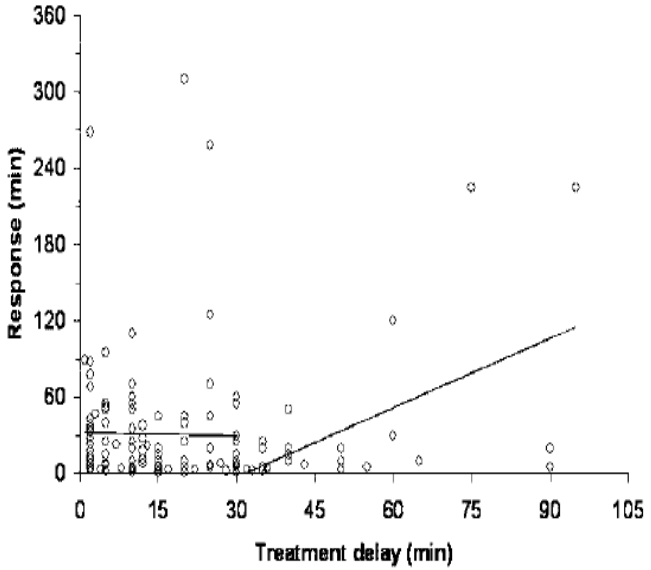


Figure 2. Association between treatment delay and response (n = 157). Solid lines indicate the estimated values of treatment response, achieved by linear modeling.

Eriksson K, et al. 2005;
Lewena A, et al. 2006;
Fernandez IS, et al. 2015

Decreased Medication Efficacy

- Benzodiazepine (BZD) efficacy may decrease by 20 times within 30 min of self-sustaining SE
  - Prolonged seizures modify GABA-A receptors (endocytosis), and can lead to electrographic status epilepticus
- Other anticonvulsants (fPHT) lose potency but more slowly
- Consideration of treatment on mechanisms other than GABA-A receptors
- NMDA blockers remain highly efficient in stopping SE, even late in course
  - This is ketamine's MOA

Chen JWY, et al. 2006;
Goodkin HP and Kapur J, 2009

Self-Sustaining Status Epilepticus

- No proof of self sustainment in humans
- Animal model data shows early treatment more effective
- 40% sz lasting 10-29min stopped spontaneously, but only 19% stop if >30min
  - Support for human self-sustaining seizures?
- Ongoing seizures rapidly modify neuronal activity and synaptic function

Chen JYW, et al. 2006; Chen JWY et al, 2007; Mazarati AM, et al. 1998; DeLorenzo RJ, et al. 1999.

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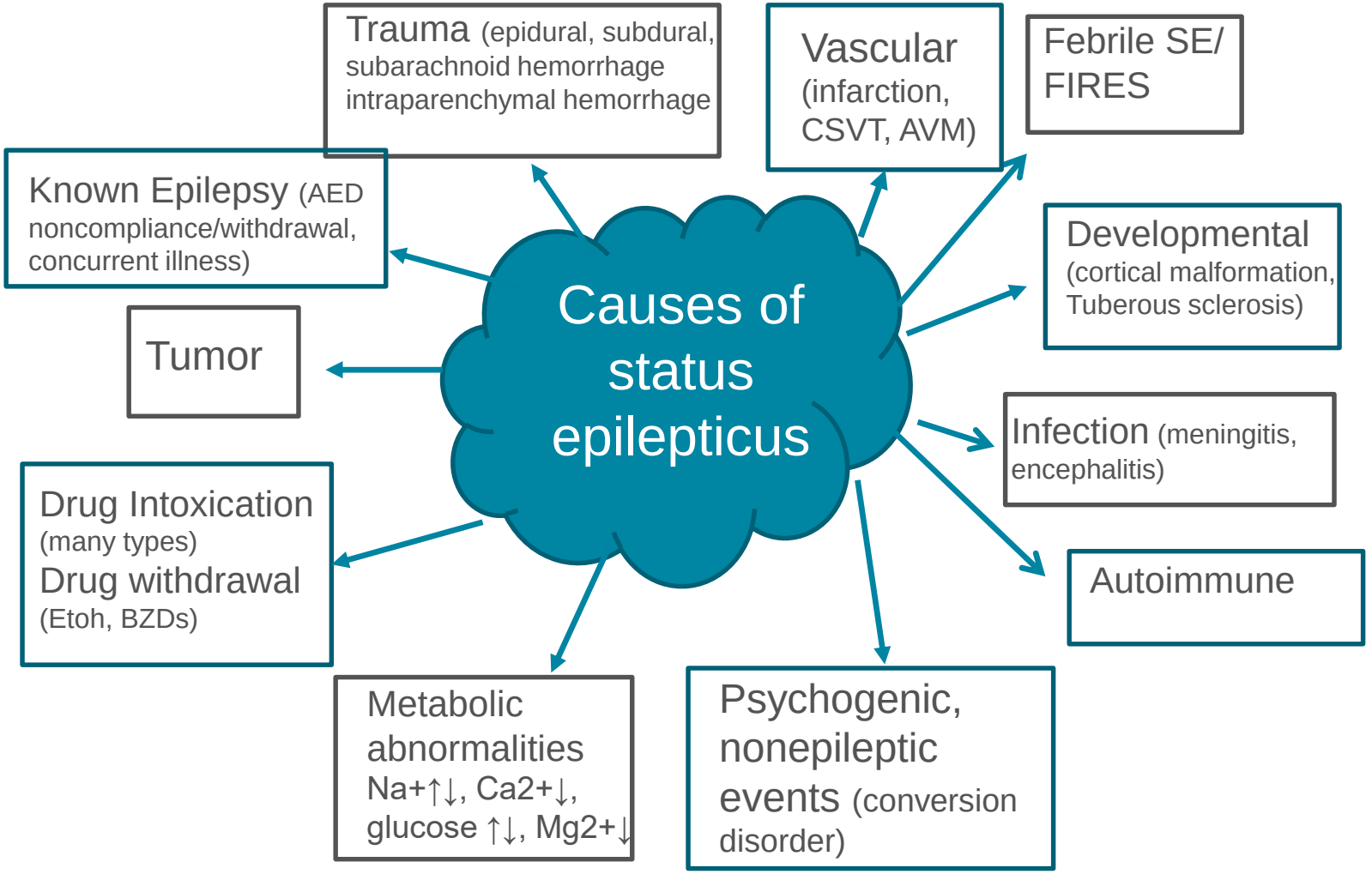
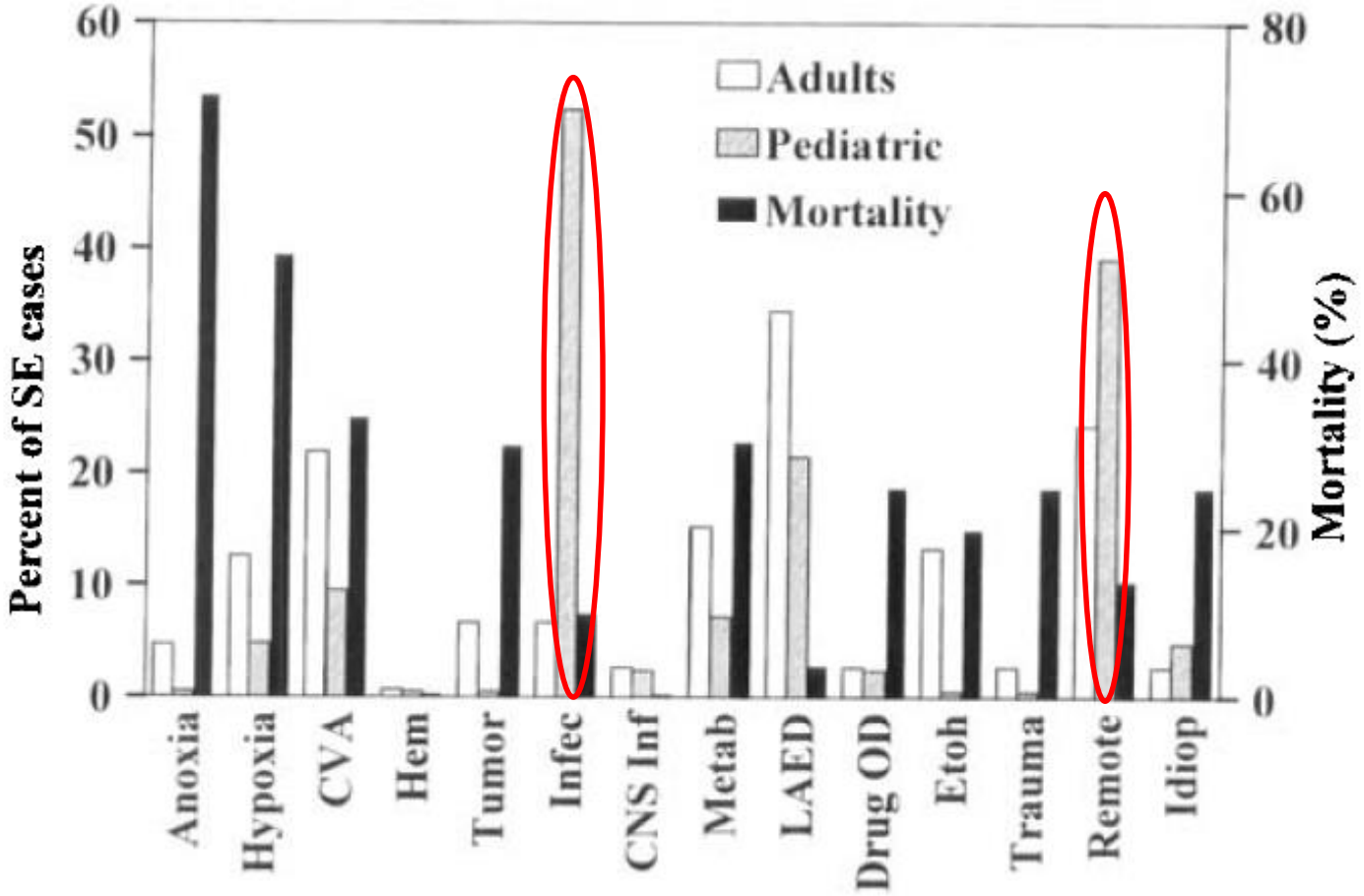
Etiologies of Status Epilepticus

SE Causes


Causes of status epilepticus
Trauma (epidural, subdural, subarachnoid hemorrhage intraparenchymal hemorrhage
Vascular (infarction, CSVT, AVM)
Febrile SE/ FIRES
Known Epilepsy (AED noncompliance/withdrawal, concurrent illness)
Developmental (cortical malformation, Tuberous sclerosis)
Tumor
Infection (meningitis, encephalitis)
Drug Intoxication (many types)
Drug withdrawal (Etoh, BZDs)
Autoimmune
Metabolic abnormalities Na+↑↓, Ca2+↓, glucose ↑↓, Mg2+↓
Psychogenic, nonepileptic events (conversion disorder)

Etiologies of CSE in Adults and Pediatrics



DeLorenzo RJ, et al. 1996

Etiologies of 1st episodes of pediatric CSE

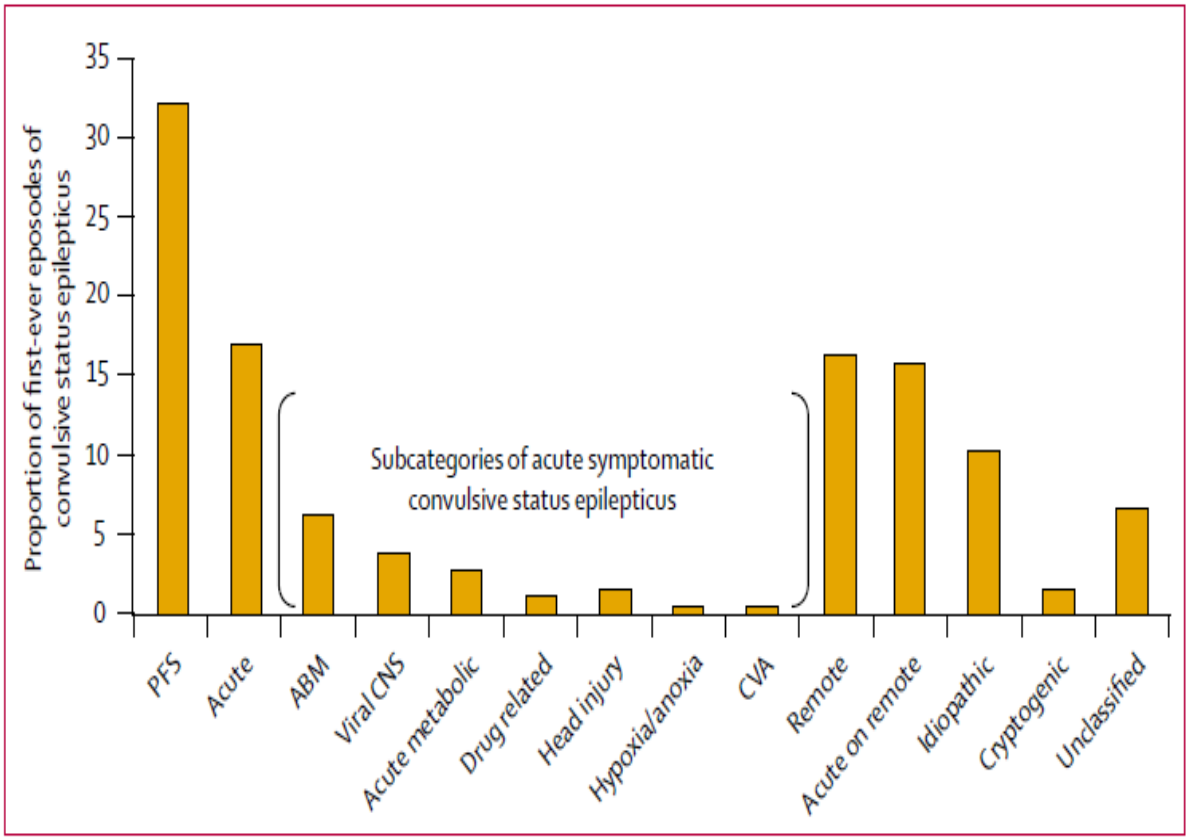


Figure 2: **Causes of first ever episodes of convulsive status epilepticus**

PFS=prolonged febrile seizure. Acute=acute symptomatic. ABM=acute bacterial meningitis. Viral CNS=acute viral CNS infection. Acute metabolic=acute metabolic disturbance. CVA=cerebrovascular accident. Remote=remote symptomatic. Acute on remote=acute on remote symptomatic. Idiopathic=ideopathic epilepsy related. Cryptogenic=cryptogenic epilepsy related.

Chin RFM, et al. 2006

Complications of SE

Cerebral	Hypoxic/metabolic damage
	Excitotoxic damage
	Edema and ↑ ICP
	Venous thrombosis, infarction, hemorrhage
Cardiac	Hypo/hypertension
	Cardiac failure/shock
	Tachy/brady-arrhythmia, arrest
Respiratory	Apnea, respiratory failure
	Pulmonary edema, hypertension, pneumonia, aspiration, PE
Autonomic	Sweating, hyperthermia
Metabolic/systemic	Hypoglycemia, ↓Na, ↓K, Acidosis Acute renal failure Acute hepatic failure DIC Rhabdomyolysis Infections Fractures
Labs (other)	Leukocytosis; CSF pleocytosis

NO! A common misperception!

ILAE Task Force 2008

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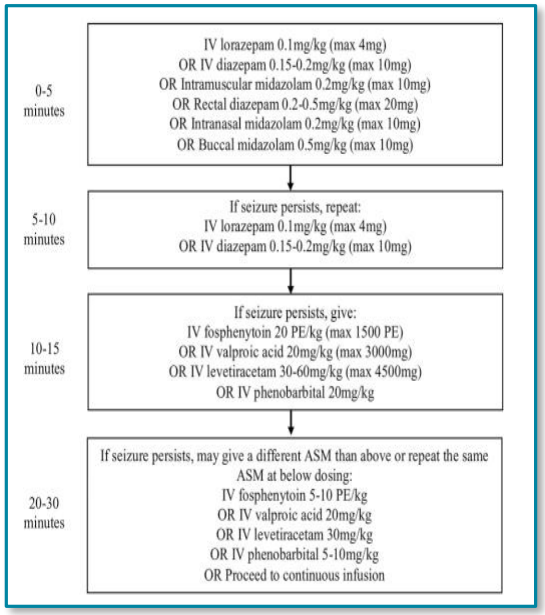
Treatment of Status Epilepticus

Timeline-based algorithm for the management of convulsive seizures

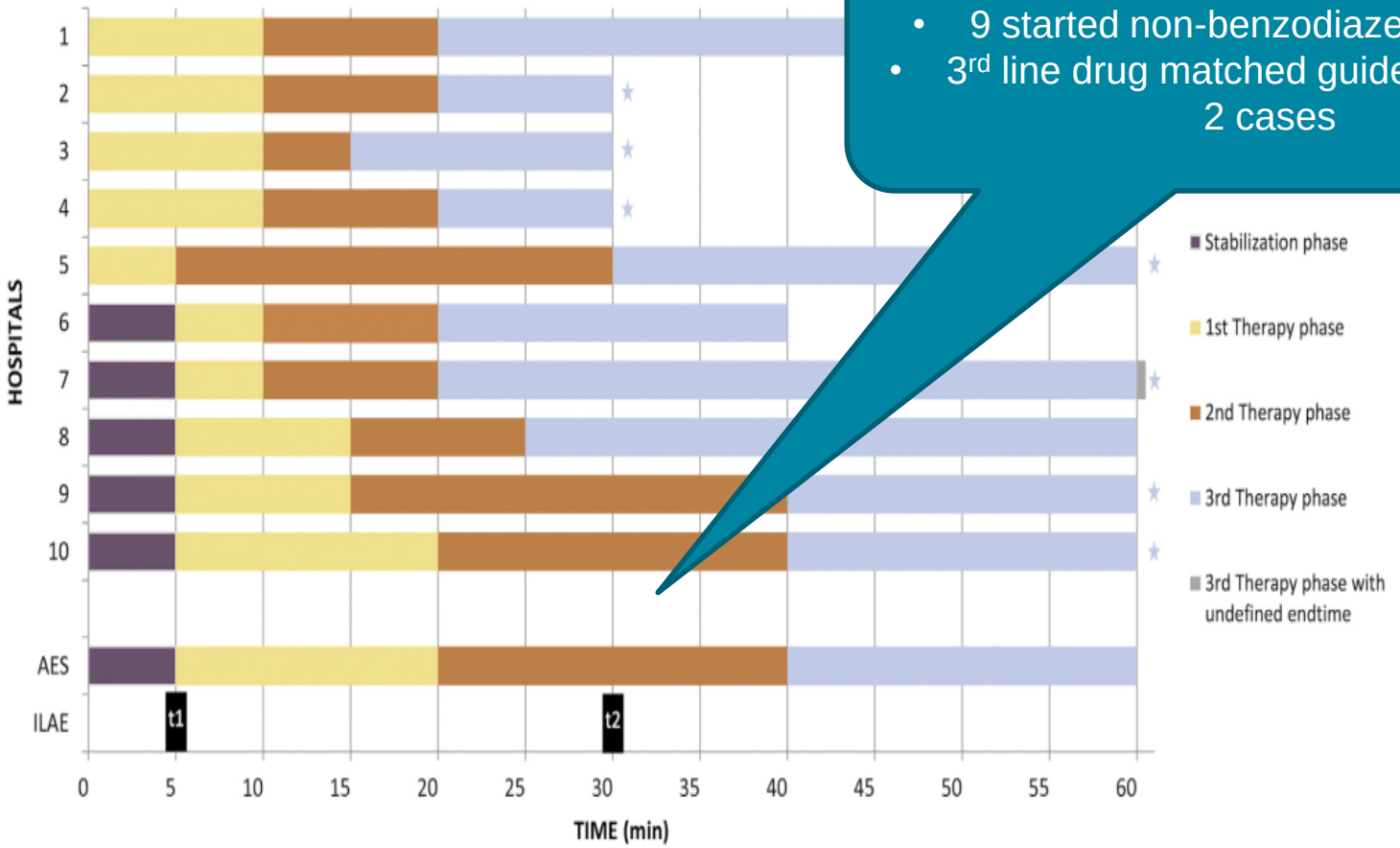
0 to 5 minutes	5 to 20 minutes	20 to 40 minutes	40 to 60 minutes
STABILIZATION	FIRST LINE THERAPY	SECOND LINE THERAPY	THIRD LINE THERAPY
• Monitor and stabilize vital signs • Laboratory tests	Administer Benzodiazepine	Administer Non-Benzodiazepine	Different 2nd line AED or general anesthetic



Glauser et al., (2016) Epil Currents 16:48-61; Stredny C et al., Seizure 58 (2018) 133–140

Multiple different interpretations of the same management recommendations

- Only 1 pathway matched AES guidelines
- 9 started non-benzodiazepine early
- 3rd line drug matched guideline in only 2 cases



Vasquez A et al., (2018) Pediatr Neurol. https://doi.org/10.1016/j.pediatrneurol.2018.06.004

Variation in dose and drug selection

	Medication	AES Guideline Recommendation*	pSERG Pathways
First-line therapy phase	Lorazepam	0.1 mg/kg (4 mg) IV, may repeat dose	0.1 mg/kg (4 mg) IV, may repeat dose (10)
	Midazolam	5 mg for 13-40 kg 10 mg for >40 kg IM, single dose	5 mg for 13-40 kg, 10 mg for >40 kg IM, single dose (1) 0.1-0.2 mg/kg (10 mg) IM (3) 0.3-0.4 mg/kg (10 mg) IM/IN (2) 0.2 mg/kg (10 mg) IN (2) 0.3 mg/kg (10 mg) buccal (1) 0.5 mg/kg (10 mg) buccal (1) 0.3-05 mg/kg (10 mg) buccal (1)
	Diazepam	0.2-0.5 mg/kg (20 mg) PR, single dose	0.5 mg/kg (20 mg) PR (4) 0.5 mg/kg for 1-5 years, 0.3 mg/kg for 6-11 years, 0.2 mg/kg for >12 years (20 mg) PR (2)
Second-line therapy phase	Fosphenytoin	20 mgPE/kg [illegible]	20 mg PE/kg (1500 mg PE/dose) IV (7) 25 mg PE/kg (150 mg PE/min) (1) 30 mg PE/kg IV (150 mg PE/min) (2)
			30 mg/kg IV (1) 50 mg/kg (2500 mg) IV (1)
			50 mg/kg IV (1) 60mg/kg IV (2)
			20 mg/kg IV (1) 40 mg/kg IV (3000 mg) (2)
			20 mg/kg (1000 mg) IV (4) 30 mg/kg (1000 mg) IV (2) 40 mg/kg IV(1)
			0.1-0.2 mg/kg (10 mg), Infusion 0.1-0.2 mg/kg/hr (9)

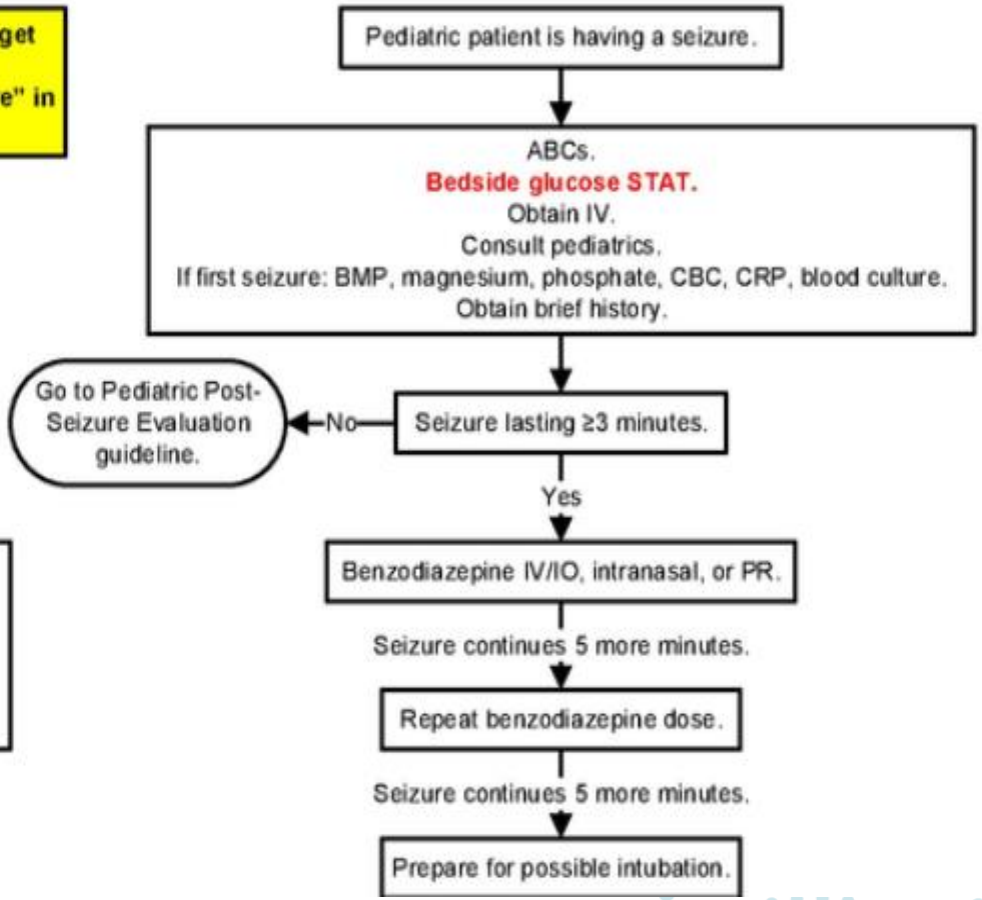
- Variation in Midazolam route and dosing
- Loading dose of fosphenytoin higher than the AES guideline
- Lower dose of levetiracetam and valproate than the AES guideline
- Higher phenobarbital dosing than the AES guideline

Yukon-Kuskokwim HEALTH CORPORATION

Seizure Treatment – Pediatric

MSEC approved 12/13/17

If in the ER, ask a nurse to get the Peds Seizure Kit.
Tell him/her to type "seizure" in the Pyxis.



Use the Pediatric Critical Care Guide and ED Peds Critical Care PowerPlan to check all medication dosing.

<u>ER Management</u>
Note: Peds Seizure Kit includes dosing.
Lorazepam 0.1 mg/kg IV/IO or midazolam 0.2 mg/kg intranasal if no IV access.

<u>Village Management</u>
-ABCs.
-**Bedside glucose STAT.**
-Get BVM with appropriate sized mask to bedside.
-Follow flow to the right, using these drugs with dosing found on Pediatric Critical Care Guide:
  • Diastat home dose PR if available or midazolam 0.2 mg/kg intranasal or diazepam 0.5 mg/kg (max 10 mg) IV solution given RECTALLY.
  • Phenobarbital 20 mg/kg IM.
-Low threshold to activate medevac for atypical or prolonged seizure.
-See Emergency RMT Seizure Scenario on wiki.

leGuidelines2017.pdf&page=37

Initial Steps in Seizing Patient

- ABCs (or CABs)
- First line medication – Benzodiazepines
- Second line medication – several options
- Continue evaluating ABCs (consider intubation)

Treatment of Status Epilepticus

- 1st line:

  benzodiazepine (may repeat once)

- 2nd line:

  fosphenytoin, phenobarbital, levetiracetam,

  (not available at YKHC: lacosamide, valproate)

  - May repeat a dose, or give a second 2nd line agent

- 3rd line:

  midazolam drip (at SCH)/propofol drip (at YKHC)

  - Should transfer to allow continuous EEG
  - Proposed MOA of midazolam: presynaptic GABA receptors internalized, extrasynaptic are not, and midaz drip works on them by potentiation of tonic inhibition

CASE

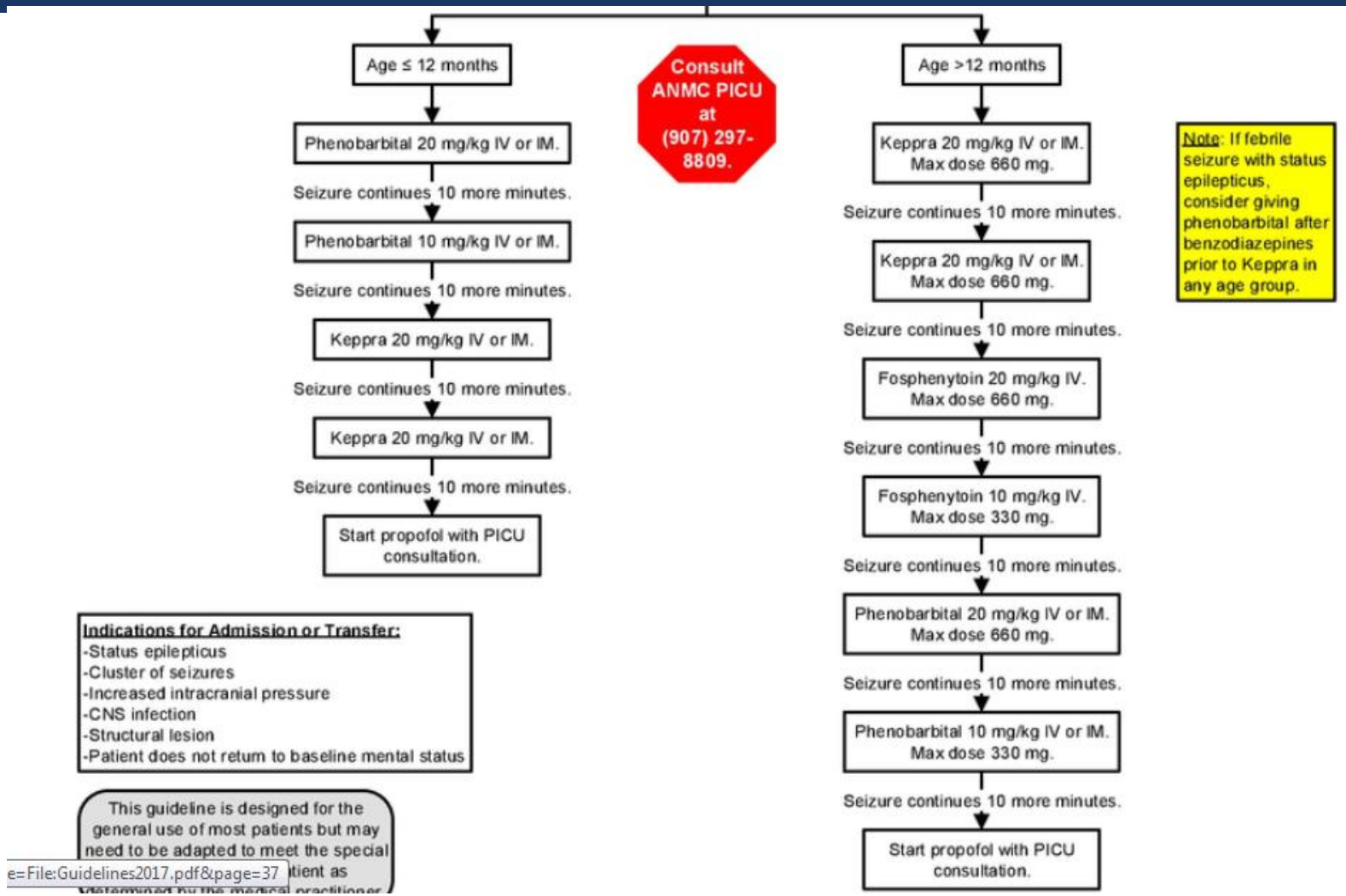
6 year old with epilepsy, had 2 seizures at home and was given IN midazolam. He presented to outside hospital and was noted to have bilateral arm and leg rhythmic jerking. IV access was obtained and he received IV lorazepam, but was still noted to have jerking. A dose of IV phenytoin 18mg/kg was given and the jerking stopped. The patient was transferred to your hospital, and on arrival you note HR 170, BP 96/66, R 11, T 37.8, O2 94% 2L NC. On physical exam, the patient is laying still, his eyes are partially open, he has no blink to threat and his pupils are dilated, and he is not responsive to voice or touch. What should you do next?

a. Admit him to the hospital for observation
b. Chest X-ray
c. Give IV phenobarbital
d. Head CT
e. Prepare for lumbar puncture

Treatment of Status Epilepticus: Meet the Medications

Medication	Mechanism of Action	Side Effects/important notes	Signs of Toxicity
Fosphenytoin	Voltage-gated Sodium channel antagonist	*groin itching Hypotension Ataxia, nystagmus Phenytoin can cause purple glove syndrome	Nystagmus, ataxia Increased seizures
Phenobarbital	GABA A receptor agonist	Respiratory depression Sedation Use with caution in hemodynamically unstable pts	sedation
Levetiracetam	Synaptic vesicle protein SV2A	Behavioral change/irritability	
Valproic Acid	*Sodium channel antagonist, Calcium channel modulator, increases GABA*	***can exacerbate metabolic disease* ***pancreatitis* ***do not give <2 years of age* ***NEVER use in POLG-1 pts*	*Liver toxicity* *tremor*

Ongoing Treatment per YKHC guidelines



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Adverse Effects of Anesthetics

- Pentobarbital contains 40% propylene glycol.
  - Propylene glycol toxicity –Unexplained anion gap, unexplained metabolic acidosis, hyperosmolality, clinical deterioration
- Pentobarbital: cardiac instability and hypotension
- Midazolam: respiratory depression, sedation, hypotension
  - Pediatric study of 27 pts. None with adverse effects
- Propofol: PRIS: metabolic acidosis, rhabdomyolysis, hyperK+, lipemia (children higher risk).
- Ketamine: cardiac arrhythmias like SVT and A fib
  - Small pediatric study with mild transient side effects

Ozdemir D, et al. 2005;
Rosati A, et al. 2012

Propofol continuous infusion at SCH

Propofol infusion for Status Epilepticus: Guidelines for use	
Titration	(Per CIS orderset) • **Start**: 2 mg/kg IV bolus + infusion at 50 mcg/kg/min • **Titrate** q10 minutes to achieve burst suppression: additional 2 mg/kg IV bolus + infusion increase 25 mcg/kg/min
Contraindications	• Sulfite allergy • Egg allergy • Soybean allergy
Laboratory Monitoring	Consider • **Serial ABG, lactate, potassium** • **Daily lipid level**

Midazolam continuous infusion at SCH

Refractory status epilepticus: CEEG and titration of midazolam infusion	
Initiation	• **Bolus 0.15 mg/kg midazolam IV** • **Initiate midazolam infusion at 0.1 mg/kg/hr** • **Q 15 minutes: Bolus 0.15 mg/kg midazolam IV AND increase infusion by 0.1 mg/kg/hr** for ongoing seizure (in communication with NEU) until burst suppression is achieved. • Airway, hemodynamic support as clinically indicated. • NPO ➢ **If difficulty achieving burst suppression** • Consider ketogenic diet preparation **(send labs; NS-based IVF)** with Neurology • By 24 hours: **discuss alternatives**
Stable burst suppression	**Minimum 24h** • Wean for over-suppression • Titrate other AEDs
Weaning	• Wean by **0.1 mg/kg/hr q 4 hours** (in communication with NEU) • Continue EEG until off of IV anesthetic x 24 hours • Hold wean & notify neurology for any **clinical seizure** • If electrographic seizures: consider increase in maintenance AEDs while continuing midazolam wean

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Why cEEG?

Earlier CASE continued

- Your 4 year old with no prior history of seizures continues to have seizures in the ED.
- He has received IV LZP x2, IV fPHT followed by IV phenobarbital and is still seizing at minute 55
- You start a propofol infusion →He stops shaking
- HR 130, BP 90/60, R 16, T 37.8, O2 94% 2L NC. Laying still, eyes partially open, no blink to threat, not responsive to voice or touch
- What are you concerned about? What test would be helpful if available?

Electrographic Seizures - Incidence

- 550 consecutive pediatric patients undergoing cEEG in ICU (median age 36.5mo)
  - 11 institutions, 50 consecutive patients from each institution
- cEEG duration 12-72h
- 30% patients (162/550) with electrographic seizures (ES)
  - 38% of those (61/162) with electrographic status epilepticus (ESE)
- Risk factors for ES
  - Younger age, clinical seizures prior to cEEG, interictal epileptiform discharges, diagnosis of epilepsy
  - More common in abusive vs accidental traumatic brain injury; sepsis
- Increased mortality in ESE (compared to ES, or no seizures)

Abend NS, et al. (2013)

Clinical Effects of Electrographic Seizures

- 259 critically ill neonates and children on cEEG at a single center
- PCPC decline had higher seizure burden
  - Mean maximum hourly seizure burden: **15.7% vs. 1.8%**
  - Odds of PCPC decline = 1.13% for each additional 1%/hr seizure burden
- **≥20% seizure burden** per hour (12 min) had a significant probability (p=0.0001) of PCPC decline at time of discharge
  - <20%/hour had same probability of PCPC decline as those without seizure

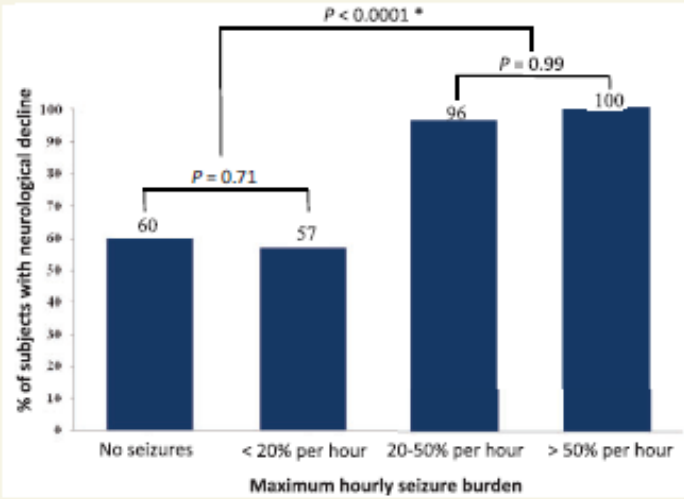

Figure 1 Maximum hourly seizure burden of 20% (12 min) is associated with neurological decline.Comparisons performed using Fisher's exact test. The single subject with a seizure burden ⩾20% per hour who did not experience neurological decline had a baseline PCPC score of 3. *Comparison of the 'no seizures' and '<20% per hour' groups combined with the '⩾20% per hour' and '>50% per hour' groups combined.

Payne ET, et al. (2014);

Electrographic Seizures - Treatment

- There is no national consensus on how aggressive one should be with electrographic seizures

- Growing evidence to suggest that electrographic seizures may impact neurodevelopmental outcome, but the extent independent of the degree of brain injury remains uncertain.

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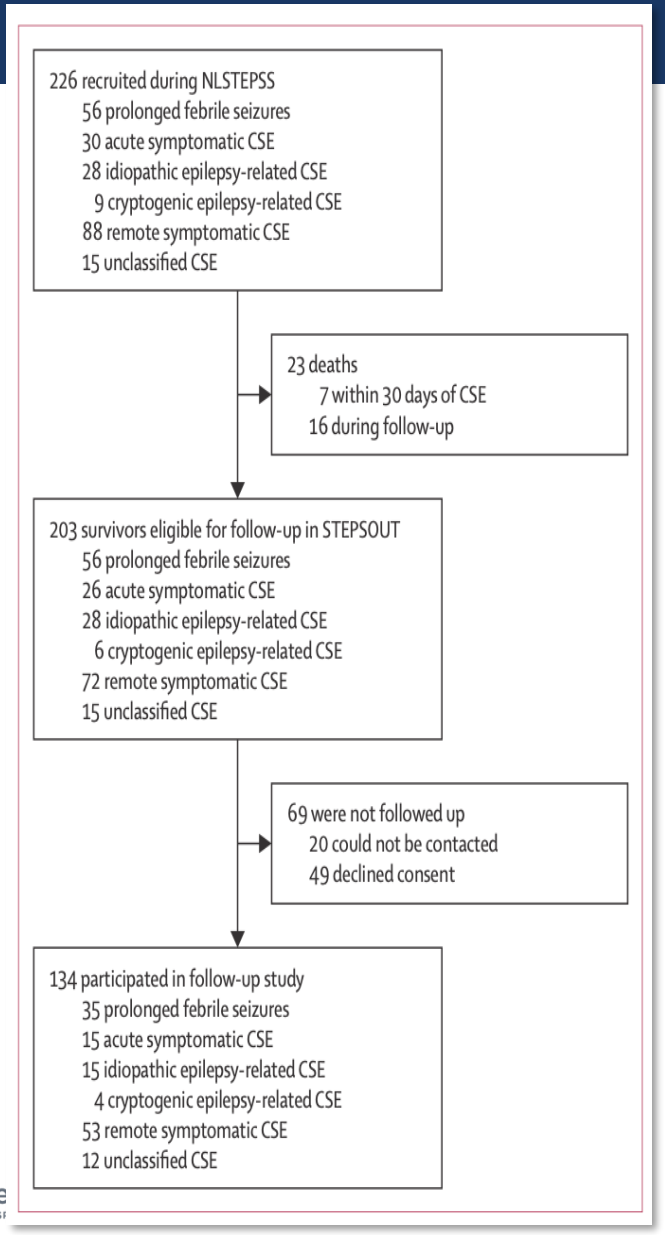
Outcomes

Long-term prognosis after convulsive status epilepticus in childhood

- Follow up of of the North London convulsive status epilepticus surveillance study cohort; NLSTEPSS
- Structured clinical neurological assessment
- MRI
- Wechsler Abbreviated Scale of Intelligence
- 203 survivors of the inception cohort; 134 followed up for this study
- Median age of convulsive status epilepticus; 2.7 yr
- Median age of enrollment in this study: 11.6
- CSE duration median 70 minutes

Pujar SP et al., Lancet Child Adolesc Health 2018; 2: 103–11

One quarter of the study group developed epilepsy



- 25% of the group developed epilepsy
- Incidence highest in remote symptomatic (46%) and unclassified SE (50%)
- Lower in febrile SE (14%) and acute symptomatic (13%)
- 90% emerged within 18 months of first SE event
- Absence of fever the only predictor of incident epilepsy

Mortality

- Pediatric SE specific mortality 0-3%
  - Overall mortality 12-15% if acute symptomatic SE
  - Younger age increased mortality
  - Long term mortality 5.4-17%
- RSE mortality: acute symptomatic 20%, idiopathic 4%
  - Up to 32% if RSE >60 min
  - Some studies do not find a correlation with duration seizure

Sahin M, et al. 2001;
Raspall-Chaure M, et al. 2006;
Shorvon and Ferlisi 2012.

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.

Morbidity

- Recurrence SE up to 16% within a year of first episode of SE
  - Risk of recurrence ever 3-56%
  - Further seizures likely to be prolonged
  - Subsequent epilepsy 13-74%
- Focal neurologic deficits
- Cognitive impairment
- Behavioral problems
- Up to 27-29% with new functional impairment at discharge
- Longer duration of treatment or younger age at RSE, higher morbidity
- Higher chance for functional deficit if RSE caused by acute symptomatic cause

Chin RFM et al. 2006;
Raspall-Chaure M et al. 2006

SUDEP

- Sudden Unexpected Death in EPilepsy
- Each year 1 in 1,000 adults, and 1 in 4,500 children will die from SUDEP
  - If seizures are uncontrolled the risk of SUDEP increases to more than 1 out of 150.
- Unclear if primary brain, cardiac or respiratory
- TALK to patients about SUDEP
- There is no data that anti-suffocation pillows prevent SUDEP
- www.epilepsy.com

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Questions?

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