Treatment of Status Epilepticus

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Outline

- Definition of status epilepticus
- Classification of status epilepticus
- Treatment of status epilepticus
- Treatment of NCSE
- Treat underlying etiology
- Treating seizure-related complications
- Outcome

Definition of status epilepticus ILAE 2015

- Condition resulting either from failure of mechanisms responsible for seizure termination or from initiation of mechanisms which lead to abnormally prolonged seizures (after time point t1)

- Condition that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on type and duration of seizures

Trinka E. et al. Epilepsia. 2015. 56(10):1515–23.

Operational dimension with t1indicating time that emergency treatment should be started and t2 indicating the time at which long term consequences may be expected

Type of SE	Time (t1)	Time (t2)
Tonic-clonic	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status	10-15 min	unknown

Trinka E et al, Epilepsia 2015. 56(10):1515–23.

Classification of epilepsy

- Semiology
- Etiology
- EEG correlates
- Age

Classification of SE: semiology

Table 2. Axis 1: Classification of status epilepticus (SE)

(A) With prominent motor symptoms
A.1 Convulsive SE (CSE, synonym: tonic–clonic SE)
- A.1.a. Generalized convulsive
- A.1.b. Focal onset evolving into bilateral convulsive SE
- A.1.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.1 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

Trinka E et al, Epilepsia 2015. 56(10):1515–23.

Etiology of status epilepticus

- Known (i.e., symptomatic)
  - Acute (stroke, intoxication, malaria, encephalitis)
  - Remote (posttraumatic, postencephalitis, poststroke)
  - Progressive (brain tumor, Lafora's disease, PME, dementia)
  - SE in defined electroclinical syndromes
- Unknown (i.e., cryptogenic)

Trinka E et al, Epilepsia 2015. 56(10):1515–23.

EEG correlate

- No evidence-based EEG criteria for SE
- Propose following terminology to describe EEG patterns in SE
  - Location
  - Name of pattern
  - Morphology
  - Time-related features
  - Modulation
  - Effect of intervention (medication) on EEG

Age

Neonatal (0-30 days)

Infancy (1 mo-2 yrs)

Childhood (> 2-12 yrs)

Adolescence and adulthood (> 12-59 yrs)

Elderly (≥ 60 yrs)

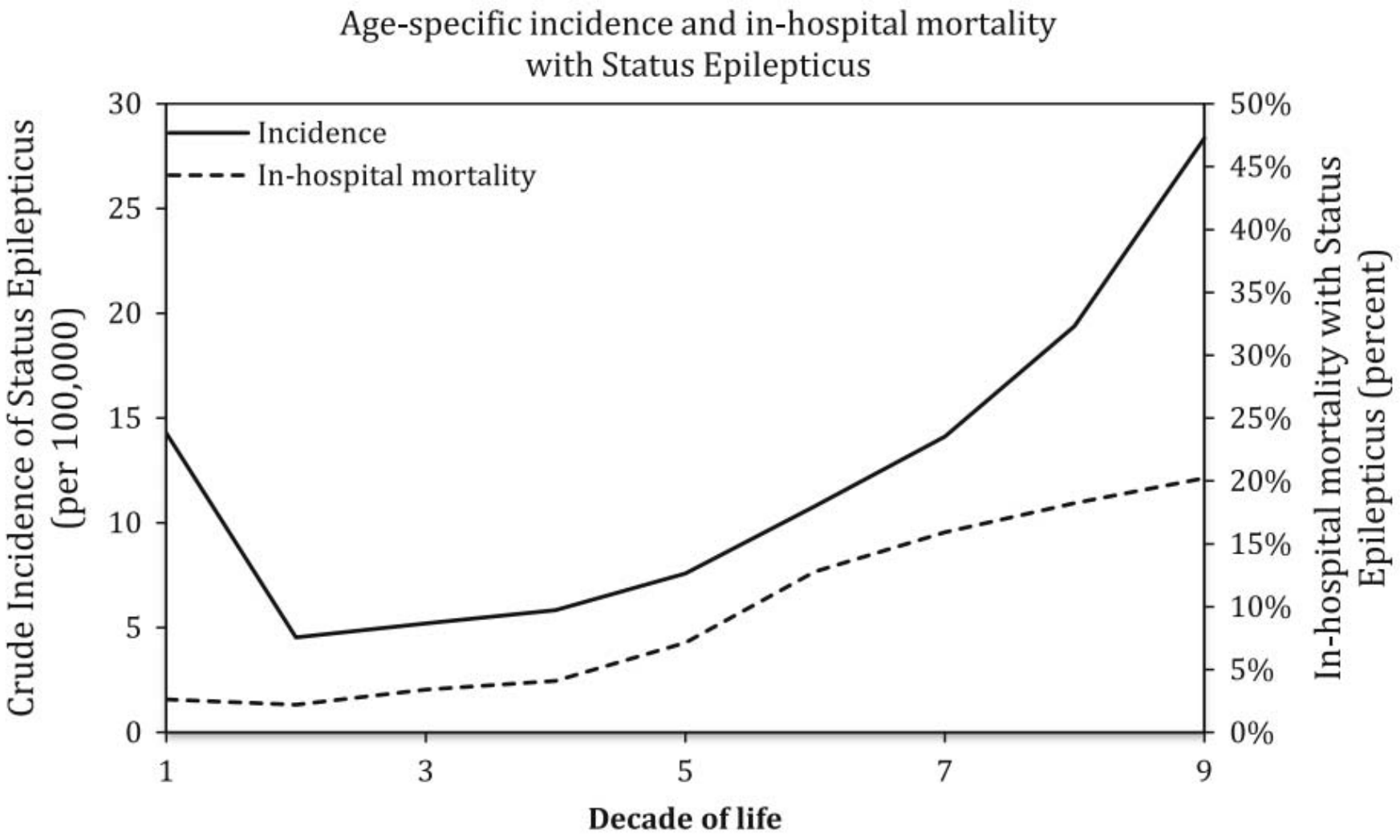
Table 5. SE in selected electroclinical syndromes according to age

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
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 1–3)
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.

Epidemiology

- Incidence of SE reportedly ranges from 10-40 per 100,000 in various databases
- Peak incidence occurs at < 10 year (14.3 per 100,000) and > 50 year (28.4 per 100,000)
- Highest mortality in elderly population
- Increasing number of patients with SE over past 10 year
  - Increased detection of NCSE in ICU
  - Aging of population
  - Less rigid definition of SE



Dham BS et al. Neurocrit Care, 2014. 20:476–483.

Staging of status epilepticus

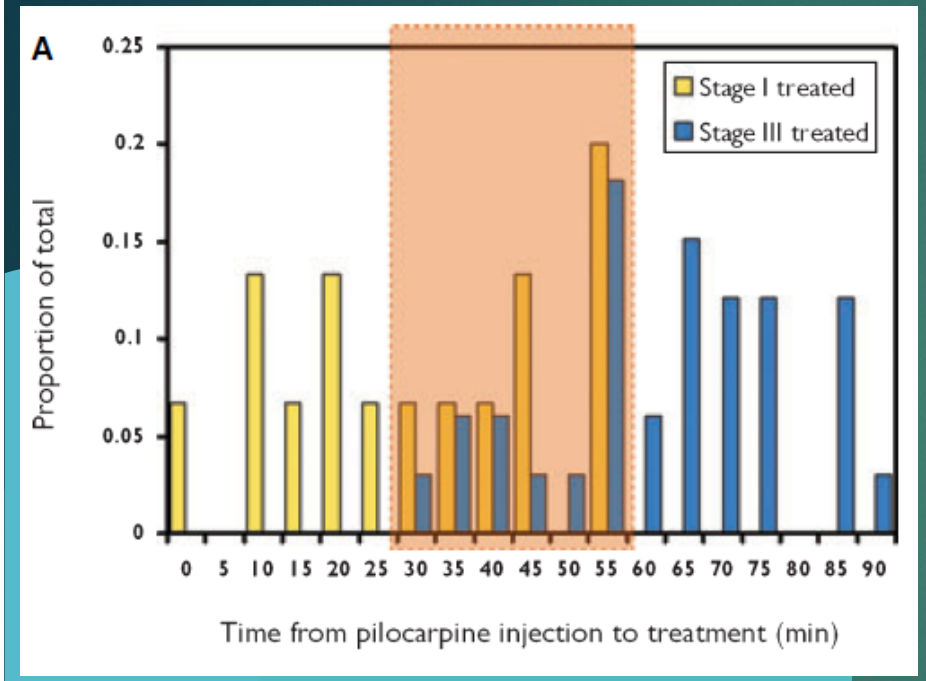
- Premonitory
  - confusion, myoclonus, increased seizure frequency
- Incipient 0-5 min
- Early: 5-30 min
- Transition: from early to established
- Established (late): 30-60 min
- Refractory SE: after 60 min
- Postictal

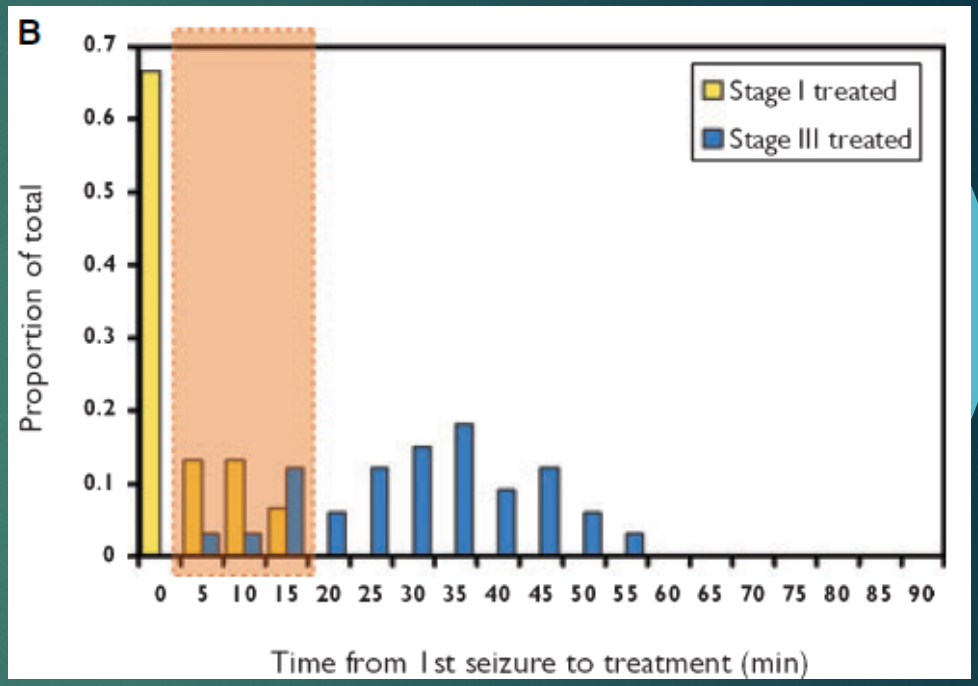
5 EEG stages of SE during course of GCSE

A. Discrete seizures w interictal slow
B. Waxing and waning of ictal discharge
C. Continuous ictal activity
D. Continuous ictal activity punctuated by flat period
E. Periodic discharges on 'flat' BG

Treiman DM et al. Epilepsy Res. 1990;5(1):49-60. Pender RA et al. Epilepsia, 2012;53(11):e193–e195.

EEG stages predict treatment response in experimental SE





Comparison of time to stage I and stage III treatment
Shaded boxes indicate time periods in which stage I and stage III onsets overlap
In this overlap, all treatments of stage I were successful, whereas those of stage III were not successful, despite sharing similar SE durations

Wang NC. et al. Epilepsia, 2009;50(4):949–52.

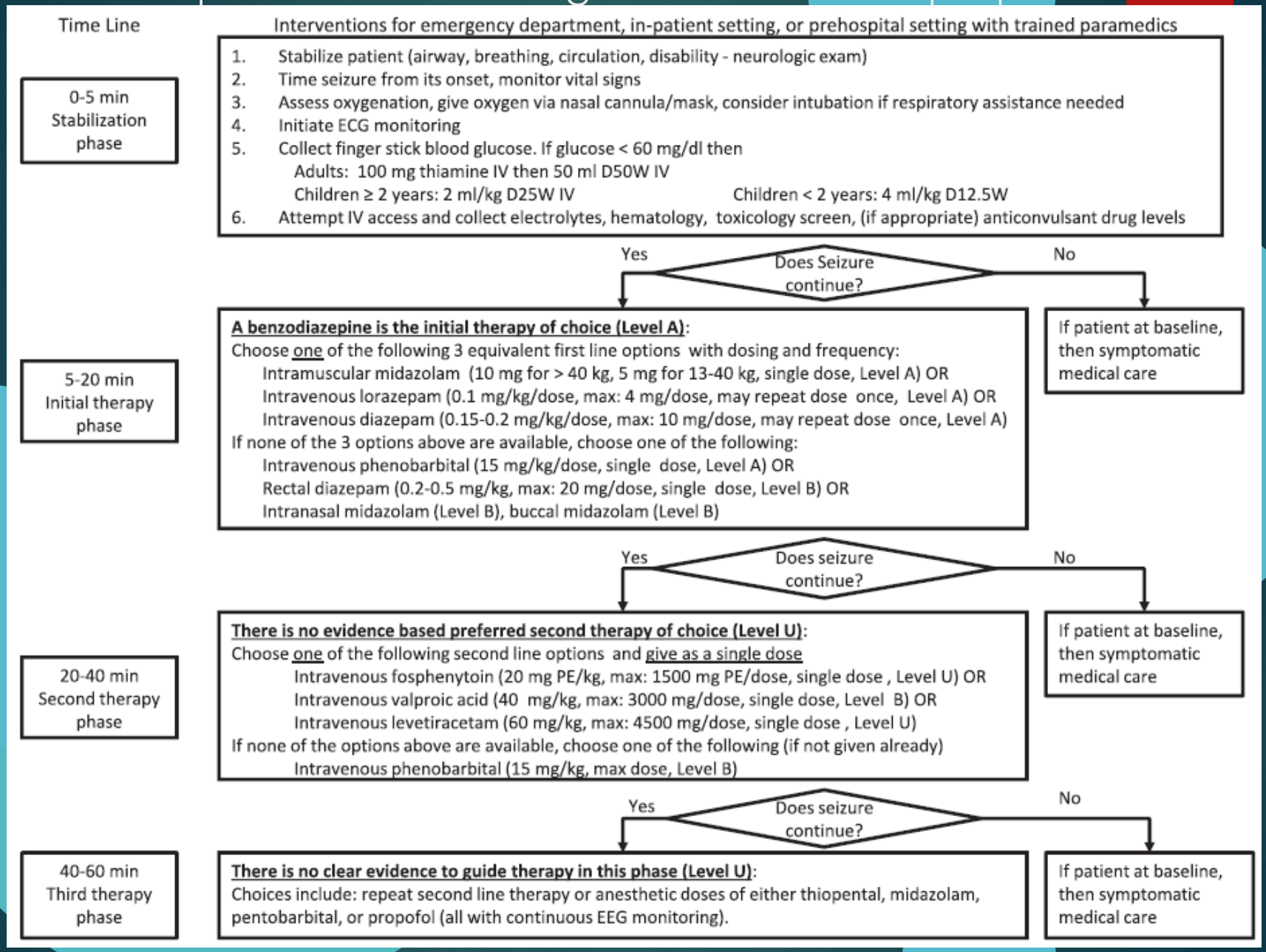
Treatment of status epilepticus

- Emphasize time to treatment rather than a certain sequence of medications
- Treat underlying etiology
- Treating seizure-related complications and preventing seizure recurrence

Treatment

- Prehospital: benzodiazepine
- Emergency department, in patient: second line agent
- ICU
  - 0.1 mg/kg lorazepam followed by third-line agent
  - Second line AEDs → to prevent return of seizures when weaning off anesthesia

Proposed treatment algorithm for status epilepticus



Glauser T. et al., Epilepsy Curr. 2016;16(1)48–61.

Initial treatment: stabilization, 0-5 min

- ABC
- Time seizure, vital sign
- Assess oxygenation
- ECG monitoring
- Finger stick glucose
- IV access, electrolyte, hematology, toxic screen, AEDs level

Initial treatment: AEDs

- Treatment of early SE relies on use of benzodiazepines
  - Lorazepam, diazepam, midazolam, clonazepam

- Benzodiazepine
  - Enhancing inhibitory neurotransmission through increasing channel opening frequency of GABA-A receptors, subsequent increased chloride conductance and neuronal hyperpolarization

Prehospital treatment

- IM midazolam 0.2 mg/kg
- IV lorazepam 0.1 mg/kg
- IV diazepam 0.15-0.2 mg/kg
  - Less optimal pharmacokinetic profile
  - Alternate to both IV lorazepam and IM midazolam
- Intranasal midazolam 0.2 mg/kg
- Buccal midazolam 0.5 mg/kg
  - Emerged as first-line non-IV drug in children with similar efficacy
- Rectal diazepam 0.2-0.5 mg/kg

Lorazepam

- Less lipid-soluble and not undergo a rapid redistribution into peripheral tissues → longer duration of action → higher seizure control
- No statistically significant difference between these 2 drugs in respiratory failure/depression

Diazepam

- Highly lipophilic, rapidly passes brain–blood barrier
- Subsequently redistributed into peripheral tissues with only 3–5% of total dose remaining in brain
- Rapid, but transient antiepileptic effect
- Route
  - IV
  - per rectum (PR)
  - IM: slow with a long time to peak serum concentration of 1 hr
- IV and PR → higher efficacy for seizure cessation and lower risk of adverse effects compared to placebo

First line AEDs data, class I study

- 1998, US Department of Veterans Affairs Cooperative Study RCT
  - 570 patients, lorazepam, DZP followed by PHT, PHT, PB
  - IV lorazepam 0.1 mg/kg, 2 mg/min was superior as compared to IV phenytoin as first-line therapy in aborting SE
    - 64.9% aborted with IV lorazepam
    - 43.5% with IV phenytoin
- 2001 study: 2mg IV lorazepam, 5 mg IV DZP, placebo
  - Lorazepam and DZP superior to placebo

First line AEDs data, class I study

- 2012 Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) data → better efficacy for IM midazolam than for standard IV lorazepam because of speed and ease of administration
  - IM midazolam (10 mg) stopped seizures in 73.4%
  - IV lorazepam (4 mg) stopped seizures in 63.4%
- Secondary analysis of this study conducted only in patients < 18 years found no difference between IM midazolam and IV lorazepam
  - Relatively few children study

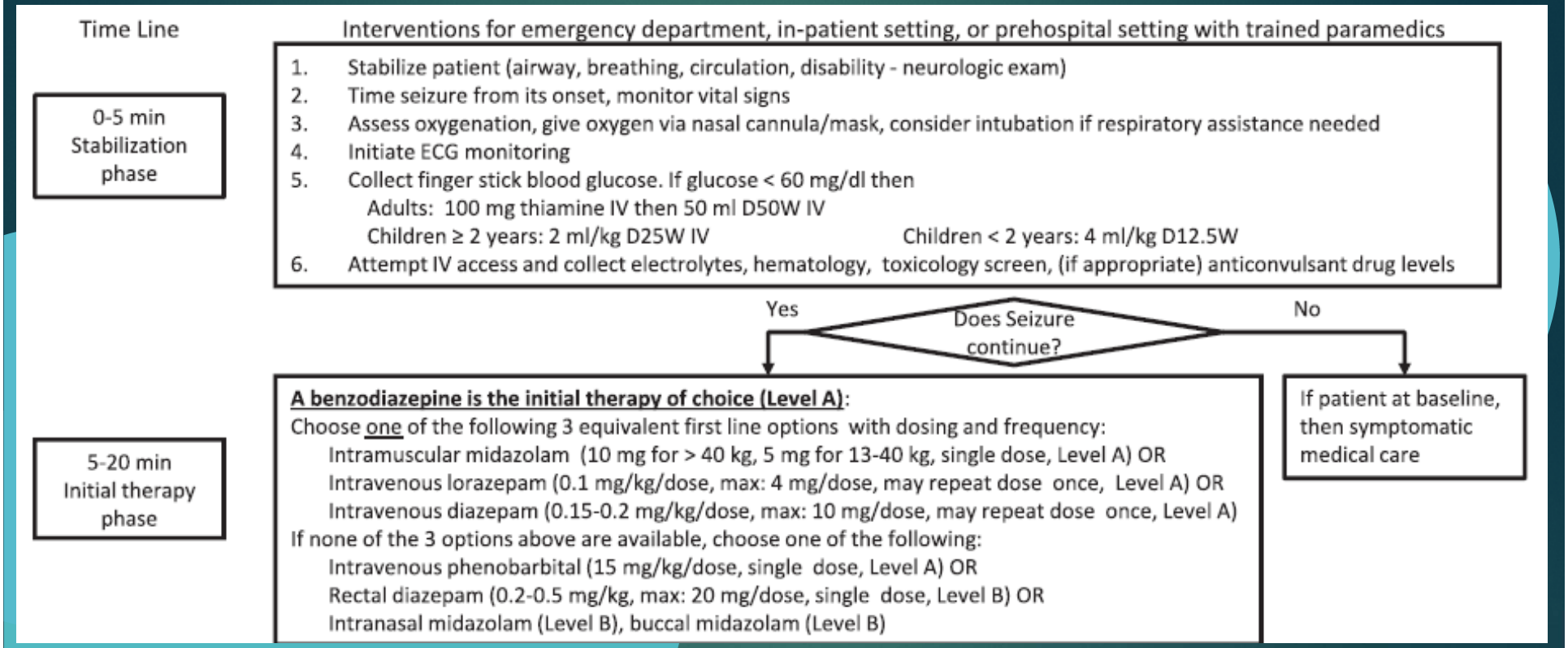
Conclusion: Adult

- IM midazolam, IV lorazepam, IV diazepam (with or without phenytoin), and IV PB are established as efficacious at stopping seizures lasting at least 5 min (level A)
- No significant difference in effectiveness between lorazepam and diazepam (level A)
- IM midazolam has superior effectiveness compared with IV lorazepam with convulsive SE without established IV access (level A)
- IV lorazepam is more effective than IV PHT in stopping seizures lasting at least 10 min (level A)

Conclusion: Children

- IV lorazepam and IV diazepam are established as efficacious at stopping seizures lasting at least 5 min(level A)
- Rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective at stopping seizures lasting at least 5 min (level B)
- Insufficient data exist in children about efficacy of intranasal lorazepam, sublingual lorazepam, rectal lorazepam, valproic acid, levetiracetam, phenobarbital, and phenytoin as initial therapy (level U)

Summary: Initial treatment



Glauser T. et al, Epilepsy Curr. 2016;16(1)48–61.

Emergency Department/ Inpatient Treatment

- IV access
- Full 0.1 mg/kg of lorazepam can be administered at 2 mg/min first-line therapy to best terminate SE
- Second-line therapy with IV AEDs

Second line AEDs

- Phenytoin/fosphenytoin
- Phenobarbital
- Valproate
- Levetiracetam
- Lacosamide

Phenytoin

- High lipid soluble, water insoluble
- Prepared in an alkaline polypropylene solvent with a pH of ~12 to prevent precipitation of substance → local irritation and thrombophlebitis at infusion site
- 18–20 mg/kg in younger adult, 15 mg/kg in elderly (>65 yr)
- Maximum infusion rate of 50 mg/minute
- Risk of cardiac arrhythmias, infusion site reactions, hypotension, liver induction
- Less sedating side effect profile compared to PB

Fosphenytoin

- Highly water soluble, phenytoin prodrug
- Completely absorbed (bioavailability 100%)
- Dosages of fosphenytoin are expressed as PHT equivalents (PE), IV rates of 100–150 mg PE/min → bioequivalent to 50 mg/min PHT
- Advantages
  - Availability for IM injection
  - Rapid than IV administration
  - Lower risk of adverse effects at injection sites
- Disadvantages: High costs

Phenobarbital

- Efficacy: 73.6% (95% CI: 58.3–84.8%)
- Disadvantages
  - Respiratory depression, arterial hypotension, deep sedation, tolerance effects, drug interactions

Valproate

- Broad spectrum of efficacy against all seizure types
- Well tolerated even in critically ill patients, in high doses and fast infusion rates
- Non-sedating
- Overall response rate of 70.9%
- Effective dose 15–45 mg/kg in bolus (6–10 mg/kg/minute) followed by 1–3 mg/kg/h infusion
- Low incidence of adverse events overall (<10%)
  - Dizziness, thrombocytopenia, mild hypotension
  - Acute encephalopathy
  - Liver failure
  - Pancreatitis

Levetiracetam

- Broad spectrum AED with a low potential of interactions, due to minimal hepatic metabolism and low plasma protein binding (<10%)
- Very low rate of adverse effects
  - Most often somnolence, sedation, rarely agitation, thrombocytopenia
- Efficacy ranged from 44-94%

Lacosamide

- Enhancing slow inactivation of voltage-gated sodium channels
- Current evidence on IV use in acute seizures and SE is restricted to (retrospective) case reports and case series
- Most commonly loading dose 200-400 mg over 5-10 min, followed by daily dose of 200–400 mg leading to abrogation of seizures in 56%
- Adverse events reported in 25%
  - Mild sedation (25 patients), angioedema (one), allergic skin reactions (two), hypotension (four), pruritus (one), third-degree AV block (one), paroxysmal asystole
- To date, there is not enough evidence to recommend lacosamide routinely in treatment of established SE

Second line AEDs

- No RCT has specifically evaluated efficacy of different sequences of IV AEDs
- Medication choices are based on comorbid conditions, side effects, and opinions

Second line AEDs data

- Available evidence suggests some degree of efficacy for IV valproate, levetiracetam, lacosamide
- A meta-analysis 8 studies, 294 episodes of SE
  - Higher rates of seizure cessation with VPA and PB > LEV, PHT
    - VPA 75.7% (95% CI 63.7–84.8)
    - PB 73.6%, (95% CI 58.3–84.8)
    - LEV 68.5% (95% CI 56.2–78.7)
    - Phenytoin 50.2% (95% CI 34.2–66.1)
- Favorable tolerability profile of LEV, VPA

Yasiry Z, Shorvon SD. Seizure. 2014;23(3):167–174.

Second line AEDs data

- In adult
  - IV VPA has similar efficacy to IV PHT or continuous IV diazepam (level C)
  - Insufficient data exist in adults about efficacy of LEV as either initial or second therapy (level U)
- In children
  - IV VPA has similar efficacy but better tolerability than IV PB (level B)
  - Insufficient data exist in children regarding efficacy of phenytoin or LEV (level U)

Summary: Second line

There is no evidence based preferred second therapy of choice (Level U):

Choose one of the following second line options and give as a single dose

- Intravenous fosphenytoin (20 mg PE/kg, max: 1500 mg PE/dose, single dose , Level U) OR
- Intravenous valproic acid (40 mg/kg, max: 3000 mg/dose, single dose, Level B) OR
- Intravenous levetiracetam (60 mg/kg, max: 4500 mg/dose, single dose , Level U)

If none of the options above are available, choose one of the following (if not given already)

- Intravenous phenobarbital (15 mg/kg, max dose, Level B)

Glauser T. et al., Epilepsy Curr. 2016;16(1)48–61.

Third line therapy for RSE

- No clear evidence to guide therapy
- AEDs should be initiated in a time-dependent fashion
- SE treatment becomes less effective as longer episode of SE lasts
- 0.1 mg/kg lorazepam followed immediately by third-line agent

Refractory SE

- NCS tend to last much longer than convulsive seizures are more difficult to treat
  - NCS has 15% response to first medication
  - GCSE has 55% response rate overall to first medication and 60-70% when medication given in prehospital setting
- Continuous EEG
  - Titrate medication to burst suppression
  - Monitor for seizure activity

Refractory SE: medication

- Continuous midazolam infusion are most widely used (59%) followed by propofol (32%) and barbiturates (8%)
- Choices are largely based on availability and comorbid conditions
- Typically, weaned off third-line agent after 24-48 hrs

Midazolam

- Often used as the initial choice for a third-line agent
- Less impact on blood pressure and often effective
- Less effective with prolonged use and requires an increase in dose for same effect because of degradation of GABA receptors during SE
- Often weaned off midazolam after 48 to 72 hours or transitioned to pentobarbital

Propofol

- Exact mechanisms are unknown
- Experimental evidence suggests that it acts as an N-methyl-D-aspartate (NMDA)antagonist
- Water insoluble fast acting anesthetic agent with antiepileptic properties
- Shorter duration of action, much lower tendency to accumulate in body than barbiturates
- Often available in ICU

Propofol: side effect

- Lower blood pressure
- Propofol infusion syndrome, estimated risk of 1%
  - Characterized by
    - Congestive heart failure
    - Lactic acidosis
    - Hypertriglyceridemia
    - Rhabdomyolysis
    - Renal failure
  - Risk factors
    - High doses > 4 mg/kg/hour and long durations of administration > 48 hr
    - Carbohydrate depletion
    - Inborn errors of fatty acid oxidation
    - Severe illness
    - Administration of catecholamine and glucocorticosteroid

Thiopenthal, pentobarbital

- Barbiturates acting as γ-aminobutyric acid-A agonists with enhanced inhibitory neurotransmission and antiepileptic action
- Long half-life and takes a number of hours to reach a therapeutic level
- Prolonged duration of action, mainly due to their accumulation in body → long recovery time
- Very reliable in ability to achieve burst suppression

Thiopenthal, pentobarbital Adverse effect

- Hypotension and cardiorespiratory depression
- Profound suppression of immune system
- Increased morbidity because of prolonged duration of pentobarbital-associated comas
  - Typically last at least a week, increasing risk for DVT/pulmonary embolism, myocardial depression/ reduced cardiac output, ileus complicating nutrition and any oral medication use

Inhalational anesthetics

- Isoflurane, desflurane
- Enhance $GABA_A$ activity, inhibit NMDA receptor
- Adverse effect
  - Hypotension
  - Infection, paralytic ileus, DVT
  - Questionable cognitive dysfunction with prolonged use

Super-refractory SE

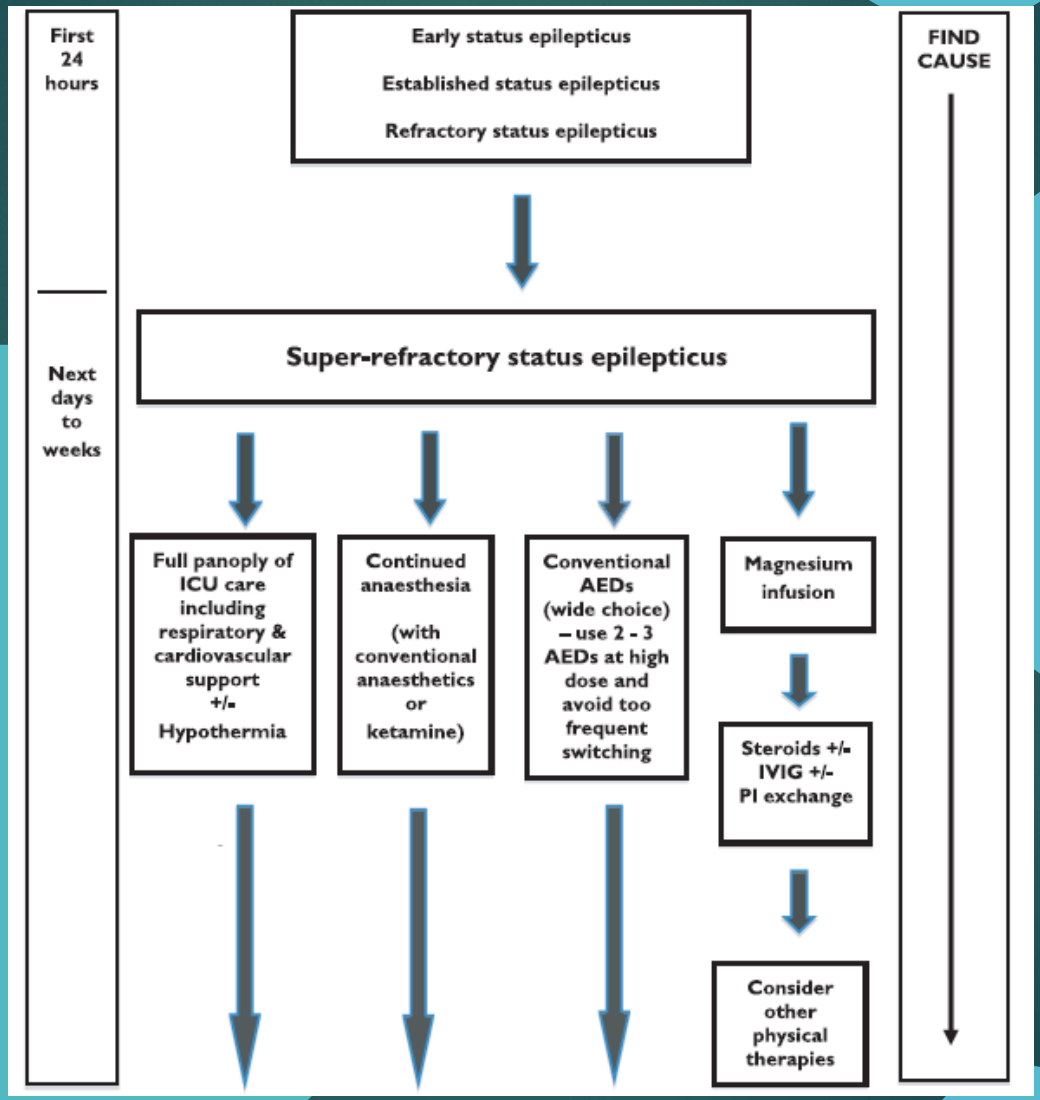
- Ongoing seizure activity or recurrence of seizure 24 hours or more after initiation of anesthetic therapy, including seizure recurrence on reduction or withdrawal of anesthesia

- No RCTs for treatment of super-refractory SE exist

Super-refractory SE

- Pharmacological treatment
  - Ketamine
  - AEDs
  - Magnesium
  - Lidocaine
  - Anti-inflammatory drug and steroid
- Non-pharmacological option
  - Ketogenic diet
  - Hypothermia
  - Electroconvlusive therapy
  - Transcranial magnetic stimulation
  - Vagus nerve stimulator

Treatment of super-refractory SE



Shorvon S. Epilepsia 2011;52 Suppl 8:53-6.

AEDs

- Topiramate (93 cases; 5 mg/kg in children, 500–1000 mg daily dose in adults)
- Lacosamide (71 cases; 200 to 400 mg daily dose)
- Levetiracetam (35 cases; 15-70 mg/kg in children, 30-70 mg/kg in adults)
- Pregabalin (23 cases; mean dose 350 mg)
- Perampanel (22 cases; initial median 4 mg were titrated up to median 12 mg)

Choices AEDs

- Patient´s risk factors
- Pharmacokinetic and pharmacodynamic of drug
- Avoiding agents with high drug–drug interaction
- Oral administration
  - Reduced absorption and gastric emptying in critically ill patient

Ketamine

- Strong antagonistic effect on N-methyl-D-aspartate (NMDA) – glutamate receptor and an additional neuroprotective potential
- Half-life of 2-3 hours
- Extensively metabolized by hepatic cytochrome P450 pathway to active metabolite, norketamine
- Overall success rate was 63%
- Hemodynamic advantages
- Adverse effects: tachycardia, acute elevation BP, increased ICP

Magnesium sulfate

- Currently used as drug of choice in treating seizures occurring in eclampsia
- Little evidence for efficacy in treatment of RSE in absence of hypomagnesemia or eclampsia
- Blocking glutamatergic N-methyl-D-aspartate (NMDA) receptor in resting state

Lidocaine

- Local anesthetic agent and a cardiac depressant used as an antiarrhythmic agent
- Effect as sodium channel blockers in neuronal membranes
- No single RCTs conducted to evaluate efficacy and safety of lidocaine in patients with SE

Anti-inflammatory drugs and steroids

- Evidence supporting use of steroids, immunoglobuline, and plasma exchange in super-refractory SE without a proven or suspected underlying immunological disorder is extremely scarce

- Potential side effects: immunosuppression, severe infections and metabolic disturbances

Neuroactive steroid: allopregnanolone

- Positive allosteric modulator of synaptic and extrasynaptic GABA-A receptors
- Efficacy of allopregnanolon in cessation of established SE observed in animal models
- In humans, only one case report of two pediatric patients with super-refractory SE with cessation of seizure activity
- Currently randomized, double-blind, placebo- controlled trial with neurosteroid SAGE-547 administered as a continuous intravenous infusion in Super-Refractory Status Epilepticus is recruiting since June 2015

General dosing recommendation for SE

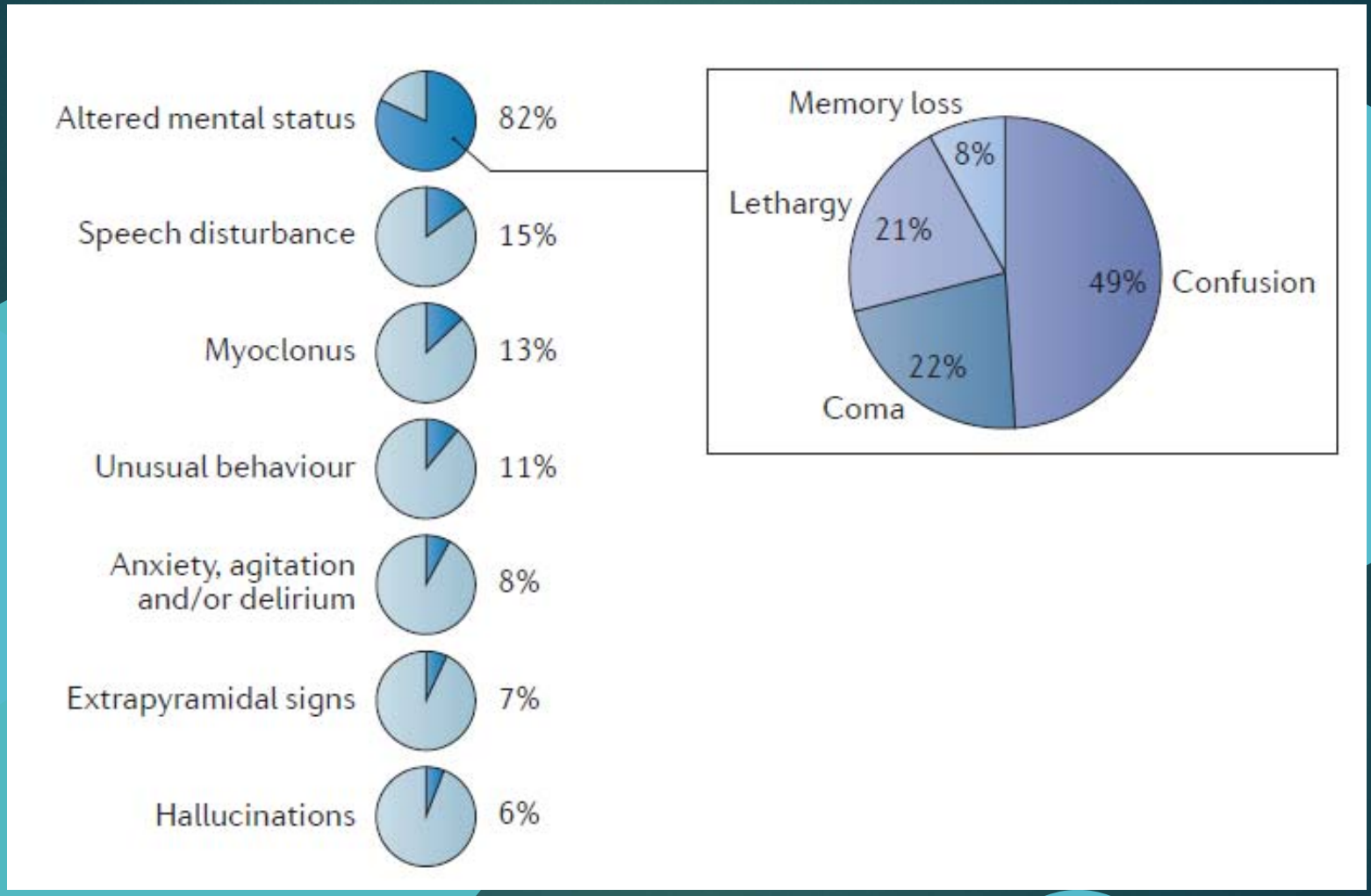
Medication	Loading Dose	Maintenance	Half-Life	Metabolism
First line				
Lorazepam	0.1 mg/kg at a rate of 2 mg/min	NA	12 hours	Hepatic
Midazolam[a]	0.2 mg/kg, initial dose of 10 mg IM	NA	2–6 hours	Hepatic; active metabolites excreted renally
Diazepam	0.2 mg/kg at a rate of 5 mg/min	NA	20–100 hours	Hepatic
Second line				
Phenytoin	20 mg/kg IV at a rate of 50 mg/min[b]; may rebolus with another 10 mg/kg as needed	100 mg IV given every 6 to 8 hours	10–15 hours	Hepatic
Fosphenytoin	20 mg PE/kg IV at a rate of 150 mg PE/min[c]; may rebolus with another 10 mg PE/kg as needed	100 mg IV given every 6 to 8 hours	10–15 hours	Hepatic
Valproate[a]	20–40 mg/kg	4–6 mg/kg given every 6 hours	9–16 hours	Hepatic
Levetiracetam[a]	2000–4000 mg	10–15 mg/kg given every 12 hours	7–11 hours	Renal excretion
Lacosamide[a]	200–400 mg	200–300 mg given every 12 hours	13 hours	95% Renal excretion
Third line				
Propofol[a]	1–2 mg/kg	2–10 mg/kg/h Risk of infusion syndrome over 5 mg/kg/h for more than 48 hours	Rapid distribution: 2–4 minutes Slower distribution: 30–60 minutes Terminal elimination: 3–12 hours	Hepatic
Midazolam	0.2 mg/kg	0.1–2 mg/kg/h	2–6 hours	Hepatic; active metabolites excreted renally
Pentobarbital	5–10 mg/kg	0.5–5 mg/kg/h	15–50 hours	Hepatic
Ketamine[a]	1.5 mg/kg repeated every 5 minutes up to a dose of 4.5 mg/kg	2–5 mg/kg/h	10 minutes–2.5 hours	Hepatic

IM = intramuscular; IV = intravenous; NA = not applicable; PE = phenytoin equivalent.
[a] Not US Food and Drug Administration (FDA) approved for the indication of status epilepticus.
[b] IV must be 18 gauge or larger and must be placed in the antecubital fossa or more proximal to prevent subcutaneous infusion/necrosis (purple glove syndrome) and venosclerosis.
[c] While fosphenytoin can be given at a faster rate than phenytoin, it does not exert its therapeutic effect any faster. Fosphenytoin is a prodrug that is converted to phenytoin in the liver before exerting any therapeutic effect.

Hantus S. Continuum (Minneap Minn) 2016;22(1):173-190.

Treatment of nonconvulsive status epilepticus

Major symptom of NCSE



Nat Rev Neurol. 2016;12(5):281-93.

Unified EEG terminology and criteria for NCSE

Table 2. Salzburg Electroencephalography Consensus Criteria for nonconvulsive status epilepticus

Patients without known epileptic encephalopathy
EDs > 2.5 Hz, or
EDs ≤ 2.5 Hz or rhythmic δ/θ activity (>0.5 Hz) AND one of the following:
EEG and clinical improvement after IV AED[a], or
Subtle clinical ictal phenomena, or
Typical spatiotemporal evolution[b]
Patients with known epileptic encephalopathy
Increase in prominence or frequency when compared with baseline with observable change in clinical state
Improvement of clinical and EEG[a] features with IV AEDs

EDs, epileptiform discharges (spikes, polyspikes, sharp-waves and sharp-and-slow-wave complexes); EEG, electroencephalography; IV AEDs, intravenous antiepileptic drugs. Reproduced with permission from [41].
[a]If EEG improvement without clinical improvement, or if fluctuation without definite evolution, this should be considered possible NCSE.
[b]Incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency >1 Hz or change in location), or decrementing termination (voltage or frequency).

Beniczky S, Hirsch LJ, Kaplan PW, et al. Epilepsia 2013; 54 (Suppl6):28–29.

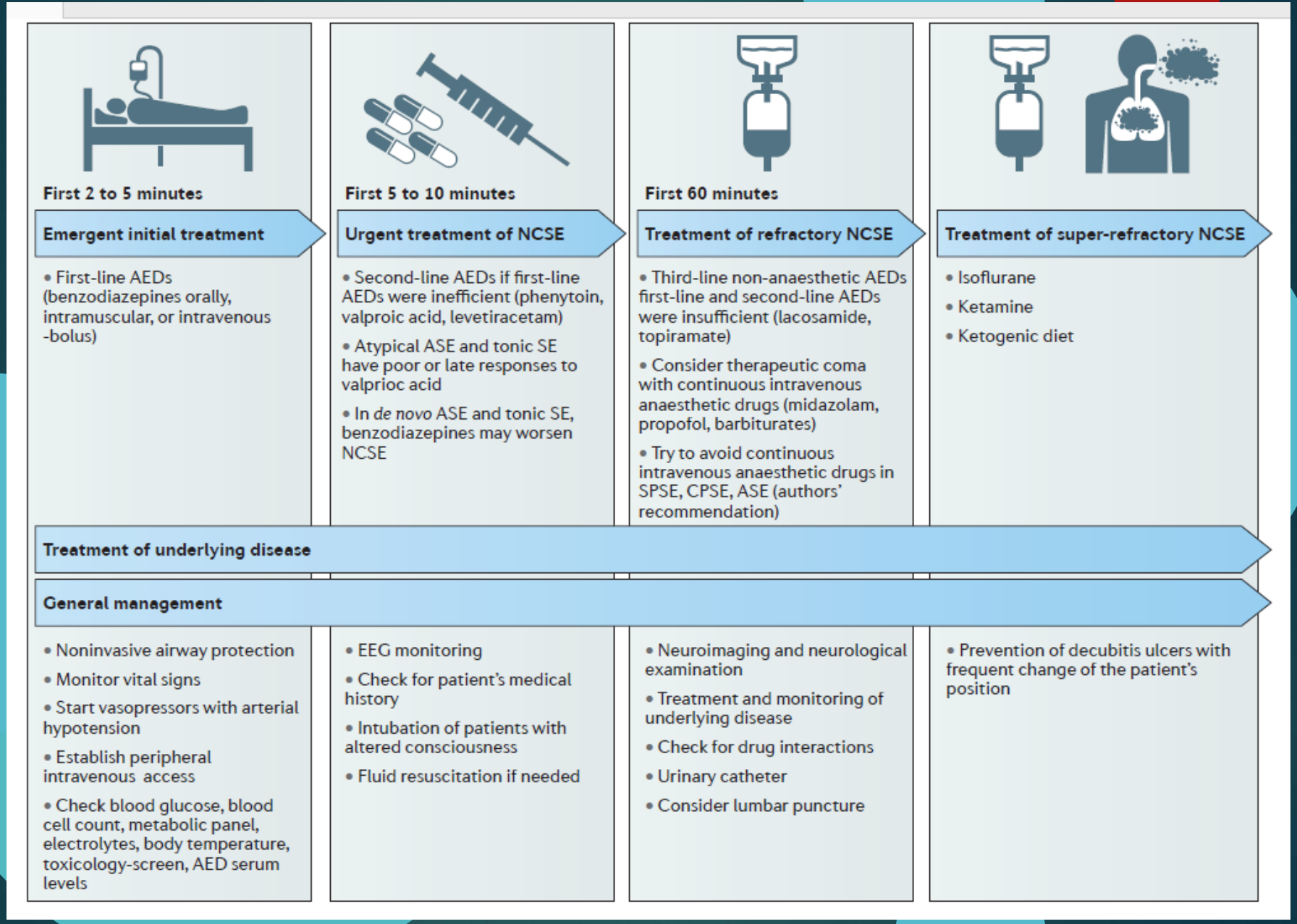
Treatment for NCSE

- Based on limited evidence and expert opinions
- Represent inferences from GCSE
- Diverse and controversial
  - Etiology
  - Type of NCSE

Treatment of NCS

- Existing data for outcome after NCS
  - 60% of pts with < 10 hours of NCS → able to return home
  - 10 to 20 hours of NCSE → permanent disability (50%)
  - >20 hours → death in 85%
- Based on consensus statement and some evidence, is to treat NCS aggressively with time to seizure termination being most important goal
- SPSE, CPSE and absence SE are not usually associated with poor outcome in contrast to generalized non-convulsive SE → avoid continuous IV anesthetic

Recommendations for treatment of NCSE in the ICU



Nat Rev Neurol. 2016;12(5):281-93.

Treating underling etiology

Addressing underlying etiology must occur concurrently with terminating seizure activity

- Acute symptomatic etiology
  - Hemorrhage, stroke, encephalitis
  - Metabolic disturbance
  - Autoimmune or paraneoplastic etiology
- Exacerbations of chronic etiologies
  - Tumor, remote stroke, TBI

Treating seizure-related complication

- Acute organ failure
- Polyneuropathy and myopathy, 30-50% of critically ill patients
- Sepsis
- DVT/pulmonary embolism
- Infections
- Aspiration

Outcome

- Some reports associate length of electrographic seizures with a poor neurologic outcome, as well as diffuse brain atrophy with prolonged seizures
- Memory loss, psychiatric issues (paranoia, hallucinations, loss of executive function), chronic epilepsy
- Etiology, management of complications, and time spent in SE are major determinants of short-term prognosis
- Long term outcome: little known

Conclusion: Status Epilepticus

- Major neurologic emergency and requires diagnostic vigilance and rapid response to prevent morbidity and mortality
- Early treatment should be emphasized over choice of medication
- No double-blind RCT study in established SE, RSE or NCSE
- Epidemiologic shift in identification of SE in inpatient population based on use of CEEG→ need more data to determine long-term benefits and treatment

Future and ongoing clinical trial

- Newer drugs targeting various other mechanisms, allopregnanolone, cannabinoids or valproate derivatives
- Phase III trial in super-refractory status epilepticus (NCT02477618) June 2015-June 2017
- Phase III trial (NCT01960075) comparing efficacy of levetiracetam, valproate and fosphenytoin in established status epilepticus (Established Status Epilepticus Trial)
  - October 2015- December 2019