Seize the moment: Management of status epilepticus in adults and children

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Presentor Disclosures

- Laura Wang
  - I have no current or past relationships with commercial entities
  - I have received no speaker’s fee for this learning activity

- Sharon Yamashita
  - I have no current or past relationships with commercial entities
  - I have received no speaker’s fee for this learning activity

Commercial Support Disclosure

- This program has received no financial or in-kind support from any commercial or other organization

Learning Objectives

- At the conclusion of this presentation, participants will be able to:
  - Define status epilepticus
  - Describe the epidemiology, pathogenesis, goals of therapy of status epilepticus in both adults and children
  - Recognize the evolution of status epilepticus over time and implications on pharmacotherapy
  - Understand the rationale for guideline recommendations on the management of status epilepticus in adults and children
  - Explore therapeutic options for the management of refractory status epilepticus

Outline

- Status Epilepticus
  - Definition, Epidemiology, Pathogenesis, Goals of Therapy
- Management in Adults
  - Guidelines and landmark trials
  - Firstline therapy
  - Refractory status epilepticus
- Management in Children
  - Guidelines and landmark trials
  - Febrile seizures
  - Neonatal seizures
- Prognosis/Outcomes

Definition

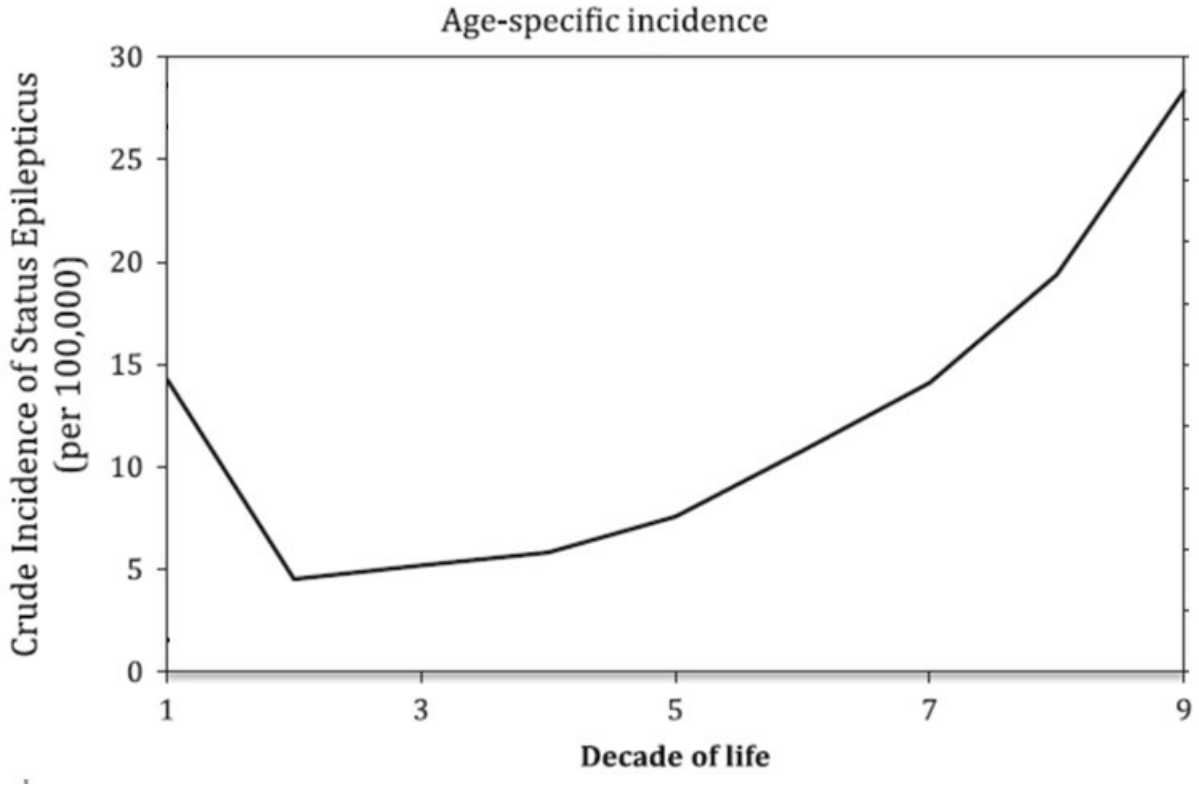
"….a condition resulting either from the **failure of the mechanisms responsible for seizure termination** or from the **initiation of mechanisms which lead to abnormally prolonged seizures** (after time point t1)…….that can have long-term consequences (after time point t2), including neuronal death,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

Type of SE	Operational dimension 1 Time (t_1), 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)
Tonic–clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10–15 min[a]	Unknown

ILAE Taskforce 2015

Epidemiology

- Incidence of 12.6 cases/100,000 person years → most common neurological emergency
- 1/3 of SE cases are the initial presentation of a seizure disorder
- 1/3 occur in patients with established epilepsy diagnosis
  - 0.5-6.6% occurrence of SE in diagnosed epileptics
- 1/3 occur as result of acute isolated brain insult



J. Clin. Med. **2016**, *5*(8), 71

Etiology in children

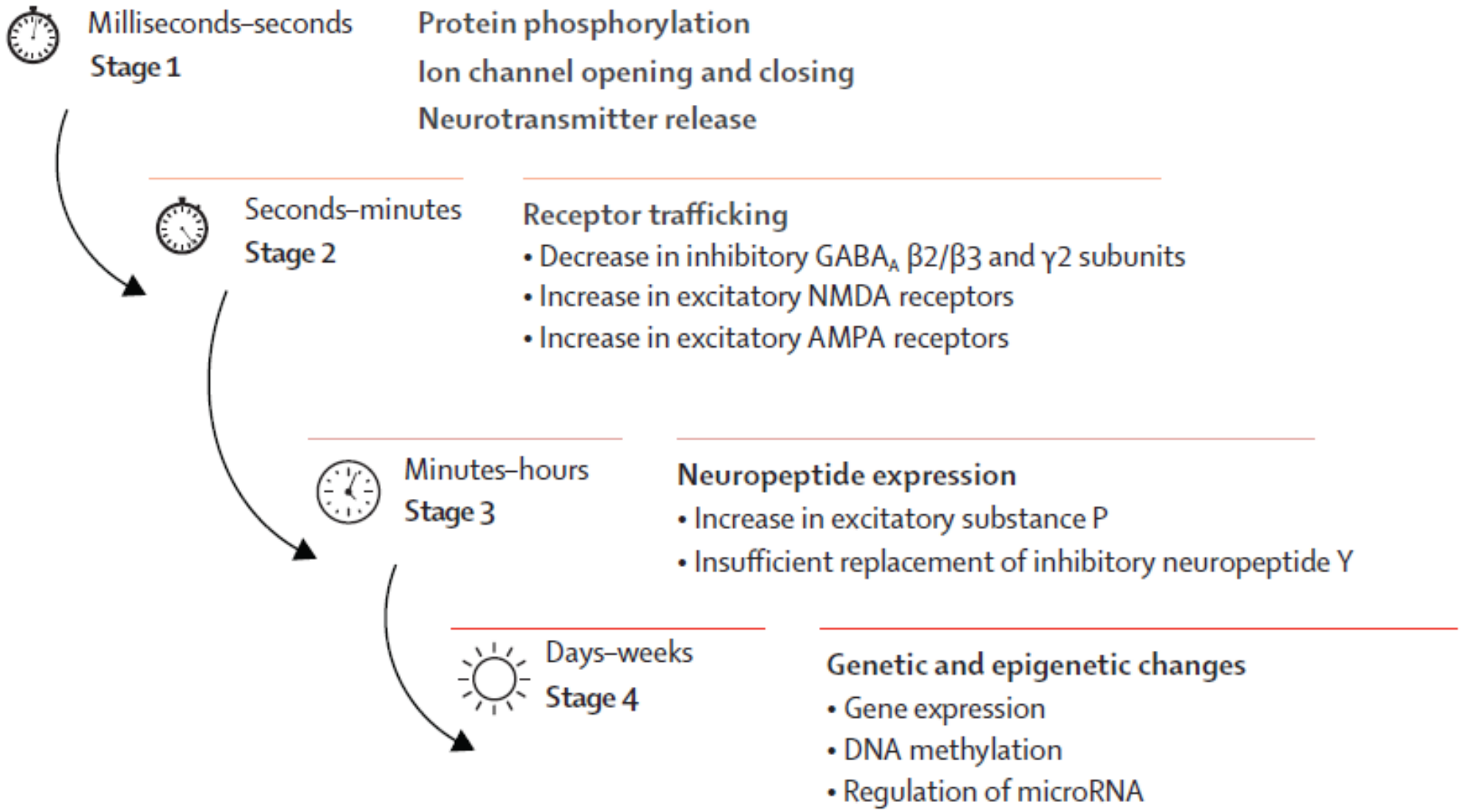
- **Remote symptomatic epilepsy** (34%)
  - CNS malformation, previous TBI, chromosomal disorder
- **Acute symptomatic seizures** (26%)
  - CNS infection 13%
  - Acute metabolic disorder 6%
  - Other: electrolyte disturbance, sepsis, hypoxia, trauma
- **Febrile** excluding CNS infections (22%)
  - URTI, sinusitis, sepsis
- Cryptogenic 15%
- Progressive encephalopathy 3%
  - Mitochondrial disorders, CNS lipid storage disease, organic acidopathies

Neurology 2006;67:1542

Etiology in adults

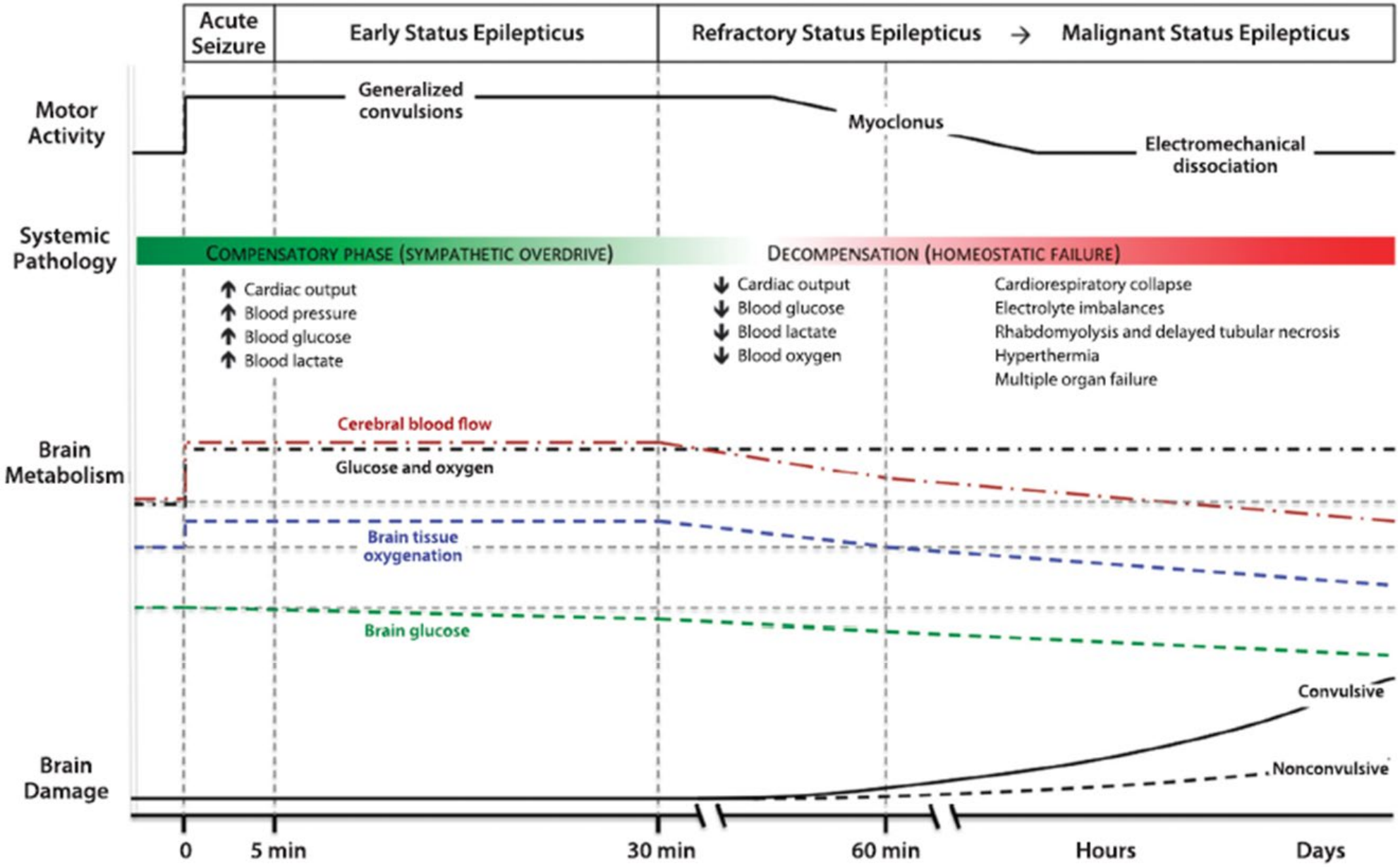
- Cerebrovascular accident (ischemic stroke, intracerebral hemorrhage
- Low antiseizure drug levels (noncompliance, drug interaction)
- Remote brain pathology (e.g. trauma, stroke, cortical dysplasia)
- Head trauma
- Infection
- Hypoxic brain injury
- Posterior reversible encephalopathy syndrome (PRES)
- Autoimmune and paraneoplastic etiologies
- Metabolic disturbances (electrolyte abnormalities, hypoglycemia)
- Drug withdrawal, toxicity

From seizure to status epilepticus



Lancet Neurol 2015; 14: 615-24.

Clinical time course of status epilepticus



Continuum (Minneap Minn) 2013;19(3):767–794

Goals of therapy

- Stop the seizure at the earliest timepoint and prevent recurrence
- Prevent progression to refractory status epilepticus (RSE)
- Identify and treat the underlying etiology
- Support ABCs (airway breathing circulation) + normoglycemia
- Anticipate and minimize adverse effects of therapy

Management of Status Epilepticus in Adults

Getting Started…

- Airway, Breathing, Circulation
- Rule out reversible causes:
  - Hypoglycemia
    - ➢ thiamine/glucose (D50W)
- Antiepileptics
  - Abort seizure
  - Prevent further seizures

- Labwork
  - Hypo/Hypernatremia
  - Renal Failure
- Consider drug-induced/drug-withdrawal
- Brain Imaging
  - CT/CTA/MRI
- Diagnostic Procedures
  - lumbar puncture
- EEG

Polling Question

- Which of the following medications would be **LEAST** appropriate for the initial management (first 5 minutes) of a patient with status epilepticus?

A. IV lorazepam
B. IM midazolam
C. IV phenytoin
D. IV phenobarbital

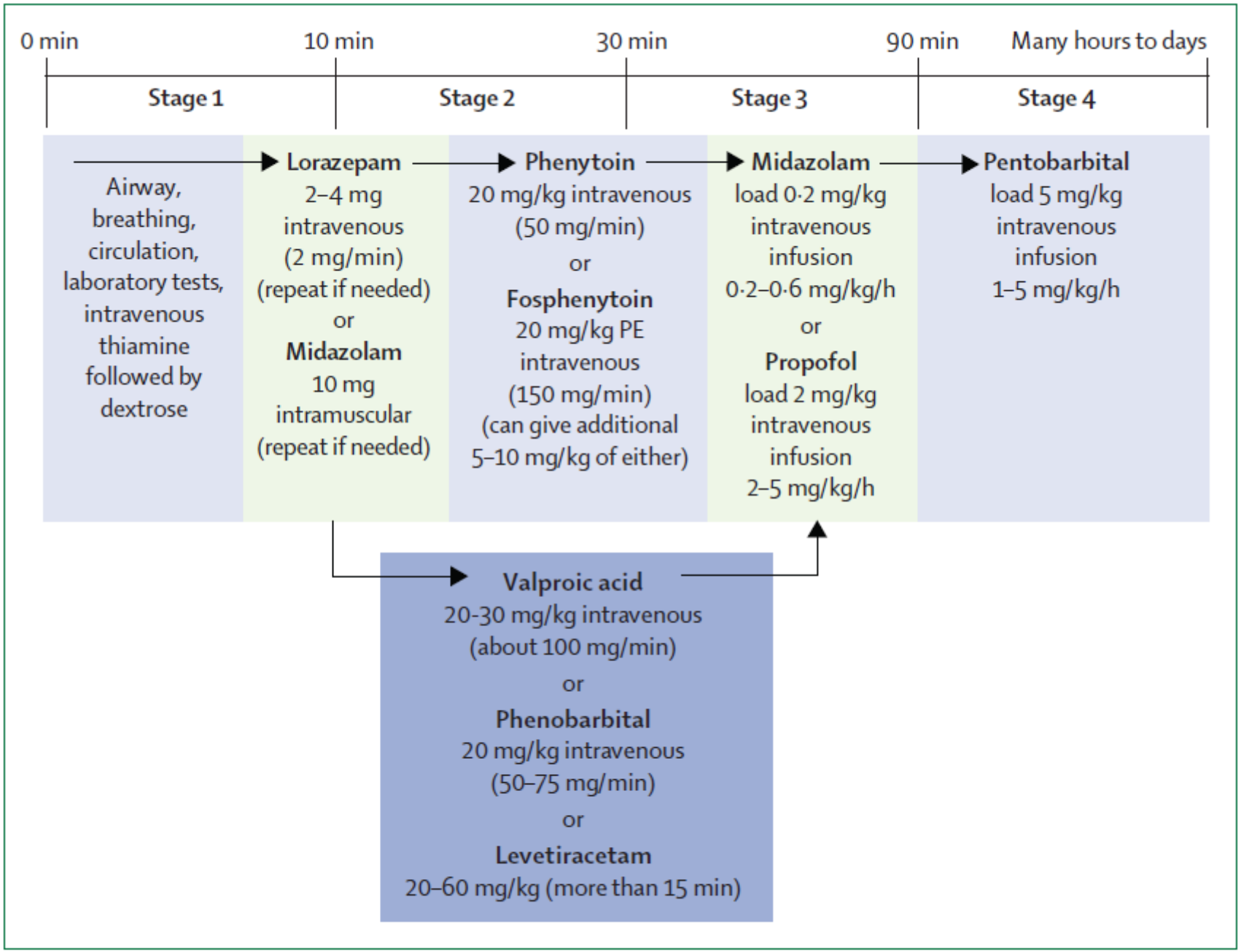


Figure 3: Updated treatment algorithm for generalised convulsive status epilepticus in adults and older children
PE=phenytoin equivalents.

Lancet Neurol 2015; 14: 615-24

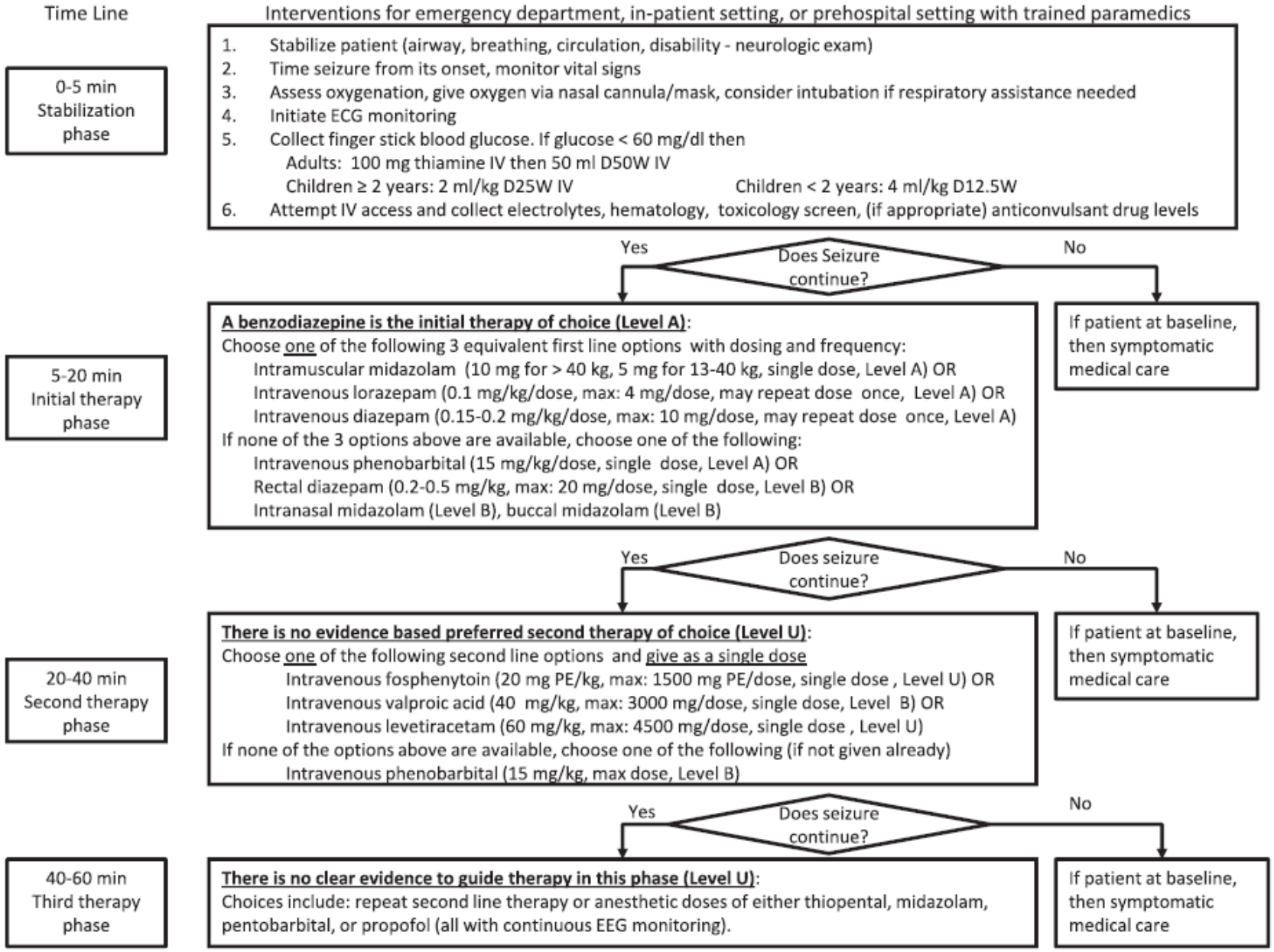


FIGURE 1. Proposed treatment algorithm for status epilepticus.

AMERICAN EPILEPSY SOCIETY

Epilepsy Currents, 2016; 16: 48–61

The First 5 - 10 Minutes

The First 5 - 10 minutes…

Benzodiazepines to stop the seizures

→ **Lorazepam** —
2–4 mg
intravenous
(2 mg/min)
(repeat if needed)
or
Midazolam
10 mg
intramuscular
(repeat if needed)

Lancet Neurol 2015; 14: 615-24

A benzodiazepine is the initial therapy of choice (Level A):

Choose one of the following 3 equivalent first line options with dosing and frequency:

- Intramuscular midazolam (10 mg for > 40 kg, 5 mg for 13-40 kg, single dose, Level A) OR
- Intravenous lorazepam (0.1 mg/kg/dose, max: 4 mg/dose, may repeat dose once, Level A) OR
- Intravenous diazepam (0.15-0.2 mg/kg/dose, max: 10 mg/dose, may repeat dose once, Level A)

If none of the 3 options above are available, choose one of the following:

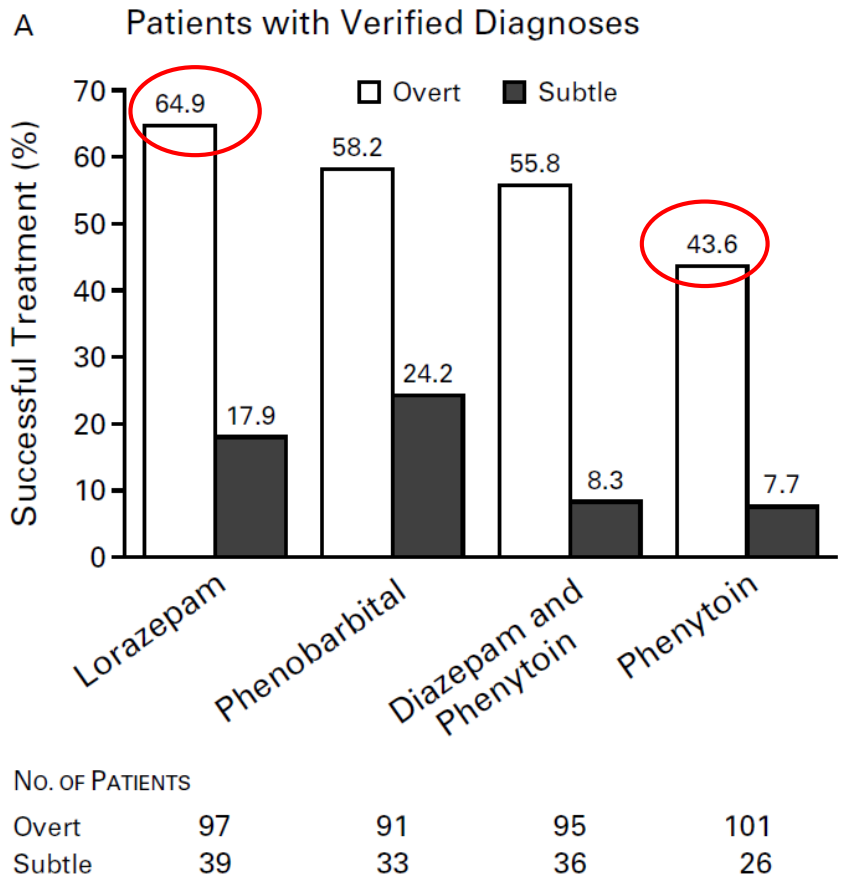
- Intravenous phenobarbital (15 mg/kg/dose, single dose, Level A) OR
- Rectal diazepam (0.2-0.5 mg/kg, max: 20 mg/dose, single dose, Level B) OR
- Intranasal midazolam (Level B), buccal midazolam (Level B)

Epilepsy Currents, 2016; 16: 48–61

Veterans Affairs Status Epilepticus Study

NEJM 1998; 339: 792-8.

- Seizures > 10 min
- Double-blind, randomized:
  - IV lorazepam (n= 136)
    - 0.1 mg/kg
  - IV phenobarbital (n=124)
    - 15 mg/kg
  - IV diazepam and IV phenytoin (n= 131)
    - 0.15 mg/kg and 18 mg/kg
  - IV phenytoin (n=127)
    - 18 mg/kg



Successful treatment:
No clinical/electrical seizures within 20 minutes and no recurrence from 20 – 60 minutes

The RAMPART Trial

NEJM 2012; 366: 591-600

- Pre-hospital (seizures > 5 min)
- Double-blind, randomized, noninferiority trial:
  - IM midazolam 10 mg (n=448)
  - IV lorazepam 4 mg (n=445)

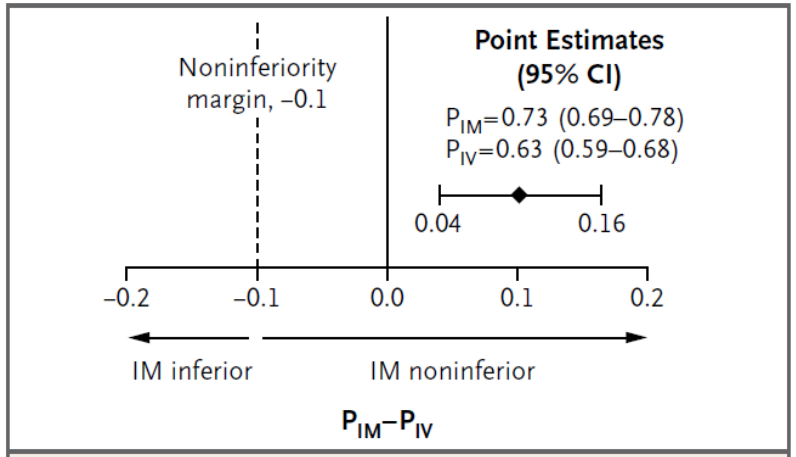


Figure 2. Primary Outcome According to Treatment Group.

Outcome (ITT)	IM Midazolam (n=448)	IV Lorazepam (n=445)	p-value
Termination of seizures (%, 95% CI)	73.4 (69.3 – 77.5)	63.4 (58.9 – 67.9)	<0.001
Rescue therapy administered (no., %)	22 (4.9)	42 (9.4)	

ITT - intention to treat, CI – confidence intervals

Within 30 minutes

Polling Question

- After initial therapy is started, which of the following medications would be LEAST appropriate to manage ongoing seizures?

A. Lorazepam 2 mg q6h IV
B. Levetiracetam 60 mg/kg IV
C. Phenytoin 20 mg/kg IV
D. Phenobarbital 15 mg/kg IV

Within 30 minutes…

Anticonvulsants to prevent ongoing seizures

Phenytoin
20 mg/kg intravenous
(50 mg/min)
or
Fosphenytoin
20 mg/kg PE
intravenous
(150 mg/min)
(can give additional
5–10 mg/kg of either)

Valproic acid
20-30 mg/kg intravenous
(about 100 mg/min)
or
Phenobarbital
20 mg/kg intravenous
(50–75 mg/min)
or
Levetiracetam
20–60 mg/kg (more than 15 min)

Lancet Neurol 2015; 14: 615-24

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, single dose, Level B)

Epilepsy Currents, 2016; 16: 48–61

The ESETT Trial

NEJM 2019; 381: 2103-13

- Seizures > 10 min
  - 5 min after receiving BZD
- Randomized, blinded, adaptive trial:
  - IV levetiracetam (n= 145)
    - 60 mg/kg
  - IV fosphenytoin (n= 118)
    - 20 mg/kg PE
  - IV valproate (n= 121)
    - 40 mg/kg

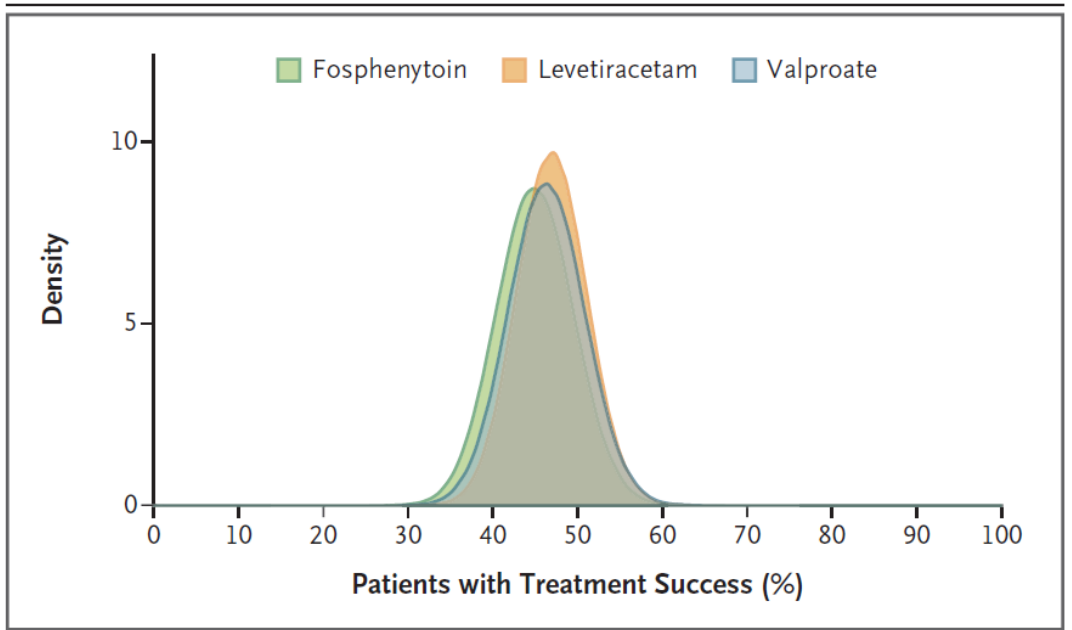


Figure 2. Posterior Probabilities of Success According to Treatment Group for the Primary Outcome of Cessation of Status Epilepticus at 60 Minutes.

BZD = benzodiazepine, PE = phenytoin equivalents

Choice of Anticonvulsant

	Phenytoin	Fosphenytoin	Phenobarbital	Valproic Acid	Levetiracetam
Short Term Adverse Effects	Hypotension, arrhythmias, vesicant, nystagmus	Pruritus, burning, parasthesias, nystagmus Less hypotension, arrhythmias	Hypotension, respiratory depression, prolonged sedation	Injection site reactions	Well tolerated
Other Considerations	Max rate 50 mg/min (~30 min)	**Max rate 150 mg/min** (PE); can be given IM (~10 min)		IV – Special Access in Canada	
Cost*	$180 (1.5g)	$ 200 (1.5g)	$200 (1.6g)		$135 (3g)

*McKesson September 2022

PE = phenytoin equivalents

After 30 minutes

After 30 minutes…

There is no clear evidence to guide therapy in this phase (Level U):
Choices include: repeat second line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring)

Thiopental – no longer available in Canada, Pentobarbital – Special Access in Canada

After 30 minutes…

Titrate to burst suppression on EEG

DRUG (OFF-LABEL USE)	USUAL DOSE	MAX DOSE	COMMENTS
MIDAZOLAM	0.3 – 20 mg/h	3 mg/kg/h	Risk of accumulation with high doses/prolonged use
PROPOFOL	20 – 100 mcg/kg/min	200 mcg/kg/min	Risk of propofol infusion syndrome with doses > 80 mcg/kg/min > 48 hours
KETAMINE	0.1 – 4 mg/kg/h	10 - 15 mg/kg/h	Less likely to cause hypotension
ISOFLURANE	2 – 5 mL/h		Contraindicated if history of malignant hyperthermia, raised intracranial pressure
SEVOFLURANE	4 - 10 mL/h		

Maintenance Therapy

- Phenytoin
- Levetiracetam
- Lacosamide
- Valproic Acid
- Phenobarbital
- Clobazam
- Lamotrigine
- Carbamazepine
- Topiramate
- Perampanel

Refractory Status Epilepticus

- Persistant seizures despite 2 antiepileptic drugs
  - 20 – 30% of patients with status epilepticus
  - “NORSE” – new onset
  - “Super-Refractory” - > 24h despite extensive antiseizure therapy
- Management
  - Anaesthetic doses of midazolam, propofol, ketamine
  - General Anaesthetic (isoflurane, sevoflurane)
  - Multiple antiepileptics as maintenance therapy
  - Immunotherapy (encephalitis): corticosteroids, IV immune globulin, plasmapheresis
  - IV magnesium, hypothermia, ketogenic diet

Volatile General Anaesthetics – isoflurane/sevoflurane

ADVANTAGES

- rapid and easy titration
  - Can turn off for EEG
- Minimal hemodynamic effects (low dose)
- Not renally/hepatically cleared
- Low systemic accumulation

DISADVANTAGES

- Feasibility limited by delivery system/ scavenging devices
  - **Ana**esthetic **Con**serving **De**vice
    - Small miniature vaporizer which can be connected to an ICU ventilator
  - Also use scavenging devices to reduce environmental emissions
- Side effects: risk of malignant hyperthermia, accumulation of fluoride, withdrawal seizures?

Isoflurane in (Super) Refractory Status Epilepticus Neurocrit Care 2021; 35:631–639

- Multi-centre, retrospective
- n=45 (2011-18)
  - 12 refractory
  - 33 super refractory
- Median # antiepileptics 5 (2-10)
- Median onset day 5 (0-58)

- Burst suppression 71%
- Termination of seizures
  - 29% isoflurane alone
  - 50% isoflurane + additional tx
- Adverse effects:
  - 80% Hypotension
  - 44% Infection

Therapies for Refractory Status Epilepticus

Brain. 2012;135:2314–28.

DRUG	NUMBER OF PATIENTS	TERMINATION OF STATUS EPILEPTICUS
MIDAZOLAM	585	78%
PROPOFOL	143	68%
PENTOBARBITAL/ THIOPENTAL	192	64%
KETAMINE	68	63%
ISOFLURANE	45	29-51%

Drug-induced seizures

- ~9% of status epilepticus cases
- Symptoms are similar to non-drug induced SE
- Common culprits:
  - Antidepressants
  - Stimulants
  - Antipsychotics
  - Antihistamines
  - Anticancer drugs
  - Hypoglycemic agents
  - Immunosuppressants
  - Antimicrobials
  - Pulmonary drugs (aminophylline, theophylline)
- AVOID phenytoin

  Shown to be ineffective, and may be harmful in lidocaine, theophylline and TCA induced seizures

1st line agents: **Benzodiazepines** **Pyridoxine if suspected isoniazid overdose**
2nd line agent: IV Phenobarbital Propofol AVOID phenytoin
3rd line agent: Midazolam continuous infusion Propofol infusion Pentobarbital/thiopental
Other therapies: Ketamine Levetiracetam GI decontamination, hemodialysis, antidote

Management of Status Epilepticus in Children

1st line - what does the literature say?

- PECARN study
  - Double-blinded multicentre RCT of 273 children aged 3 mos – 18 years
  - Randomized 1:1 to IV diazepam 0.2 mg/kg (max 8 mg) or IV lorazepam 0.1 mg/kg (max 4 mg), with the option to repeat half of the initial dose if seizures persisted after 5 mins
  - **No difference between IV diazepam (72.1%) and IV lorazepam (72.9%) in termination of SE by 10 min, without recurrence within 30 min**
  - **16%-17% incidence of respiratory depression requiring assisted ventilation in both groups**

JAMA. 2014;311(16):1652– 60

1st line - what does the literature say?

- RAMPART (analysis of pediatric cohort)
  - 120 children randomized 1:1 to receive IV lorazepam or IM midazolam
  - For primary outcome of seizure cessation before reaching ED, no significantly difference between IV lorazepam (71.6%) group vs IM midazolam (68.3%) group
  - For secondary endpoints: rates of hospital and ICU admission, endotracheal intubation, and recurrent seizure, point estimates are all favorable for IM midazolam

Epilepsia. 2015;56:254-262

1st line – what does the literature say?

- A network meta-analysis[1] of 16 RCTs including 1821 patients compared the efficacy of midazolam, lorazepam, and diazepam in treating pediatric SE
  - Non-IV midazolam and IV lorazepam were more efficacious than diazepam
  - IV lorazepam was noninferior to non-IV midazolam
  - Intramuscular midazolam most efficacious non-IV medication
  - Intranasal midazolam most efficacious non-IV medication for achieving seizure cessation within 10 mins, and for non-recurrence within 1hr
  - Very limited evidence for sublingual/buccal lorazepam use; one study shows it is even less effective than rectal diazepam (56% vs 79%)

[1]J Child Neurol. 2016;31(9):1093–107

Putting it to practice

- **Prehospital:**
  - IM/Buccal/IN midazolam → preferred choice in children without IV access
  - Buccal lorazepam → easiest, but of lowest efficacy
  - PR diazepam → slowest onset, variable absorption, ?socially acceptable
- **In hospital:**
  - With IV access:
    - IV lorazepam or IV/IM midazolam have similar efficacy
  - Without IV access:
    - Buccal, IN, IM midazolam is drug of choice
- Treating with more than 2 doses of benzodiazepines associated with increased risk for respiratory depression and decreased efficacy

Benzodiazepines – 1st line therapy

- Adverse effects and management
  - Sedation, respiratory depression, hypotension
  - Rare at appropriate dosing and at <2 doses
  - Paradoxical reaction (1-10% incidence?)
    - Transient sedation followed by extreme agitation, aggression, hyperactivity, hallucination
    - May be due to genetically mediated alterations in GABA binding sites
    - May react paradoxically to one benzodiazepine but not others
    - Requires more research

Agent	Dose	Max dose
Midazolam IV/IO	0.1 mg/kg	5 mg
Midazolam IM/IN	0.2 mg/kg	10 mg
Midazolam buccal	0.5 mg/kg	10 mg
Lorazepam IV/IO	0.05-0.1 mg/kg	4 mg
Diazepam IV/IO	0.3 mg/kg	5 mg (<5 yr) 10 mg (>/= 5 yrs)
Diazepam PR	0.5 mg/kg	20 mg

Paediatr Child Health. 2021 Jan 21;26(1):50-

2nd line – what does the literature say?

- ConSEPT
  - Open-label, multicentre RCT in Australia and New Zealand
  - Enrolled 244 children 1:1 to receive IV LEV 40 mg/kg or IV PHT 20 mg/kg
  - LEV NOT superior to PHT for seizure cessation after 5 min (60% vs 50%)

- EcLipSE
  - Open-label, multicentre RCT in UK
  - Enrolled 286 children 1:1 to receive IV LEV 40 mg/kg vs IV PHT 20 mg/kg
  - No difference between LEV or PHT for seizure termination (70% vs 64%)

- ESETT
  - Enrolled 225 children >2 yo
  - No differences in efficacy between IV LEV **60 mg/kg**, IV VPA 40 mg/kg, IV **FosPHT** 20 mg/kg
  - IV LEV is the safest option

ESETT – secondary outcomes

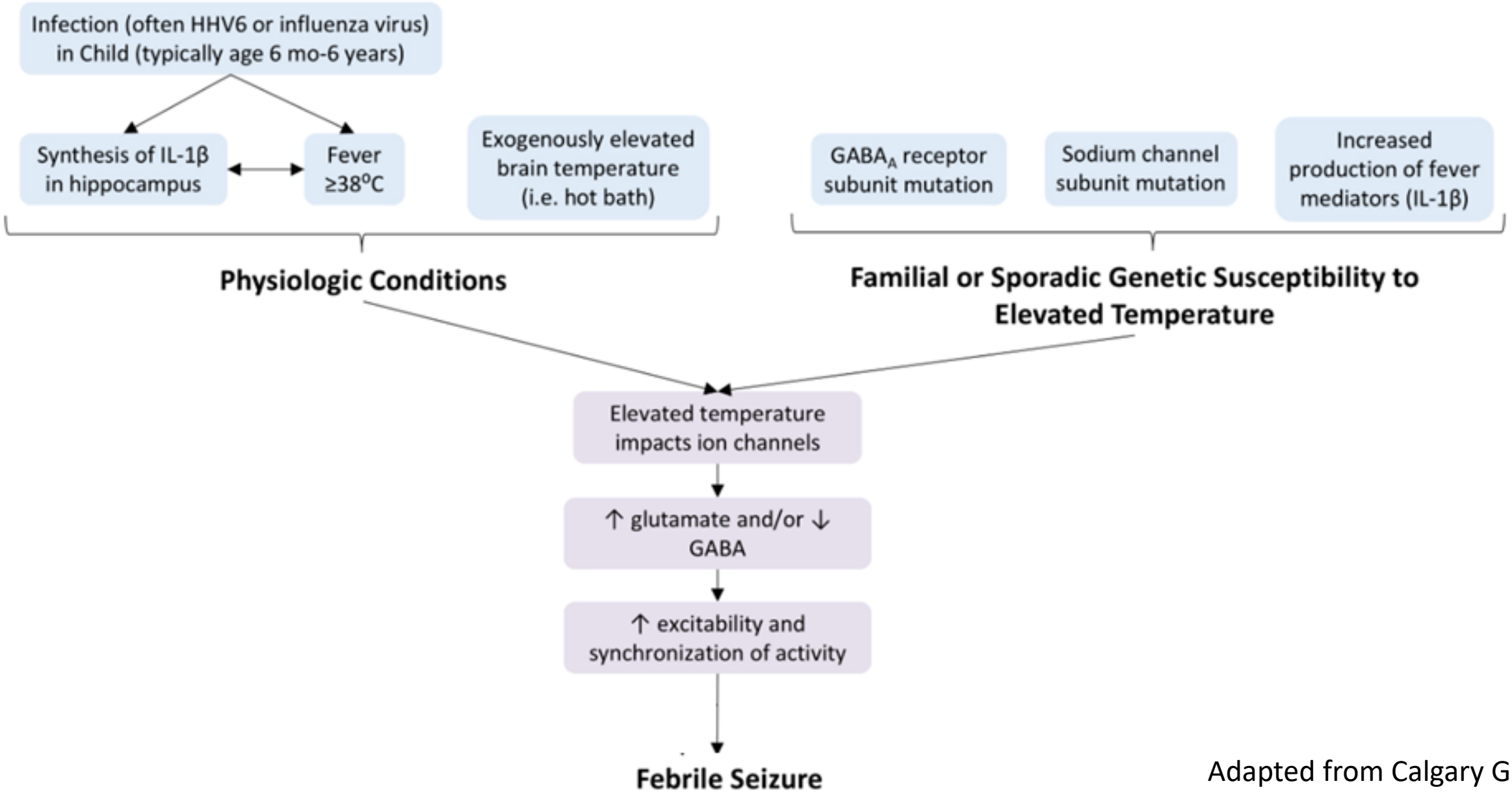
	Levetiracetam	Fosphenytoin	Valproate
ITT population	85	71	69
Admission to ICU	53 (62%)	45 (63%)	43 (62%)
Length of ICU stay, days	1 (0–2)	1 (0–2)	1 (0–2)
Length of hospital stay, days	2 (1–3)	2 (1–3)	2 (1–4)
Safety population	86	73	70
Life-threatening hypotension within 60 min of start of study drug infusion	0	2 (3%)	3 (4%)
Life-threatening cardiac arrhythmia within 60 min of start of study drug infusion	0	0	0
Acute respiratory depression	5 (6%)	13 (18%)	7 (10%)
Endotracheal intubation within 60 min of start of study drug infusion	7 (8%)	24 (33%)	8 (11%)
Acute seizure recurrence 60 min-12 h after start of study drug infusion	8 (9%)	11 (15%)	6 (9%)
Death	1 (1%)	0	1 (1%)

2nd line treatment in children

If <18 months, consider a dose of pyridoxine 100 mg IV

Levetiracetam IV (avoid or adjust dose in severe renal impairment)	60 mg/kg (max 4500 mg/dose), diluted in NS or D5W to final concentration of 15-50 mg/mL and given over 5-15 min.
OR	
Fosphenytoin IM or IV (contraindicated in drug-induced seizures)	20 mg phenytoin equivalents (PE)/kg (max 1500 mg PE/dose); if using IV give in NS or D5W over 5-10 min; max volume per IM site: 3 mL (If child >30 kg, IM dosing may not be practical because of large volume requiring multiple IM sites)
OR	
Phenytoin IV (use if fosphenytoin not available; contraindicated in drug-induced seizures)	20 mg phenytoin equivalents (PE)/kg (max 1500 mg PE/dose) in NS only over 20-30 min
OR	
Phenobarbital IV (preferred for refractory febrile seizures in <6 mo or drug-induced seizures)	20 mg/kg undiluted over 5-10 min (max: 1000 mg/dose); MD must be present to monitor for cardiorespiratory depression
OR	
Valproic Acid IV (available only through SAP)	30 mg/kg in NS over 5 min, followed by 10 mg/kg if ineffective after 10 min

Pathogenesis of febrile seizure



Adapted from Calgary Guide

Febrile status epilepticus

- FEBSTAT
  - Multicentre prospective observational study of FSE treatment and outcomes
  - Enrolled 199 patients between 4 months – 6 years old
  - FSE stopped spontaneously in only 20 children (10%)
  - 140 (78%) required more than one medication before FSE termination
    - Most received a benzodiazepine
    - Almost 40% of benzodiazepine doses were inadequate
  - Median time from the seizure onset to first medication was 30 min
  - FSE proved difficult to terminate, even with medication administration
  - Earlier onset of treatment results in shorter total seizure duration
  - No clear evidence that barbiturate coma or midazolam infusion was better than IV fosphenytoin or IV phenobarbital after initial benzodiazepine failure

Refractory status epilepticus in children

- Multivariate analysis showed that patients who received untimely first-line benzodiazepine treatment had:
  - higher odds of death (adjusted odds ratio 11.0; 95% CI, 1.43 to ∞; *P* = .02)
  - greater odds of receiving continuous infusion (AOR, 1.8; 95% CI, 1.01-3.36; *P* = .047)
  - longer convulsive seizure duration (AOR, 2.6; 95% CI, 1.38-4.88; *P* = .003)
  - more frequent hypotension (AOR 2.3; 95% CI, 1.16-4.63; *P* = .02)

JAMA Neurol. 2018;**75**:410–418

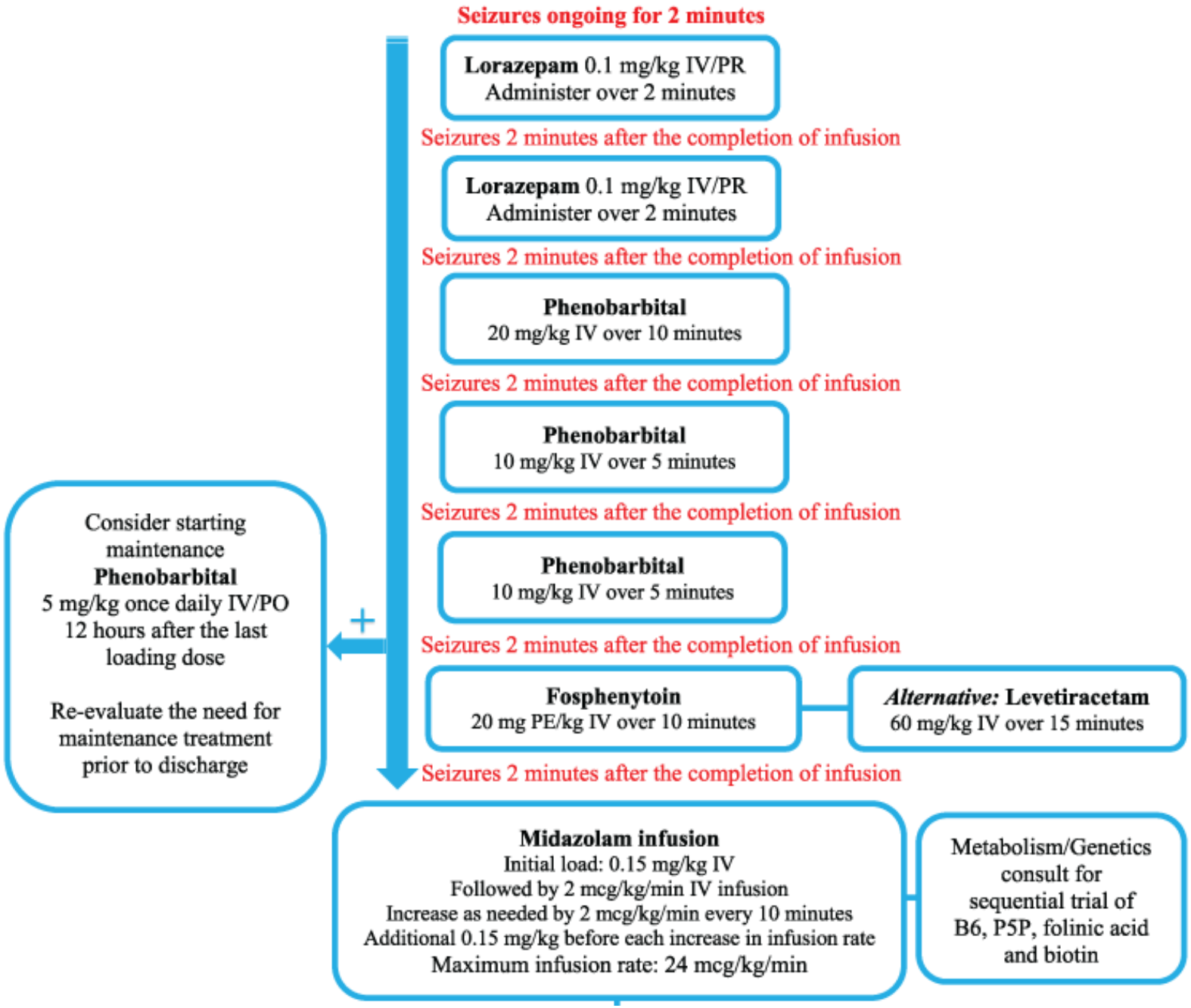
Neonatal seizures

- Neonatal brains are immature, with excitatory (glutaminergic) pathways predominating inhibitory (GABAergic) pathways
- Inborn errors of metabolism and congenital brain malformations first declare themselves in perinatal period
- Incidence of seizures in the neonatal period is high, estimated at 1-5/1000 live term births
- Pharmacotherapy focuses on GABAergic stimulation

Neonatal seizure pharmacotherapy

- Phenobarbital → Considered first line
  - RCT data; most clinical/historical experience
  - Complete cessation of seizures in 40-50%
  - 80% reduction in seizure frequency in 80%
- Levetiracetam → 2nd line
  - Retrospective data; lacking clinical experience (relatively new)
  - 88% seizure free in one study of 23 neonates
  - 100% seizure free in 72h in another study of 22 neonates
- Phenytoin → alternative 2nd line
  - RCT data showing 45-60% complete cessation
  - Unpredictable metabolism and enteral absorption in neonates

J Child Neurol. 2013 March; 28(3): 351–364.
Phenobarbital RCT - N Engl J Med. 1999; 341:485–489.
Levetiracetam - Pediatr Neurol. 2011; 44:265–269. J Child Neurol. 2011; 26:465–470

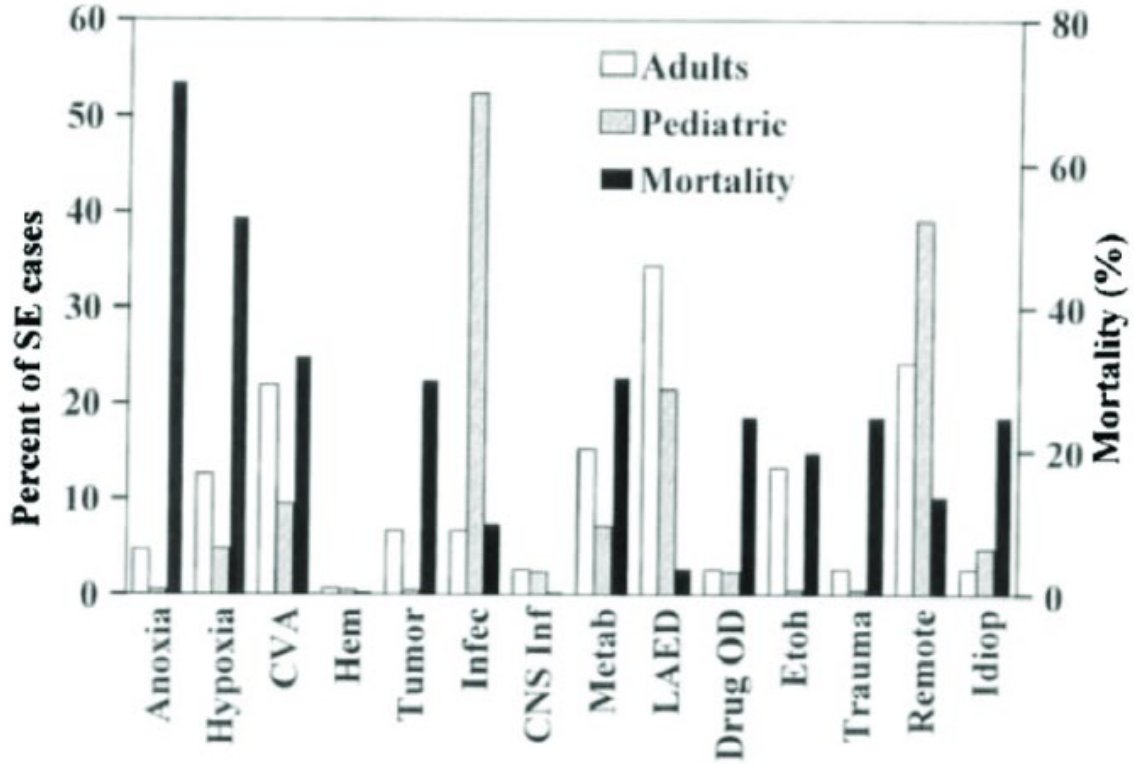


Neonatal seizure guidelines. Hospital for Sick Children.

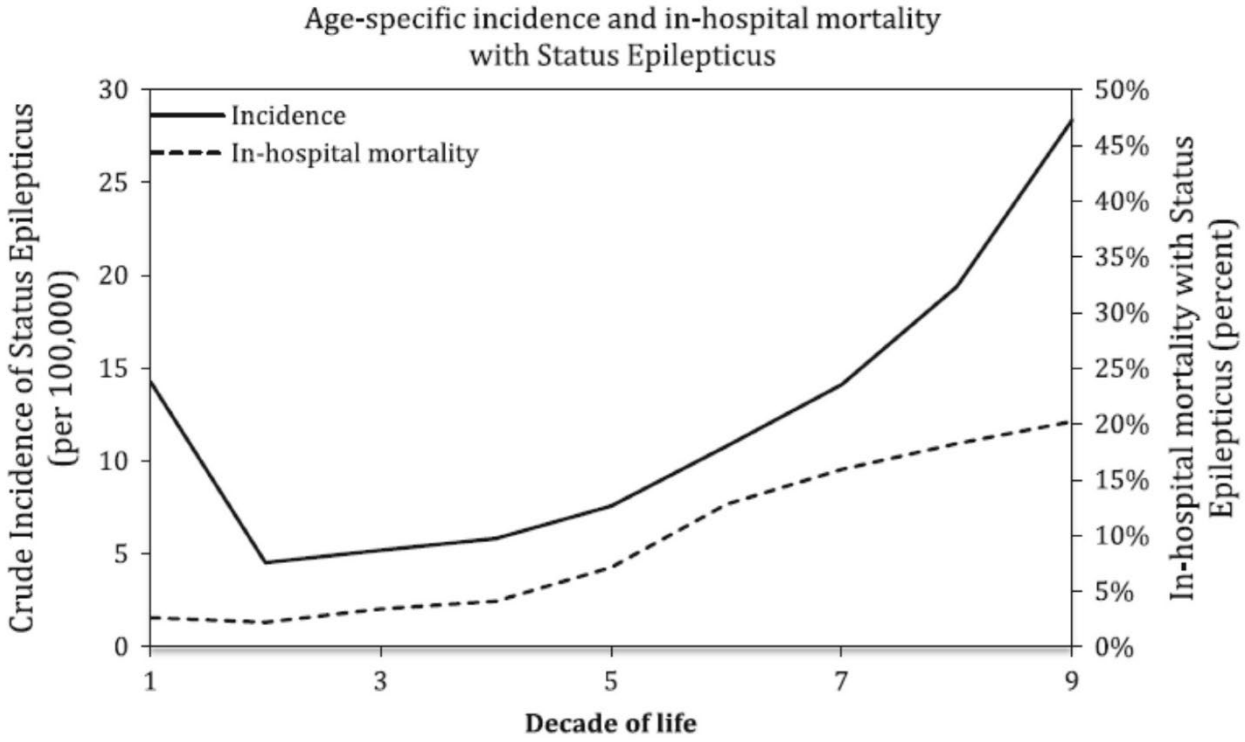
Prognosis

- Underlying etiology is primary predictor of long-term outcomes
  - Febrile seizures in absence of other complications have excellent prognosis
- Failure of compensatory mechanisms in RSE leads to brain damage: lesions in cortex and cerebellum and hippocampal sclerosis
- Survivors often have neurological and cognitive deficits
- The risk for developing epilepsy ***after*** SE ranges from 22%-40%
- 30 – 40% of SE cases will evolve to refractory status epilepticus
  - Mortality 10 – 40%
  - 15 – 20% → super-refractory status epilepticus
    - Mortality 35 - 65%

Survival by etiology



Survival by age

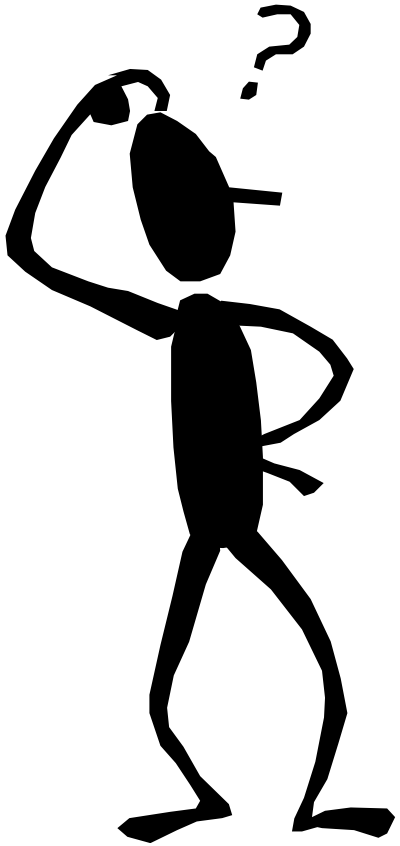


J. Clin Med 2016; 5(8):71.

Summary

- Timely administration of optimal doses of benzodiazepines is of paramount importance in firstline management, with midazolam being preferred agent
- All secondline IV agents (levetiracetam, valproate, phenytoin) are roughly equivalent in terms of efficacy (~50%)
- Reserve IV phenobarbital for use in children <6 mo and SE caused by drug ingestion
- Refractory status epilepticus is very difficult to treat and associated with significantly increased morbidity and mortality
- Standardized treatment protocols and trained staff drive outcomes

Questions



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