Status epilepticus: news and perspectives

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Objectives

- History
- Definition of status epilepticus
- Diagnostic modalities
- Incidence of status epilepticus
- Treatment of status epilepticus

Physiological processes that are important to monitoring

- Clinical evaluation
- Systemic hemodynamics
- Intracranial pressure and cerebral perfusion pressure
- Cerebrovascular autoregulation
- Systemic and brain oxygenation
- Cerebral blood flow and ischemia
- Electrophysiology
- Cerebral metabolism
- Glucose and nutrition
- Hemostasis and hemoglobin
- Temperature and inflammation
- Biomarkers of cellular damage and degeneration

Neurological injury

- Primary injury
  - Spectrum of intracranial injuries
  - Not preventable
- Secondary injury
  - Other insults that contribute to a worse outcome
  - Potentially preventable/treatable

NeuroICU : prevent secondary brain injury

- Hypoxaemia
- Hypotension
- Hyponatraemia/Hypernatraemia
- Hyperpyrexia
- Hypoglycaemia
- Seizures

Status epilepticus: history

- 1691: Wurffbain describe cerebellar seizures; original paper published by Leopold Academy of Nuremberg, the oldest scientific society in the world
- In the early years of 19th century Marshall Hall postulated that the "seat of epilepsy" was in the spinal cord
- Brown-Sequard, Kussmaul, Tenner postulated a brainstem and/or a spinal basis for the epilepsy
- 1890 John Hughlings Jackson responsible for the modern concept of epilepsy
- SE (considered the most extreme form of a seizure): was first included in the classification of seizures of the ILAE in 1970.

The proposed new definition of SE : ILEA 2015/American Epilepsy Society 2016

- *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 t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.*

The Commission on Classification and Terminology and the Commission on Epidemiology of the International League Against Epilepsy (ILAE)
American Epilepsy Society 2016

- Time point t_1 (5 min): indicates when treatment should be initiated

- Time point t_2 (30 min): indicates when long-term consequences may appear

A new diagnostic classification system of SE

- There are four axes:

1. **Semiology**:
   - SE with prominent motor systems
   - SE without prominent motor systems
   - indeterminate conditions (confusional states with epileptiform EEG patterns).
2. **Etiology**: SE of known and unknown causes
3. **Electroencephalography (EEG) correlates**
4. **Age**

Status epilepticus: definitions

- Status Epilepticus: clinical and electrophysiological epileptic activity that lasts for more than 5 min or recurrent epileptic activity without recovery of the pre-existing level of consciousness over a period of 5 min.
  - For practical purposes : any person still seizing upon arrival of medical help
  - 3 - 7% mortality
- Refractory Status Epilepticus (RSE)
  - Seizures persist > 60 mins up to 2 hours
  - Fail to respond to adequate doses of 2 anticonvulsants
  - 16- 32% mortality
  - 50% have neurological sequelae

Status epilepticus: definitions

- Super-Refractory Status Epilepticus (SRSE)
  - Seizures persist > 24 hours after the onset of anaesthesia
  - SE recurs on the reduction or withdrawal of anesthesia
  - 35-45 mortality
  - ~10–15% of patients with SE develop SRSE

Novy and Rossetti, 2010

Status epilepticus: definitions

- Myoclonic status epilepticus
  - Acute onset: in context of severe brain injury, usually anoxic (post cardiac arrest)
  - Deep coma
  - Myoclonic jerking, ocular movements
  - Treatment controversial: anaesthetic AED versus none
  - Poor prognosis: >80% death rate
  - Form of SE or simply a reflection of severe brain injury?

Status epilepticus: definitions

- Pre-existing epilepsy: two or more unprovoked epileptic seizures that occurred more than 4 weeks before the onset of SE .

- Post-status epilepticus symptomatic epilepsy: condition established in patients without pre-existing epilepsy, with the occurrence of at least one unprovoked epileptic seizure occurring not earlier than 4 weeks after termination of SE.

Holtkamp, M., Othman, J., Buchheim, K., and Meierkord, H. **Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit.** *J Neurol Neurosurg Psychiatr*. 2005; 76: 534–539

Non-convulsive seizures/ non-convulsive status epilepticus

- Frequent as a progression of convulsive status epilepticus
- In the following 24 hours after SCE:
  - 48% have NCS
  - 14% have NCSE

Friedman, Claassen, Hirsch. Anesth Analg 2009: 109:506-23)

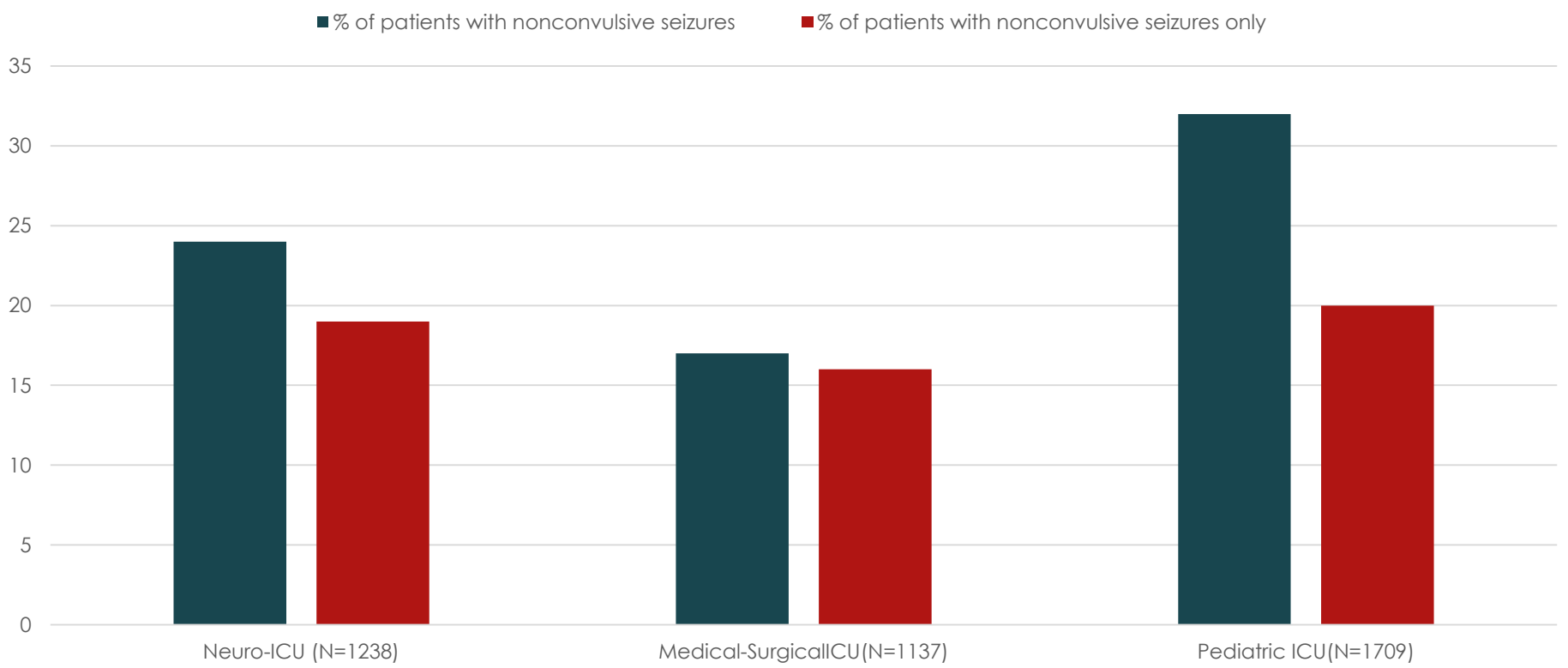
Pediatrics non convulsive status epilepticus

- 33% of comatose children - EEG NCSE
  - Hosain et al. Pediatr Neurol 2005;32:162-5
- 25% children presenting to ED with ↓LOC - EEG NCSE
  - Alehan et al. J Child Neurol 2001;16:484-7
- Progression from convulsive status epilepticus
  - Time dependent pharmacoresistance

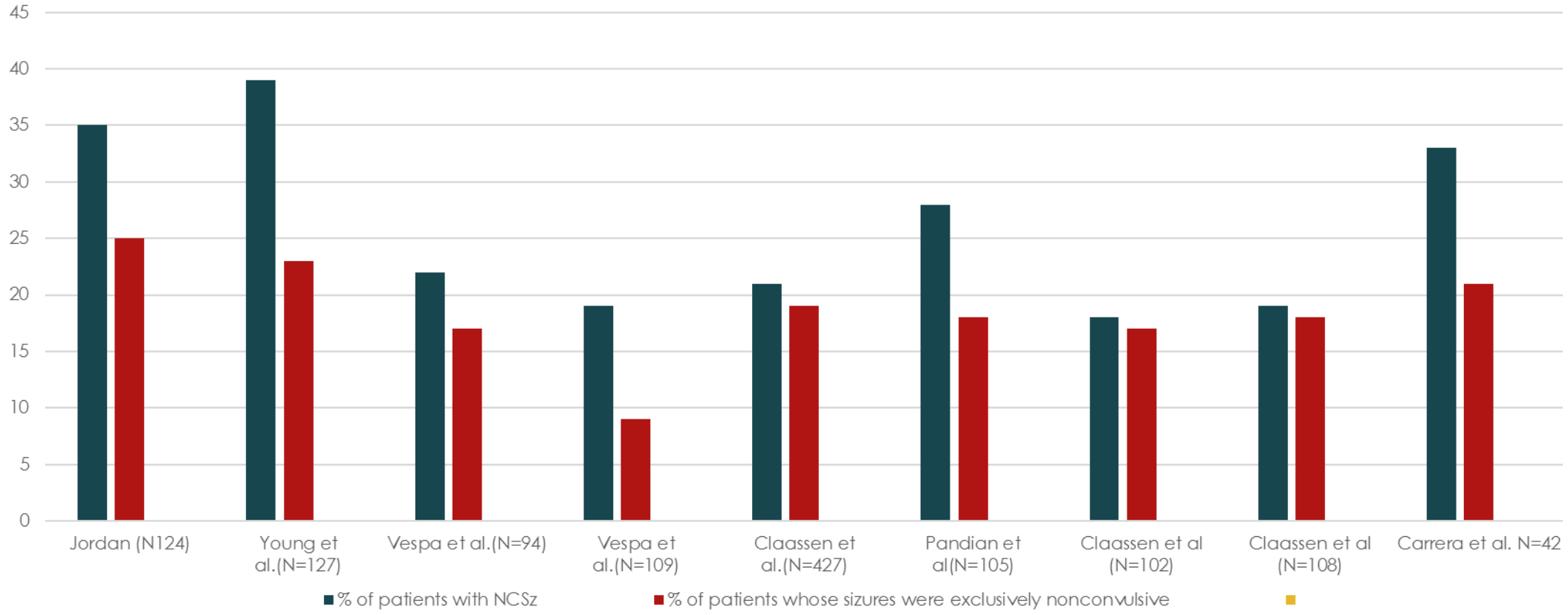
NCSz in the ICU: a clinical challenge

- NCSz are common
  - 25 % of patients in a neuro-ICU have seizures
- NCSz are hard to diagnose
  - 80% of NCSz are electrographic and detected only with cEEG
  - A "routine" EEG detects 50% of patients with NCSz
- NCSz are harmful
  - Worse outcome
  - Hematoma expansion, mass effect, ICP crisis
  - Excitotoxicity
  - Metabolic impact(LPR, PbtO2)
- We do not know how to treat: which drugs?/ how aggressively?
  - Anecdotal evidence
  - Ongoing trial (TRENdS)

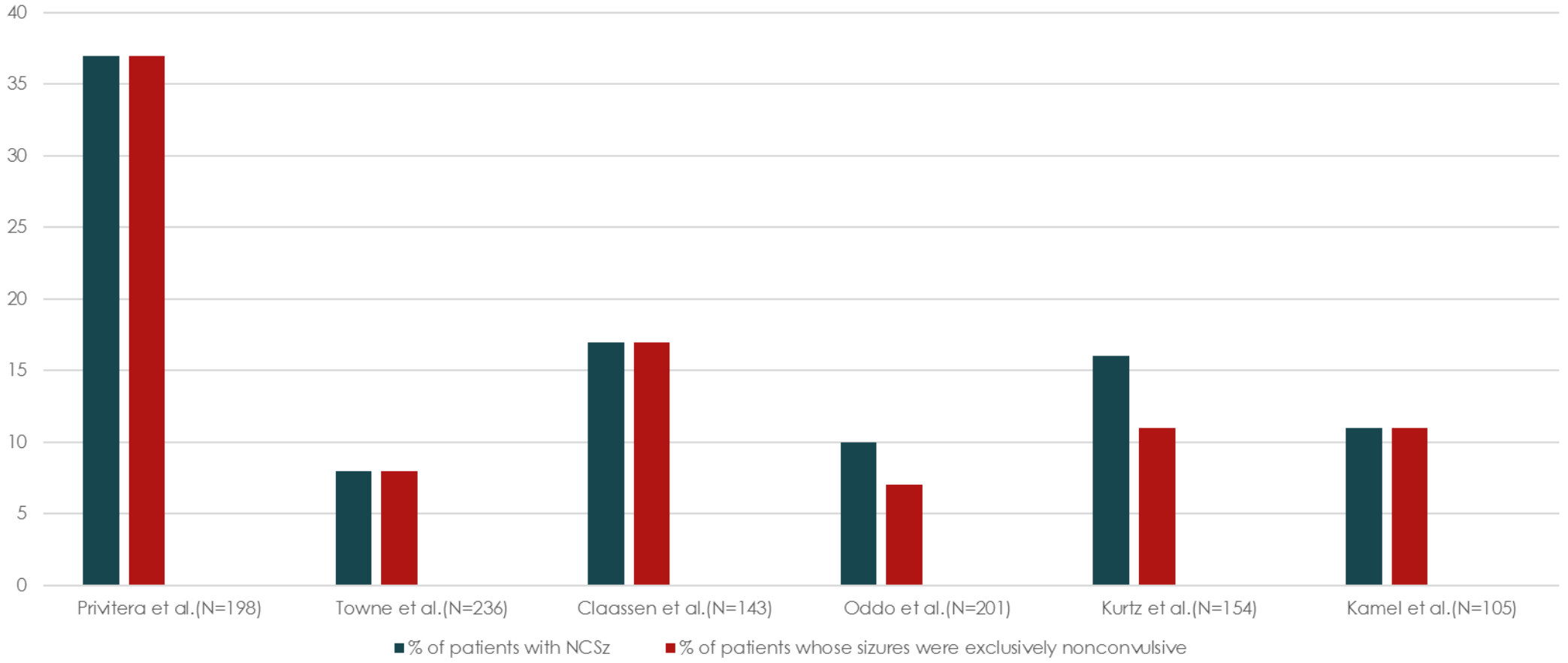
Prevalence of nonconvulsive seizures in ICU



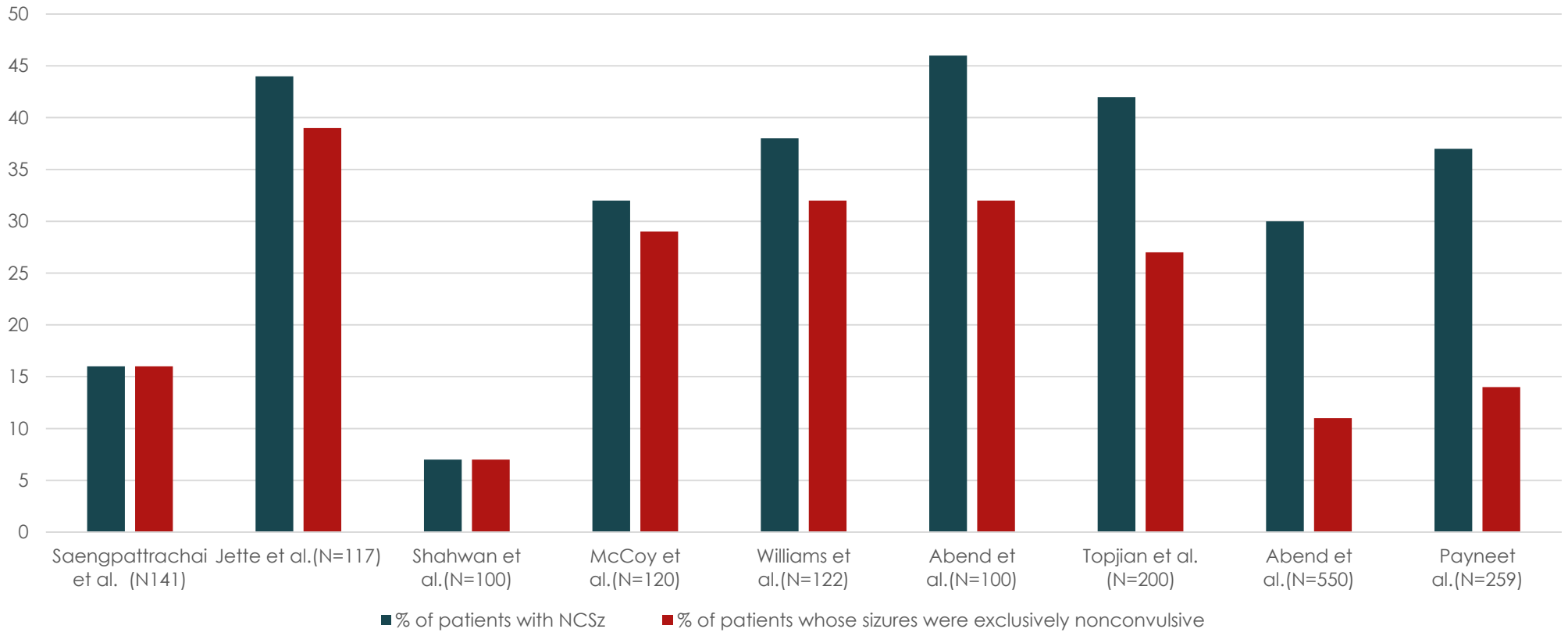
Nonconvulsive seizure prevalence in the neuro-ICU



Nonconvulsive seizures prevalence in the non neurological ICU



Nonconvulsive seizures prevalence in PICU



Etiology:

Intracranial hypertension

Cerebral hemorrhage

Cerebral tumor or encephalitis

Traumatic brain injury, cerebral hypoxia

Septic encephalopathy

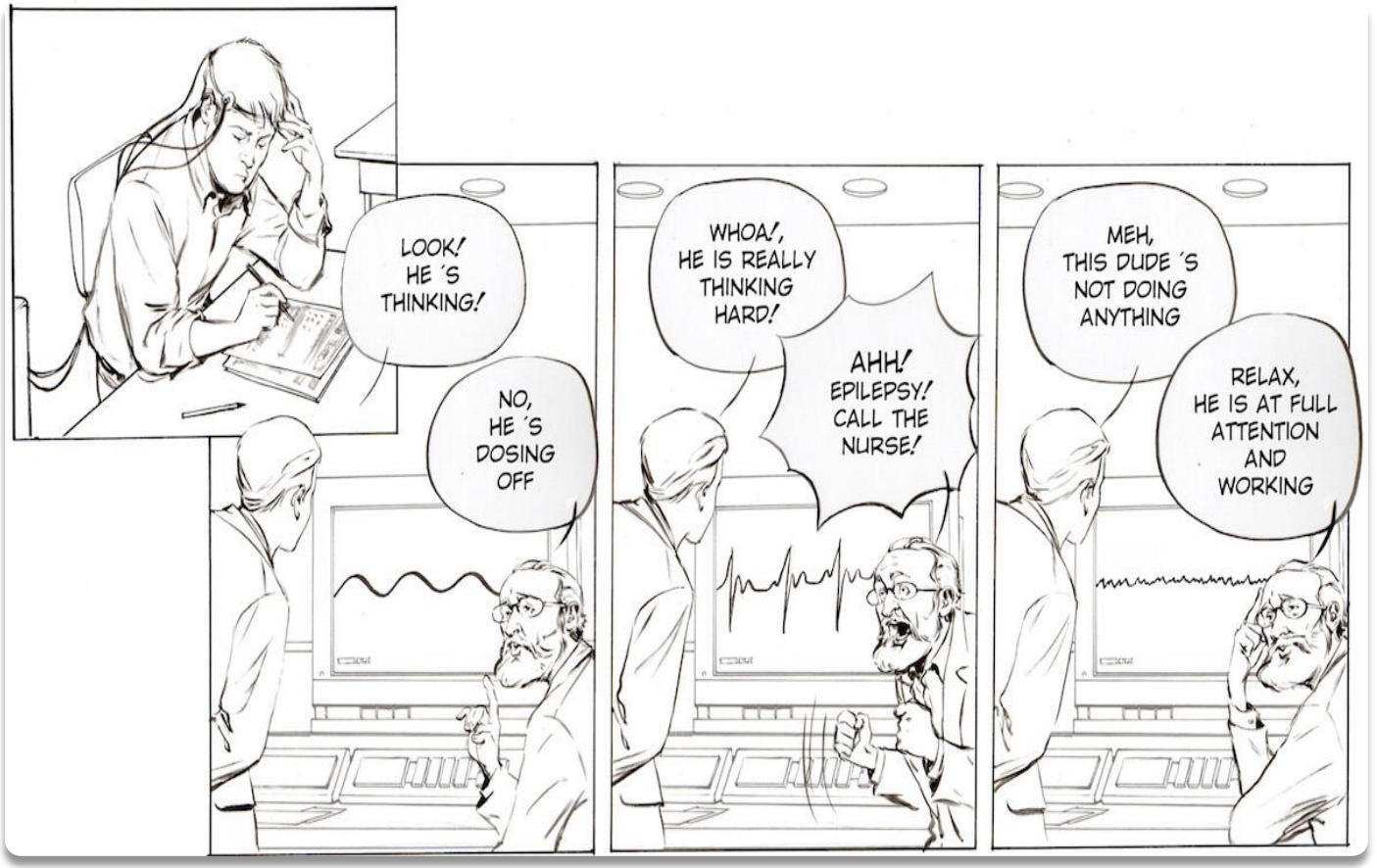
SE is not a disease entity but rather a symptom with a myriad of etiologies.

Depending on etiology

Structural SE	Epilepsy related	Nonstructural SE

How to diagnose status epilepticus

- Clinical exam
- cEEG with video monitoring
- INVOS
- PIC monitoring
- Cerebral microdyalisis



Why difficult to diagnose status epilepticus in neuro-ICU?

- Comatose patients
- Needs to be sedated and/or paralyzed
- High incidence of septic encephalopathy (CVC with MRSA infections)
- Necessity of continuous recording of EEG , synchronized with video
- C EEG difficult to read
  - "expert" necessary
  - Very sensitive to artifacts
  - Reading is time-consuming

Subtle movements that can be due to seizures

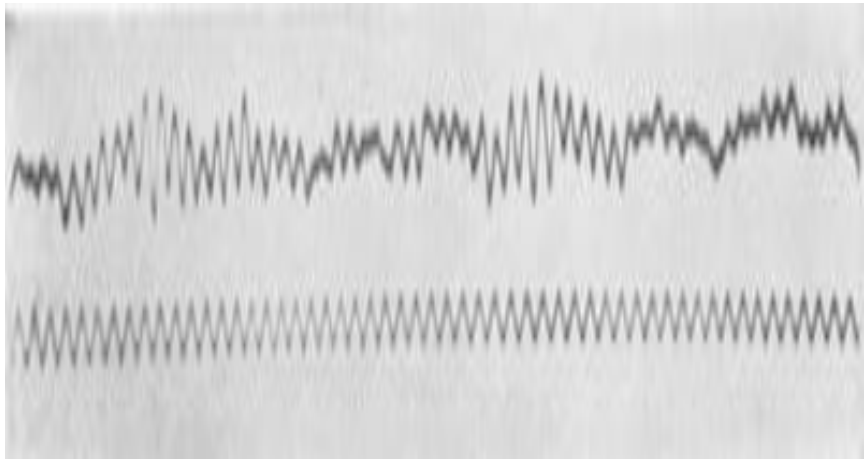
- Nystagmus
- Tonic gaze deviation
- Hippus
- Facial twitching (mouth, eyelids)
- Subtle finger twitching

Effect of NCSz on ICP and cerebral metabolism

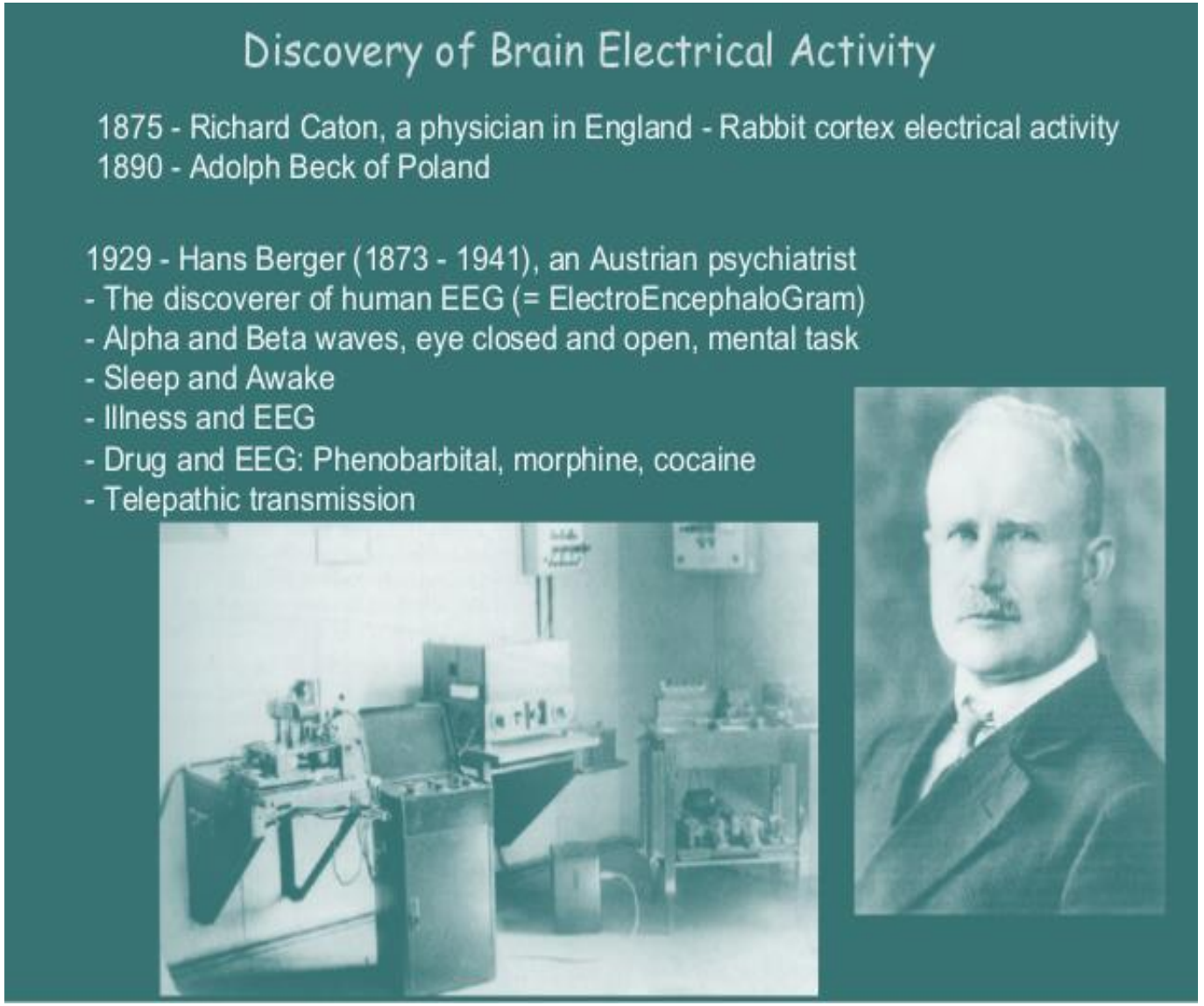
	ICP (mmHg)	LPR	Glutamate
Inter-ictal	9,6+/-5	23.8	2.6
Ictal	22,4+/-7	49.4	13.1
	P<0.002	**P<0.02**	**P<0.001**

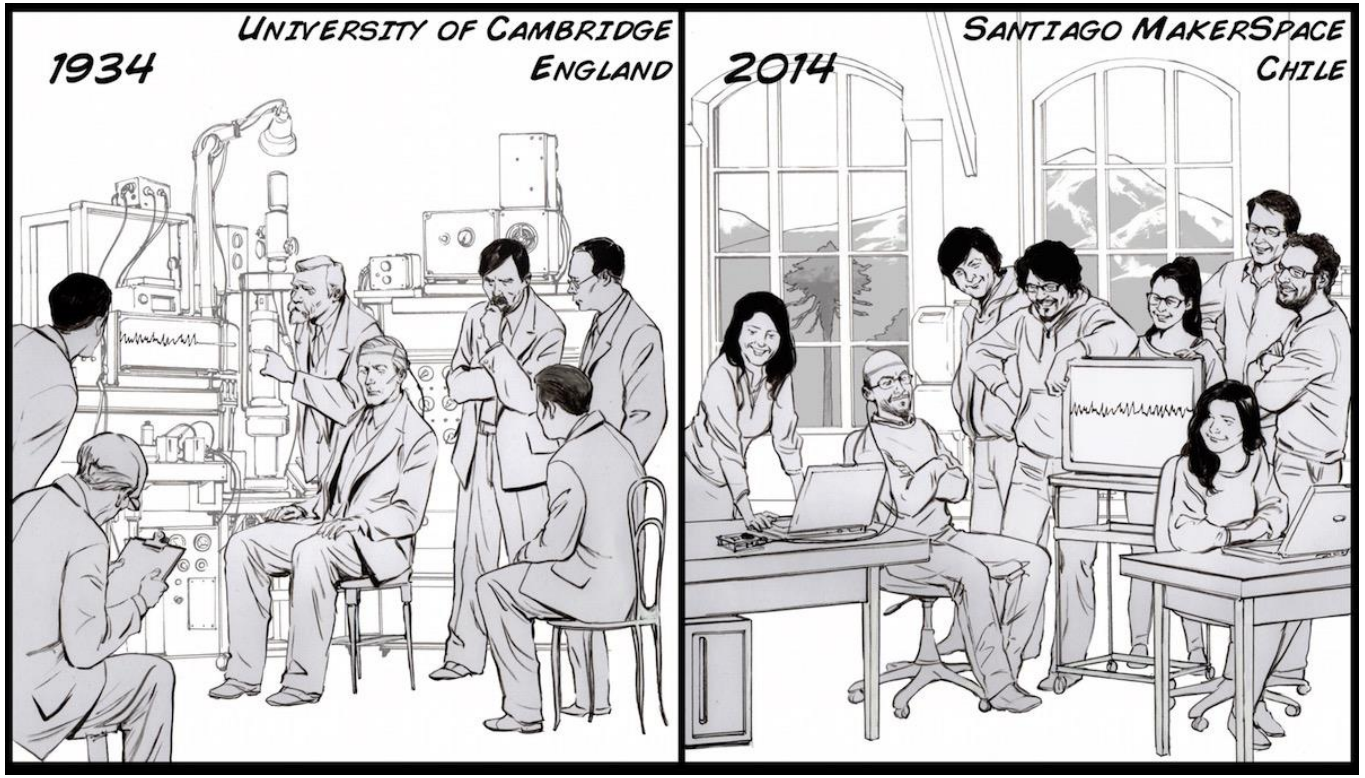
Vespa, P.M.et al. CCM 2007

EEG



The first human EEG recording obtained by Hans Berger in 1924. The upper tracing is EEG, and the lower is a 10 Hz timing signal.





Progression of EEG recording

EEG abnormalities

- Epileptiform discharges
- Focal slowing
- Diffuse background slowing
- Intermittent diffuse intermixed slowing

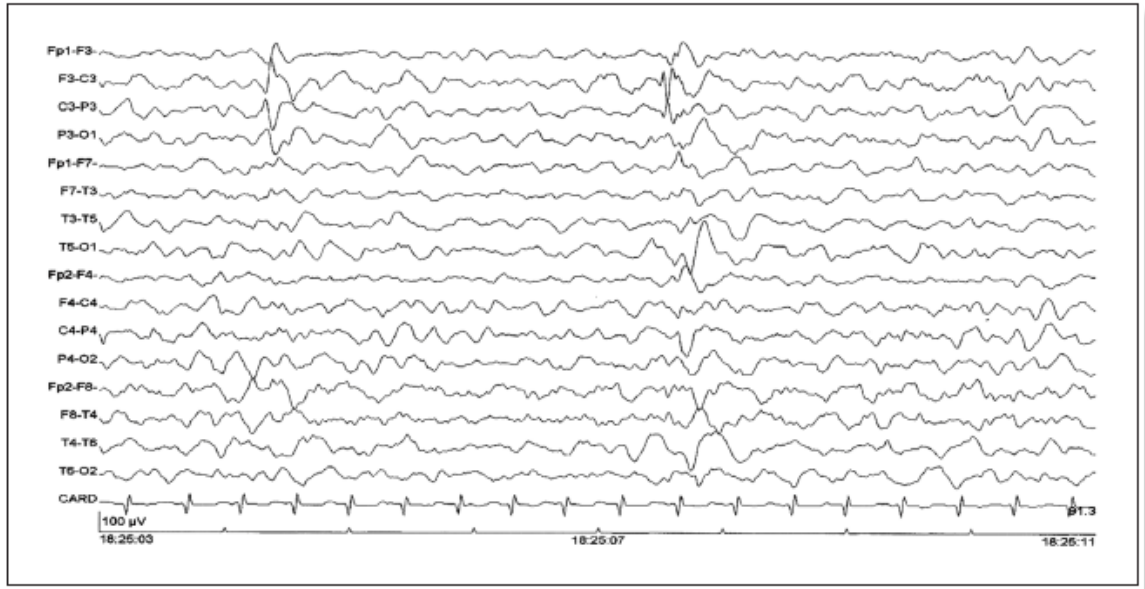


Figure. EEG with focal paroxysmal activity in the left rolandic region with some propagation to temporal areas.

cEEG indications

- **Detections of nonconvulsive seizures** :
  - A history of epilepsy
  - Fluctuating level of consciousness
  - Acute brain injury
  - Recent convulsive status epilepticus
  - Stereotyped activity such as paroxysmal movements, nystagmus, twitching, jerking, hippus, autonomic variability

cEEG indications

- **Monitoring of ongoing therapy**
  - Induced coma for elevated intracranial pressure or refractory status epilepticus
  - Assessing level of sedation
- **Ischemia detection**
  - Vasospasm in subarachnoid hemorrhage
  - Cerebral ischemia in others patients at high risk for stroke
- **Prognosis**
  - Following cardiac arrest
  - Following acute brain injury

Friedma, Claassen, Hirsch. Anesth Analg 2009

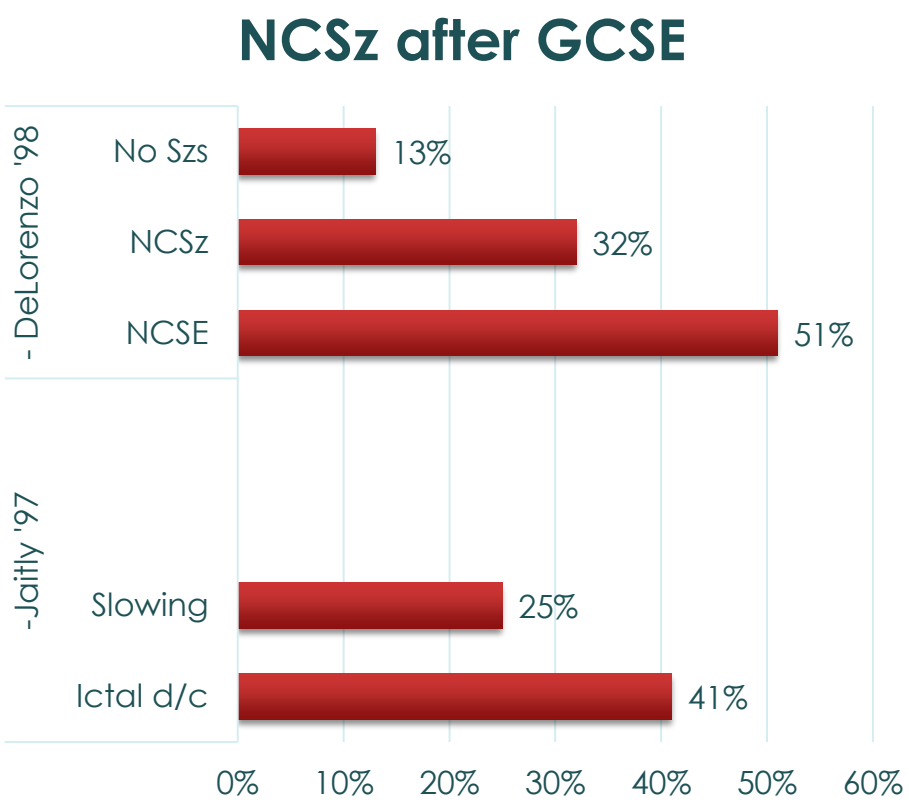
Consensus Statement on Continuous EEG in Critically Ill Adults and Children, Part I: Indications

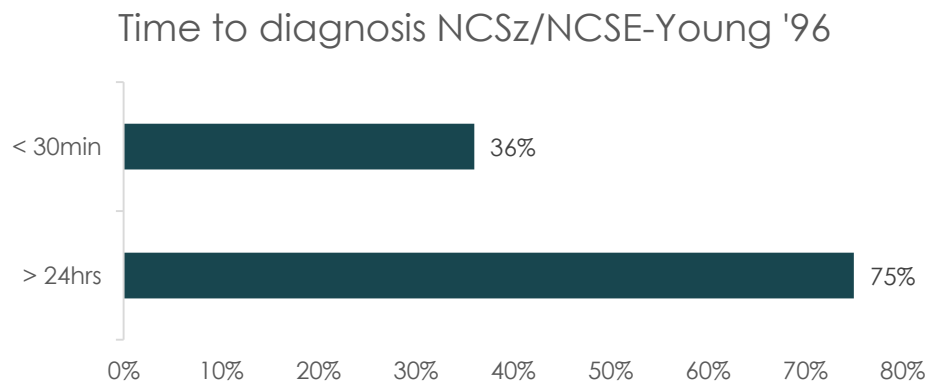
Impact of cEEG monitoring on patient management

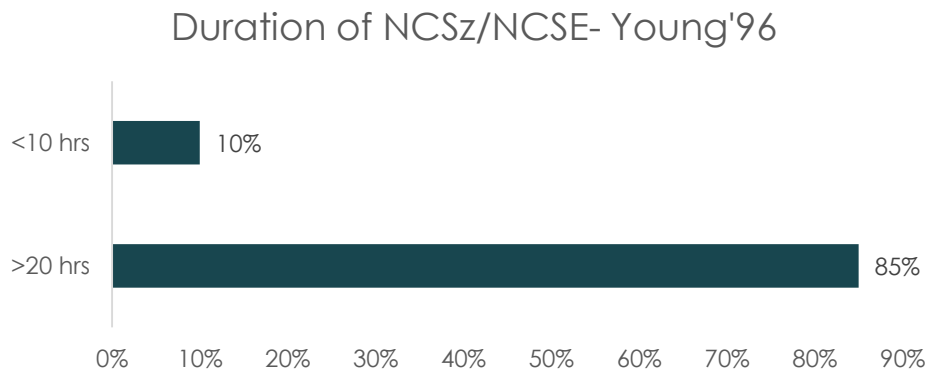
- 300 cEEG reviewed - 28% with seizures
  - 52% had a change in AED regimen
  - 13,7% : drug initiation
  - 33% : drug modification
  - 5%: drug discontinuation

Kibride et al. Arch. Neurol.2009

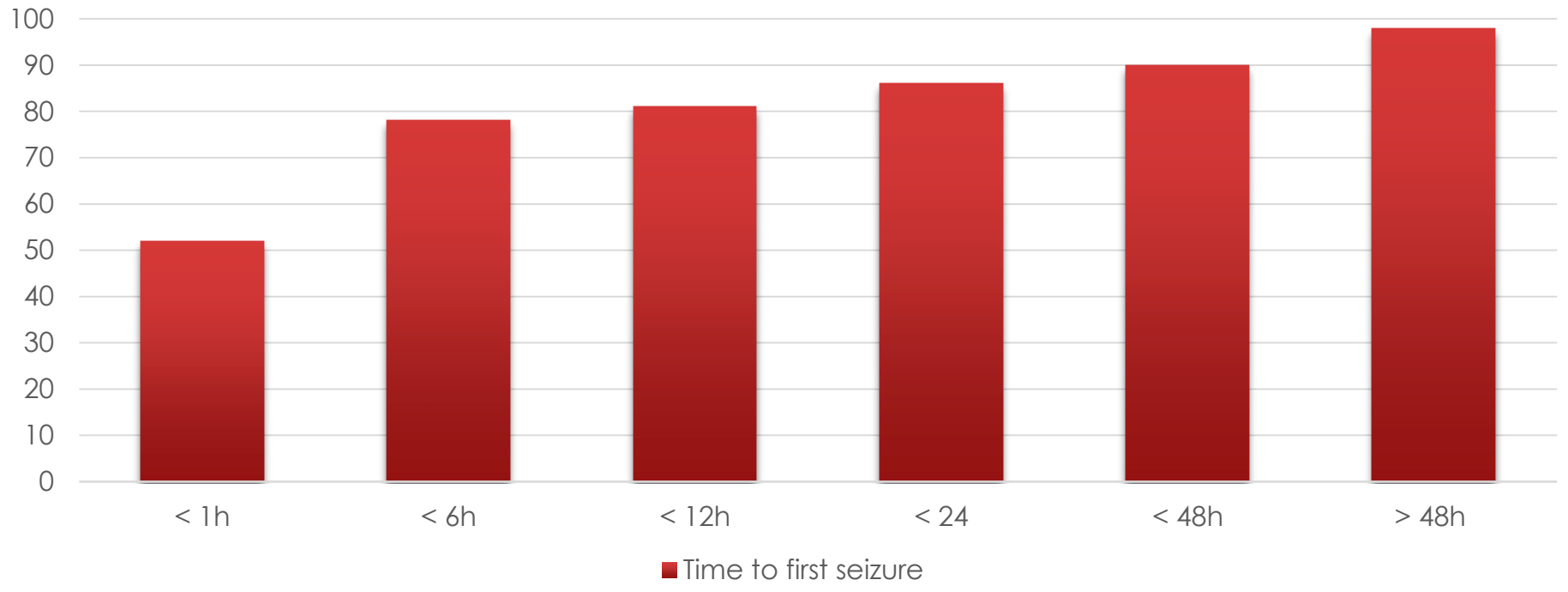
The presence of NCSz/NCSE is an independent predictor of mortality







Detection of NCSz increase with duration of cEEG monitoring



At least 24h; 48h if coma or lateralized periodic discharges

Systemic alterations and brain metabolism in status epilepticus

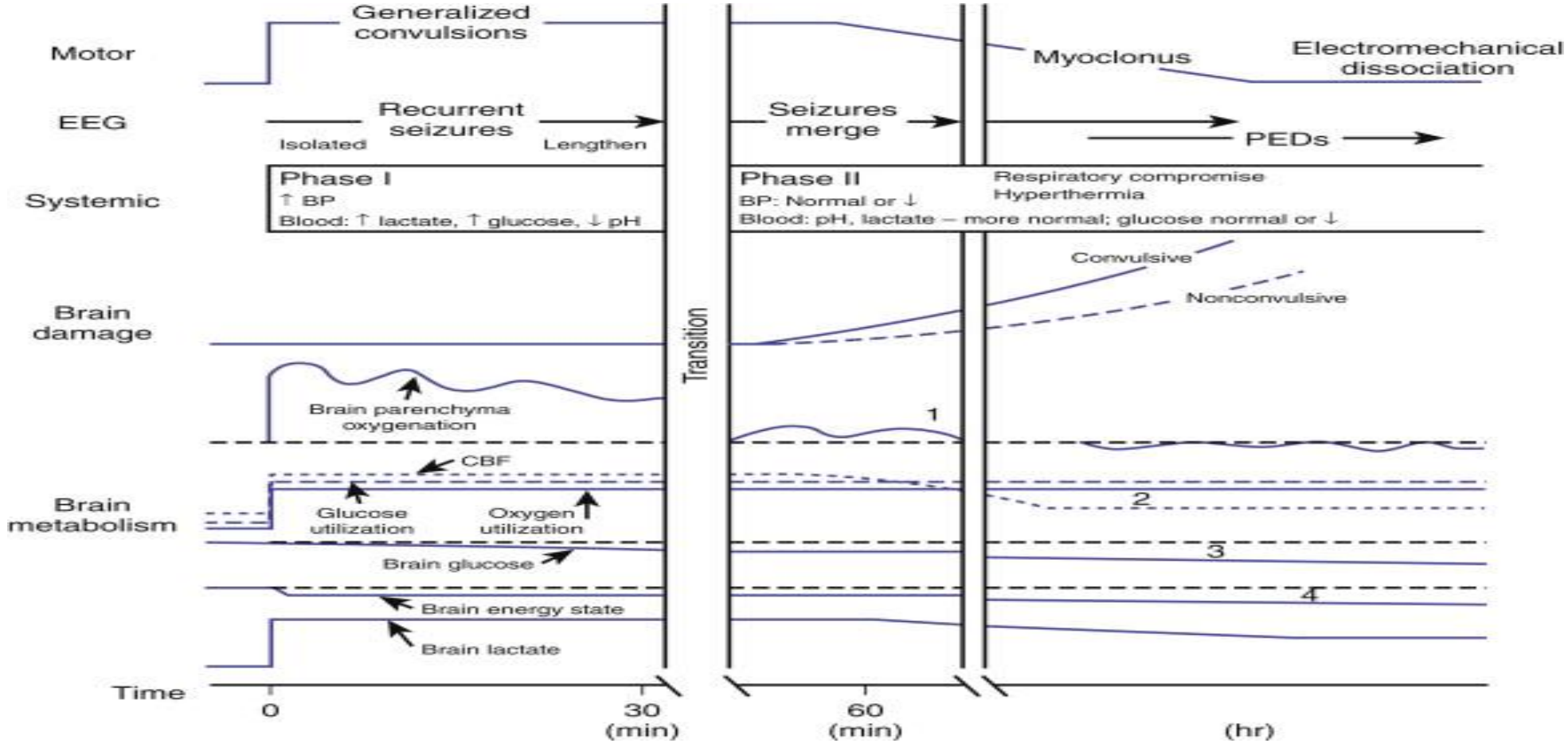


Figure from Lothman E. The biochemical basis and pathophysiology of status epilepticus. Neurology 1990

Outcome at the refractory and super-refractory stages of status epilepticus

Outcome	***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%)

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
Shorvon et al . Brain 2012

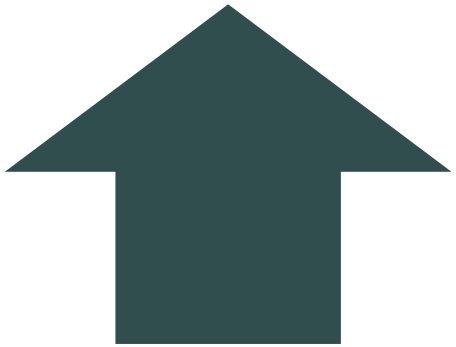
The goal of treatment in patients with epileptic seizures

- To achieve a seizure-free status without adverse effects.

- Accomplished in more than 60% of patients who require treatment with anticonvulsants.

The risk of recurrence

- The patient is not treated



15% the risk of recurrence if:
1 generalized tonic-clonic seizure,
a normal EEG,
a normal brain MRI,
no evidence of focal onset

- The patient need to be treat

80 % risk of recurence if:
1 generalized tonic-clonic seizure,
abnormal EEG,
abnormal brain MRI,
evidence of focal onset

Outcome at the refractory and super-refractory stages of status epilepticus

- Successful therapy: SE is completely controlled by the therapy, without breakthrough or withdrawal seizures, or discontinuation due to side-effects, or death during the therapy.
- Initial failure: the therapy failed to control status epilepticus at all.
- Breakthrough seizures: recurrence SE during the treatment, despite initial control, resulting in the need for a change of AED

"The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy" Simon Shorvon, Monica Ferlisi

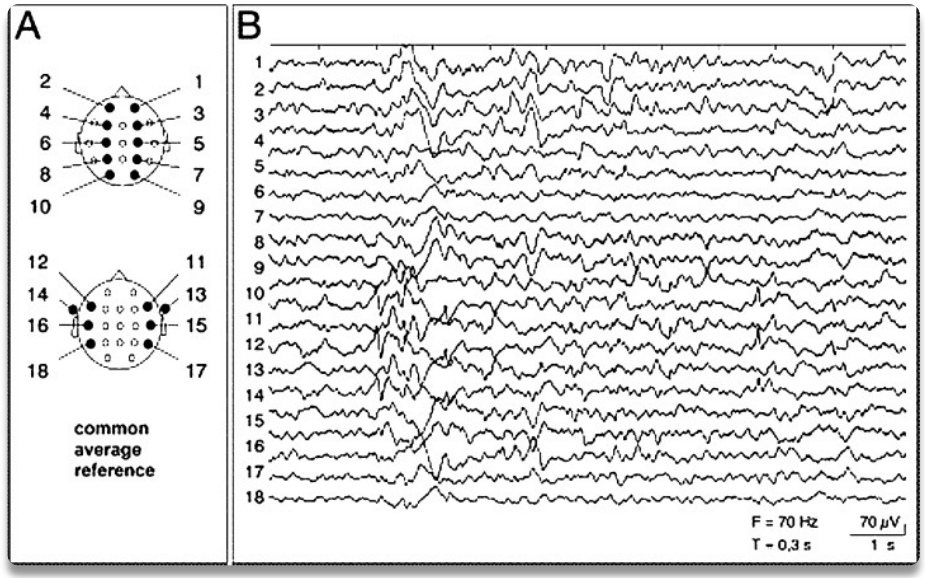
Outcome at the refractory and super-refractory stages of status epilepticus

- Withdrawal seizures: recurrence of SE during or immediately after the tapering or withdrawal of the therapy, resulting in the need for a change of AED.
- Intolerable side-effects: the therapy resulted in side-effects necessitating alternative therapy.
- Death during the course of the treatment: some of these deaths will be due to the underlying cause

"The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy"
Simon Shorvon, Monica Ferlisi

Failure of treatment in SRSE

- Target dose to low
- Dose limitation caused by side effects (usually hypotension or cardio-respiratory depression, hepatic failure)



Conclusions on treatment failure

- The lack of randomized or controlled studies
- The small number of individuals treated: many treatments discussed have a total published outcome data in less than 40 patients, and most in less than 10 patients
- Co-medication and changing doses of co-medication
- Delay in responses.
- Some therapies are widely used and yet the published literature is extremely small
- Refractory status epilepticus is heterogeneous and its ultimate prognosis depends on factors other than treatment such as age and etiology

Neligan and Sharvan 2010,2011

Treatment of super-refractory SE
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

Treatment of super-refractory SE
The published literature on treatment outcomes

Therapy	Number of published papers reporting outcome data	Number of published cases in which outcome data are provided
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
Levitiracetam	8	35
Lacosamide	2	10

Suggested approach to antiepileptic drug therapy in refractory status epilepticus

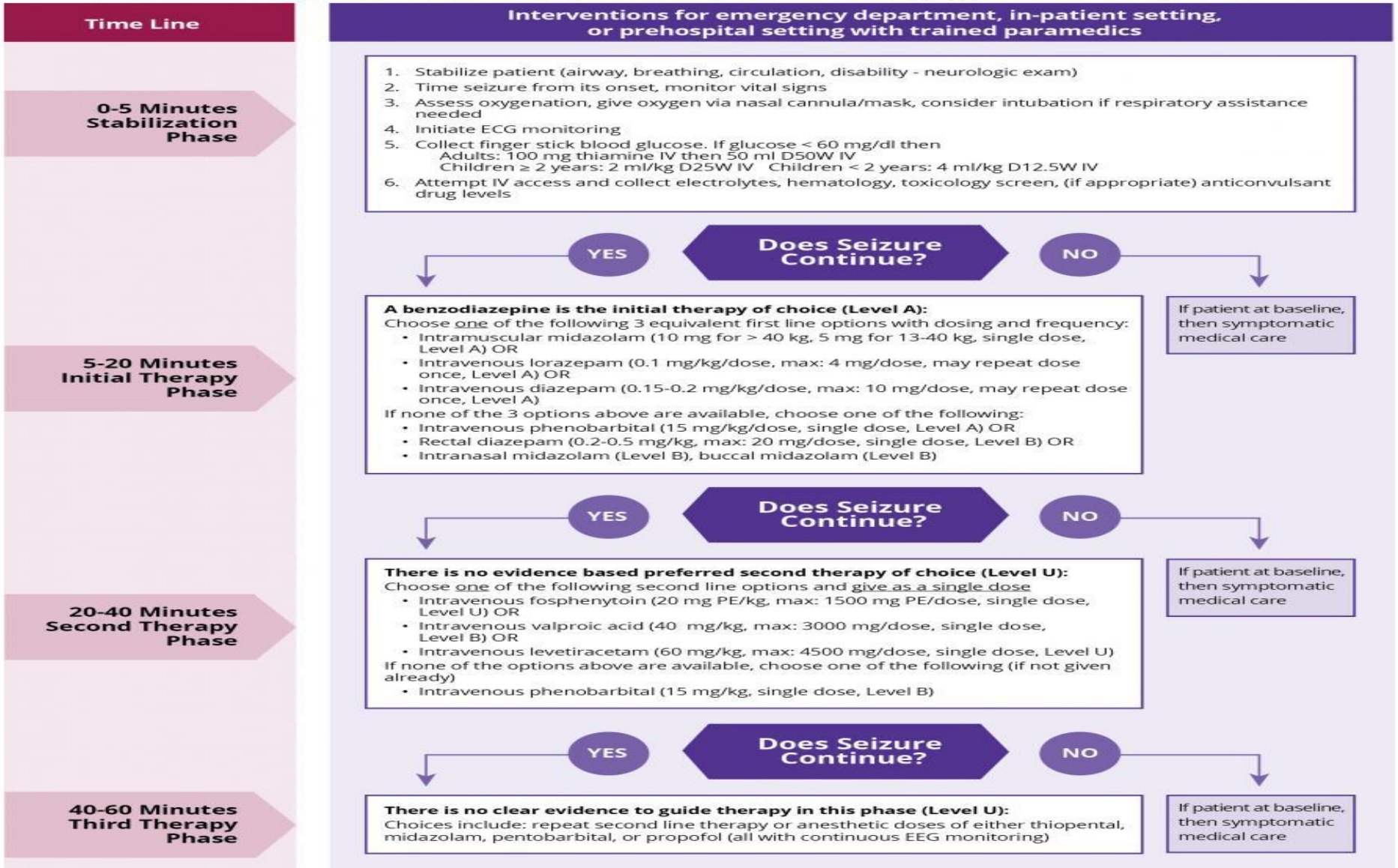
Choice of drug regimen depends on clinical context
Polytherapy with two antiepileptic drugs
High-dose regimens
Avoid frequent switching
Favour antiepileptic drugs with low interaction potential
Favour antiepileptic drugs with predictable kinetic properties
Favour antiepileptic drugs without renal or hepatic toxicity
Avoid GABAergic antiepileptic drugs

The treatment of convulsive status epilepticus

- **Stabilization phase** (0-5 minutes of seizure activity)
- **Initial therapy phase** (5-20 minutes of seizure activity)
- **Second therapy phase** (20-40 minutes of seizure activity)
- **Third therapy phase** (40+minutes of seizure activity)

Proposed Algorithm for Convulsive Status Epilepticus

From "Treatment of Convulsive Status Epilepticus in Children and Adults," *Epilepsy Currents* 16.1 - Jan/Feb 2016



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Disclaimer: This clinical algorithm/guideline is designed to assist clinicians by providing an analytic framework for evaluating and treating patients with status epilepticus. It is not intended to establish a community standard of care, replace a clinician's medical judgment, or establish a protocol for all patients. The clinical conditions contemplated by this algorithm/guideline will not fit or work with all patients. Approaches not covered in this algorithm/guideline may be appropriate.

Conclusions : cEEG monitoring

- Mandatory for efficient management
- Useful, safe, cost effective
- Should be used more widely
  - Need of machines
  - Need of neurologists
  - Need of EEG technicians
  - Need of collaboration between ICU and neurophysiologists

Conclusions

- Status epilepticus is a life threating condition, requiring immediate treatment
- Unfortunately few evidence-base data
- Adapt the treatment to the patient's condition, especially in NCSE and in patients with comorbidities

Thank you!

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