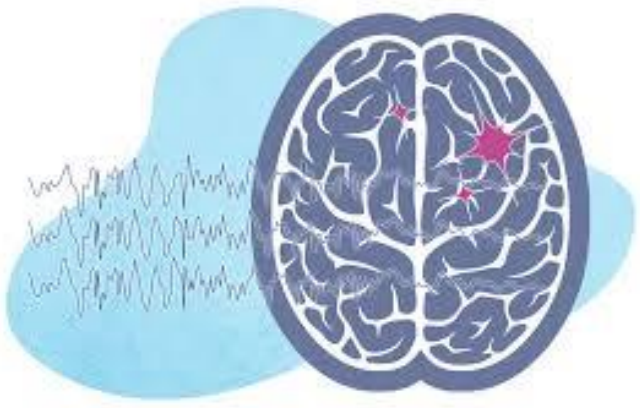
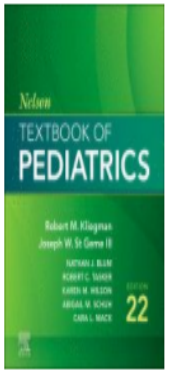
STATUS EPILEPTICUS

Dr **Maryam Naseri**
Pediatric intensivist
Mashhad university

Shiraz ۲۴ Oct **2024**





Nelson Textbook of Pediatrics, 2-Volume Set - Twenty Second Edition

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STATUS EPILEPTICUS (SE)

a medical emergency

should be anticipated in any patient who presents with an acute seizure

definition of SE to reflect :

time at which treatment should be initiated (t 1)

and

time at which continuous seizure activity leads to long-term sequelae (t 2) such as neuronal injury

For **generalized tonic-clonic seizures**, SE is defined as **continuous convulsive activity** or **recurrent generalized** convulsive seizure activity **without regaining consciousness**

(t 1 = 5 minutes, t 2 ≥30 minutes).

The definition differs for SE consisting of **focal** seizures with **impaired awareness** (t 1 = 10 minutes, t 2 = 30 minutes)

an **absence SE** (t 1 = 10-15 minutes, t 2 = unknown).

Refractory SE:

is SE in which a child's seizures fail to resolve despite therapy with both a **benzodiazepine** and a **non**-benzodiazepine medication.

Superrefractory SE:

is SE that has failed to resolve, or recurs, **within 24 hours** or more despite therapy that includes a **continuous infusion such as midazolam and/or pentobarbital**.

THERAPY

Ketamine infusion is a recognized treatment option for **SRSE**.

It is an **NMDA receptor antagonist** and may be of particular benefit because NMDA receptors are upregulated in SE.

ketogenic diet has also been found to be effective in children, although the response may take up to a **week after** diet initiation and **ketosis may be more difficult to achieve if the patient is receiving pentobarbital**, which has a carbohydrate-rich carrier fluid.

Immunotherapy:

IV steroids

immunoglobulins

and/or **plasma exchange** is often used in cases of **SRSE** of unclear etiology

Inhaled anesthetics :

such as **isoflurane** have been used for **SRSE**

adverse reactions and require the presence of an anesthesiologist at bedside, which limits their use.

phenobarbital dose used in **neonates**

is usually **20 mg/kg** as a loading dose,

but in **infants and children** the dose is often **lower** to avoid respiratory depression

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Table: Medications for CSE in pediatric patients

Benzodiazepines

- IV or IO access available:
  - Lorazepam 0.1 mg/kg IV or IO, max 4 mg
  - Diazepam 0.2 mg/kg IV or IO, max 10 mg
- If IV/IO access not achieved within 3 minutes:
  - IM midazolam 0.2 mg/kg, max 10 mg
  - Rectal diazepam 0.5 mg/kg, max 20 mg
  - Buccal midazolam 0.3 to 0.5 mg/kg, max 10 mg
  - Intranasal midazolam§

Antiseizure medications

- Levetiracetam 60 mg/kg IV or IO (maximum 4500 mg)
- Fosphenytoin 20 mg PE/kg IV or IO (maximum 1500 mg)*¥‡
- Valproate 20 to 40 mg/kg IV or IO (maximum 3000 mg)
- Phenobarbital 20 mg/kg IV or IO (maximum 1000 mg)*†

Medications for refractory SE

- Requires mechanical ventilation, cardiovascular monitoring, and continuous EEG monitoring:
  - Midazolam infusion: 0.2 mg/kg IV bolus followed by continuous infusion; start infusion at 0.05 to 0.1 mg/kg per hour; titrate to achieve cessation of clinical and electrographic seizures using continuous EEG; max dose 2 mg/kg per hour
  - Pentobarbital infusion: 5 to 15 mg/kg IV bolus followed by continuous infusion; start infusion at 0.5 mg/kg per hour; titrate to achieve cessation of clinical and electrographic seizures using continuous EEG; max dose 5 mg/kg per hour

REFRACTORY STATUS EPILEPTICUS

If convulsive SE **persists for 30 min** after initial measures are instituted (**immediate BZD treatment followed by second therapy** with an antiseizure medication),

third therapy is required:

usually with continuous infusion of **midazolam** (preferred) or **pentobarbital**

patient will require **endotracheal intubation**, mechanical ventilation, emergency

neurologic consultation if not already obtained,

and **transfer to a PICU** with continuous EEG capability.

The clinician should also **anticipate** the need to treat **iatrogenic hypotension**

Rapid infusion of isotonic crystalloid (eg, 20 mL/kg NS or RL) followed by a continuous infusion of a vasopressor such as **epinephrine** or **norepinephrine** are frequently necessary to maintain adequate tissue perfusion and blood pressure.

CONTINUOUS EEG MONITORING

is critical during the treatment of refractory SE.

The longer convulsive SE continues, the less convulsive it appears clinically, and **continuous (cEEG)** monitoring should be instituted.

Once infusion of **midazolam** or **pentobarbital** has begun, cEEG monitoring is necessary to confirm that seizures have been treated adequately;

to guide use of antiseizure medications and **assess the level of suppression** achieved;

and to monitor for relapse of seizures and SE, especially when infusions are **tapered**.

SPECIFIC AGENTS

Midazolam :can be given as a continuous IV infusion for refractory SE and is usually associated with minimal cardiovascular side effects.

is given as an initial bolus infusion of 0.2 mg/kg IV followed by a continuous infusion of 0.05 to 2 mg/kg per hour;

for breakthrough seizures, additional 0.1 to 0.2 mg/kg boluses can be given and the continuous infusion rate increased by 0.05 to 0.1 mg/kg per hour every three to four hours.

Hypotension may be less common than with pentobarbital but commonly occurs at higher doses of midazolam.

The short half-life of midazolam (1 to 4 hours) can increase markedly after days of use.

Tachyphylaxis is common, and the anticonvulsant effects of midazolam can cease rapidly when it is stopped.

Withdrawal seizures and recurrent SE are therefore an important concern.

In a **prospective** multicenter study of **54 children** with refractory SE who underwent continuous infusion of an anesthetic drug,

78% received **midazolam** as the first-choice agent .

Pentobarbital was the most commonly used therapy after midazolam failure (**82%).**

Seizure termination was achieved in 30 out of 42 patients

(**71 %**) who received first-line **midazolam**,

and an additional **8 patients** achieved seizure termination with **one more drug** (mostly pentobarbital).

PENTOBARBITAL

is given as an initial bolus infusion of 5 to 15 mg/kg IV followed by a continuous infusion of 0.5 to 5 mg/kg per hour.

Significant side effects include **respiratory depression**, hypotension, myocardial depression, and reduced CO.

Thus, **intubation** and mechanical ventilation with intravascular pressure monitoring are required prior to treatment, and **inotropic** agents frequently are needed.

Other important potential complications include pulmonary edema, ileus, and prolonged sedation.

OTHER THERAPIES

In addition to **levetiracetam**, observational data suggest that other antiseizure medications, including :

lacosamide

and **topiramate**

may play a role in the management of SE, particularly in the refractory setting.

Other emerging therapies include **ketamine**

and the **ketogenic diet**

PROPOFOL

is rarely used for the treatment of SE in children because doses and duration of therapy necessary to control refractory seizures are associated with life-threatening **propofol infusion syndrome** characterized by one or more of severe metabolic acidosis, rhabdomyolysis, and ECG changes, with or without cardiovascular collapse, hyperlipidemia, renal failure, elevated liver enzymes, or elevated lactate.

Risk factors : >4 mg/kg per hour),

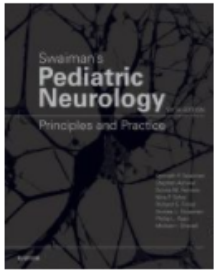
prolonged administration (>48 hours),

administration to children on the ketogenic diet.

Doses of Commonly Used Antiepileptic Drugs in Status Epilepticus

DRUG *	ROUTE	DOSAGE
Lorazepam	Intravenous	0.1 mg/kg up to maximum of 4 mg, may repeat in 5-10 min
	Intranasal	0.1 mg/kg up to maximum of 5 mg
Midazolam	Intravenous	0.2 mg/kg up to 10 mg total dose, may repeat in 5-10 min Continuous infusion maintenance: 0.05-2 mg/kg/hr
	Intramuscular	0.2 mg/kg
	Intranasal	0.2 mg/kg
	Buccal	0.5 mg/kg
Diazepam	Intravenous	0.15 mg/kg up to a maximum total dose of 10 mg; may repeat in 5-10 min
	Rectal	2-5 yr: 0.5 mg/kg
		6-11 yr: 0.3 mg/kg
		≥12 yr: 0.2 mg/kg
Fosphenytoin	Intravenous	Loading: 20 mg/kg PE, infusion rate maximum 50 mg PE/min Maintenance: 4-8 mg/kg/24 hr divided tid
Ketamine	Intravenous	Loading: 1 mg/kg Maintenance: 0.5-2 mg/kg/hr

Phenobarbital	Intravenous	Loading: 15-20 mg/kg (maximum 1,000 mg) Maintenance: 3-5 mg/kg/24 hr divided bid
Pentobarbital coma	Intravenous	Loading: 5-15 mg/kg Maintenance: 1-5 mg/kg/hr
Propofol	Intravenous	Loading: 1-2 mg/kg Maintenance infusion: 1.2 -3.9 mg/kg/hr
Thiopental	Intravenous	Loading: 2-7 mg/kg, infusion rate maximum 50 mg/min Maintenance infusion: 0.5-5 mg/kg/hr
Valproate	Intravenous	Loading: 20-40 mg/kg Maintenance: 30-60 mg/kg/24 hr divided bid
Lacosamide †	Intravenous	Loading: 4-8 mg/kg (maximum 400 mg) Maintenance: 4-12 mg/kg/day divided bid (maximum 400 mg/day)
Levetiracetam	Intravenous	Loading: 30-60 mg/kg (maximum 4,500 mg) Maintenance: 30-60 mg/kg/24 hr divided bid (maximum 3,000 mg/day)
Topiramate	Enterally	Loading: 5-10 mg/kg Maintenance: 5-12 mg/kg/day divided bid (maximum 400 mg/day)



Swaiman's Pediatric Neurology - Sixth Edition

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This definition emphasizes the importance of time by defining two time points:

t1—the time beyond which the seizure should be considered as "**continuous seizure activity**";

t2—the time beyond which there is a **risk of long-term consequences**.

How long a seizure or a cluster of seizures **must last to be** considered SE **is a matter of discussion**.

seizures which last **longer than 5 minutes** are unlikely to stop spontaneously and may be referred to as **impending SE**—consistent with the concept of **t1**.

The classical definition of **established SE**—consistent with the concept of **t2**— requires that seizures (continuous or intermittent without return to baseline mental status) **last for a minimum of 30 minutes.**

Management at time t1 may be indicated to prevent the seizure from reaching t2, at which time it may be producing secondary brain injury.

The classical **30-minute cut-off** is based on the fact that approximately after 30 minutes of seizures, the **compensatory mechanisms** fail against acidosis, hyperthermia, hyperkalemia, and cardiocirculatory collapse.

Thus **SE-induced irreversible neuronal damage** occurs and seizures become self-sustained and **refractory** to treatment.

The 30-minute cut-off is consistent with epidemiologic studies such as the Richmond SE study, in which **mortality** for seizures lasting **10 to 29 minutes** was **2.6%,** whereas mortality for seizures lasting **longer than 29 minutes was 19%.**

Treatment in SE:

should not be delayed until patients reach the established SE stage when neuronal injury and pharmacoresistance have already occurred.

The **5-minute cut-off** emphasizes this window of opportunity for treatment by identifying seizures with a high risk of progressing to cause neuronal damage and becoming pharmacoresistant at a stage when treatment still can prevent these outcomes.

The 5-minute cut-off for SE is most frequently used in **clinical** practice as treatment should be initiated after 5 minutes of seizure duration.

The **30-minute cut-off** is more commonly used in **retrospective** investigations to study a relatively homogeneous group of patients in whom some degree of neuronal damage and pharmacoresistance have already developed.

There are limited studies comparing the clinical characteristics of impending and established SE.

A series of **226 patients** (135 adults and 91 children) compared seizures lasting **10 to 29 minutes** with seizures lasting **more than 29 minutes.**

Demographic characteristics such as gender, race, age, and etiology were similar between the two groups.

In the 10- to 29-minute group, 43% of patients stopped having seizures spontaneously whereas 57% did not.

In a series of **445 children** aged 1 month to 21 years with seizures lasting **more than 5 minutes,**

a comparison was made between the **296** patients with seizures of **5 to 29** minutes duration and the **149** patients with seizures **30 or more minutes** in duration.

Patients with seizures of **more than 29 minutes** duration were **younger** at the time of seizure onset and were more likely to present with SE.

However, there were **no differences** in seizure frequency, seizure types, presence of developmental delay, and

EEG abnormalities at baseline.

Recommended Initial Medication Doses for SE

Drug	Dose	Maximum Dose	Route and Rate
Lorazepam iv	0.1 mg/kg	4 mg	iv push
Diazepam iv	0.3 mg/kg	10 mg	iv push
Diazepam rectally	0.2–0.5 mg/kg	20 mg	Rectal, bolus
Midazolam nasally	0.2–0.3 mg/kg	10 mg	Nasal, bolus
Phenobarbital iv	20 mg/kg	40 mg/kg or 1000 mg	2 mg/kg/min
Fosphenytoin iv	20 mg phenytoin equivalents/kg	300 mg phenytoin equivalents	3 mg phenytoin equivalents/kg/min
Valproate iv	20–40 mg/kg	40 mg/kg	3–6 mg/kg/min
Levetiracetam iv	30–60 mg/kg	2500 mg	Over 5 min

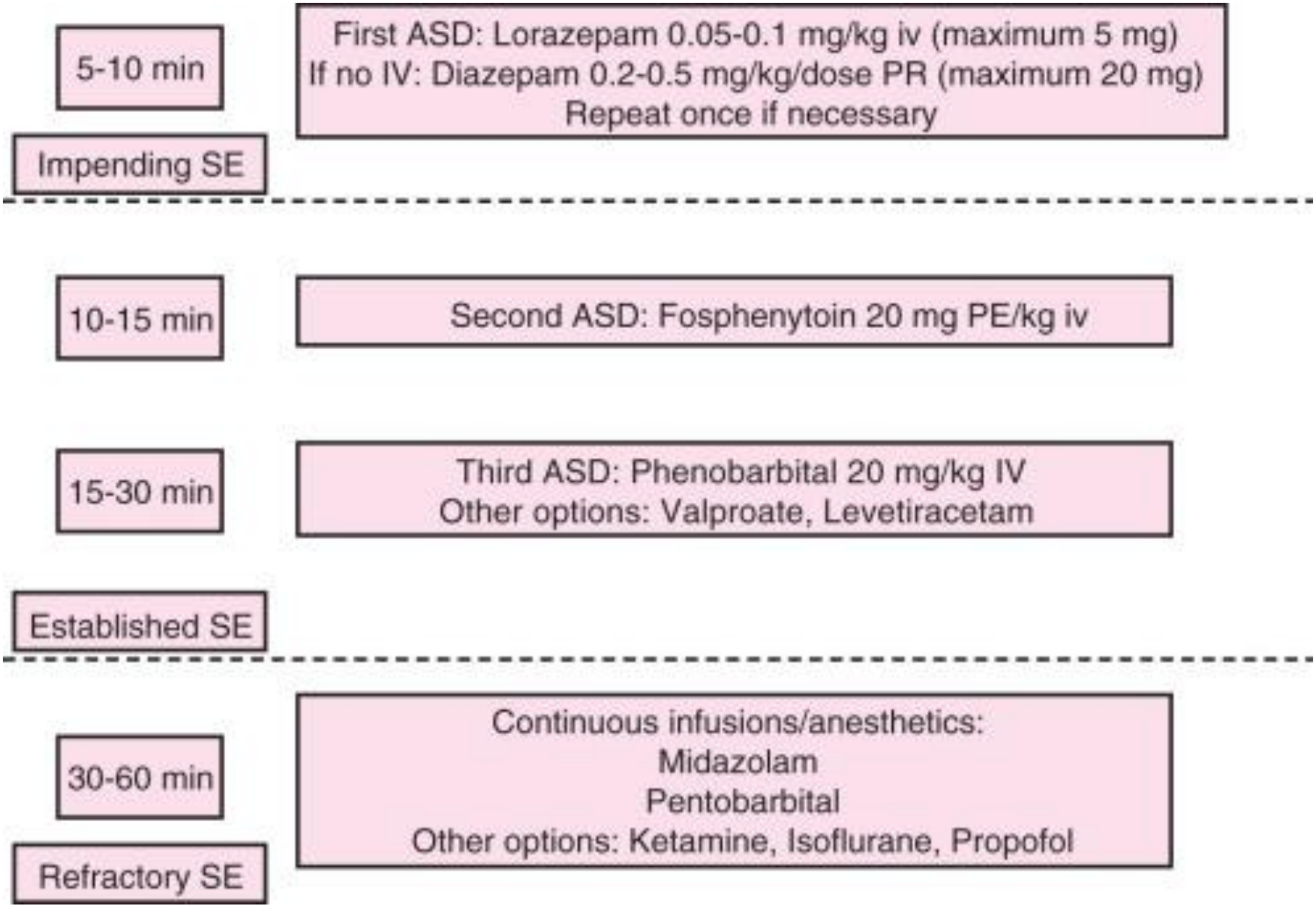
neonatal status epilepticus :

is defined as seizures that occupy

more than 50% of any 1-hour EEG

(e.g., a newborn **with 30 1-minute seizures in an hour**

single seizure that lasts 30 minutes or greater)


5-10 min
First ASD: Lorazepam 0.05-0.1 mg/kg iv (maximum 5 mg)
If no IV: Diazepam 0.2-0.5 mg/kg/dose PR (maximum 20 mg)
Repeat once if necessary
Impending SE
10-15 min
Second ASD: Fosphenytoin 20 mg PE/kg iv
15-30 min
Third ASD: Phenobarbital 20 mg/kg IV
Other options: Valproate, Levetiracetam
Established SE
30-60 min
Continuous infusions/anesthetics:
Midazolam
Pentobarbital
Other options: Ketamine, Isoflurane, Propofol
Refractory SE

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EDITED BY
Carlotta Spagnoli,
Santa Maria Nuova Hospital, Italy

REVIEWED BY
Lucio Parmeggiani,
Servizio di Neurologia e Neuroriabilitazione dell'Età Evolutiva - Ospedale di Bolzano, Italy
Asuri Narayan Prasad,
Western University, Canada

*CORRESPONDENCE
Angela M. Kaindl
angela.kaindl@charite.de

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Treatment of pediatric convulsive status epilepticus

Lena-Luise Becker[1,2,3], Alexander Gratopp[4], Christine Prager[1,2], Christian E. Elger[1,2,5] and Angela M. Kaindl[1,2,3]*

[1]Department of Pediatric Neurology, Charité-Universitätsmedizin Berlin, Berlin, Germany, [2]Center for Chronically Sick Children, Charité-Universitätsmedizin Berlin, Berlin, Germany, [3]Institute of Cell Biology and Neurobiology, Charité-Universitätsmedizin Berlin, Berlin, Germany, [4]Department of Pediatric Pneumonology, Immunology and Intensive Care, Charité-Universitätsmedizin Berlin, Berlin, Germany, [5]Beta Clinic, Bonn, Germany

Status epilepticus is one of the most common life-threatening neurological emergencies in childhood with the highest incidence in the first 5years of life and high mortality and morbidity rates. Although it is known that a delayed treatment and a prolonged seizure can cause permanent brain damage, there is evidence that current treatments may be delayed and the medication doses administered are insufficient. Here, we summarize current knowledge on treatment of convulsive status epilepticus in childhood and propose a treatment algorithm. We performed a structured literature search *via* PubMed and ClinicalTrails.org and identified 35 prospective and retrospective studies on children <18 years comparing two and more treatment options for status epilepticus. The studies were divided into the commonly used treatment phases. As a first-line treatment, benzodiazepines buccal/rectal/intramuscular/intravenous are recommended. For status epilepticus treated with benzodiazepine refractory, no superiority of fosphenytoin, levetirazetam, or phenobarbital was identified. There is limited data on third-line treatments for refractory status epilepticus lasting >30 min. Our proposed treatment algorithm, especially for children with SE, is for in and out-of-hospital onset aids to promote the establishment and distribution of guidelines

that 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 ILAE task force suggested treatment to be initiated at t1, and if t2 is reached, that treatment should be exacerbated to prevent long term damage.

They further **delineated t1**, i.e., the time when a seizure is **likely <u>not to be</u> self-limiting,**

to be **5 min in generalized tonic–clonic (GTC) SE**

10 min in focal SE with impaired awareness

and **10–15 min** in **absence SE**

Furthermore, they **defined t2** to be:

30 min for GTC SE and

>60 min for focal SE with **impaired awareness** .

For other **SE subtypes**, including **febrile seizure SE** and **focal SE with awareness** no duration has been proposed, leaving **the older definition of >30 min**.

This earlier initiation and more aggressive therapeutic approach

in the **new ILAE** definition is based on the knowledge that:

treatment becomes **increasingly difficult** the longer a SE lasts, in part due to:

receptor trafficking such as a **reduction of GABAA receptor-mediated inhibition**

Phase 0
0 - 5 min

General considerations:

> Stabilize patient, check ABCDE and adress basic life support > monitor vital signs/ECG
> Establish IV line, check and start diagnostic work up: laboratory parameters, glucose
> Time duration of the seizure

Phase 1
> 5 min

After **5 min** administer a first **benzodiazepine:**

Medication	**Dosage per dose**	**Maximal dosage**
Midazolam, buccal	3 mos.-1 yr.: 2.5 mg, 1-5 yr.: 5 mg 5-10 yr.: 7.5 mg, 10-18 yr.: 10 mg	10 mg
If not available:		
Diazepam, rectal	<15 kg: 5 mg, >15 kg: 10 mg	5-10 mg

Phase 2
5 - 10 min

After **5 min** administer another **benzodiazepine** intravenously:

Medication	**Dosage per dose**	**Maximal dosage**
Lorazepam IV	0.1 mg/kg	4 mg
If not available:		
Diazepam IV	0.2-0.3 mg/kg	5-10 mg
Midazolam IV	0.1 mg/kg	10 mg

If no IV access could be obtained, consider midazolam IM (0.2-0.3 mg/kg, max. 5 mg), midazolam buccal or an intraossear access.

Phase 3
10 - 30 min

- > Evaluate indication of cranial imaging (CT, MRI) and of further diagnostics
- > Start continuous EEG, but do not delay treatment
- > Inform intensive care unit

After **10 min** another **antiseizure medication** should be started intravenously.
Choose from the following:

Medication	**Loading dose**	**Max. rate**	**Comment**
Levetiracetam IV	40-60 mg/kg (max. 4500 mg)	2-5 mg/kg/min	KI: reduce in renal insuff.
Fosphenytoin IV	20 mg PE/kg (max. 1500 mg)	150 mg PE/min	KI: AV Block (monitor EKG/BP)
Alternatives:			
Valproic acid IV	20-40 mg/kg (max. 3000 mg)	10 mg/kg/min	KI: liver insuff., mitochondriopathy
Phenobarbital IV (neonates)	10-20 mg/kg (max. 1g)	50 mg/min	KI: porphyria, liver- or respiratory insuff.
Phenytoin IV	18-20 mg/kg (max. 1g)	1 mg/kg/min	skin reaction KI: II-III AV-Block
Lacosamide IV	4-10 mg/kg (max. 600 mg)	10 mg/min	KI: II-III AV-Block

Phase 4
> 30 min

- > Move to intensive care unit
- > Intubation, induce therapeutic coma
- > Continuous EEG monitoring to monitor treatment response

After **30 min** induce a **pharmacological coma.** Choose from the following:

Medication	**Loading dose**	**Maintenance**	**Comment**
Midazolam IV	0.2 mg/kg	0.05-2 mg/kg/hr	accumulation in fat and kidney failure
Propofol IV	1-2 mg/kg	1-5 mg/kg/hr (only 24 hr)	PRIS, cardiorespir. depression
Thiopental IV	2-7 mg/kg	0.5-12 mg/kg/hr	cardlorespir. depression, Illeus, hypernatriemia
Ketamine IV	0.5-5 mg/kg	1-10 mg/kg/hr	tachycardia, arrhythmia, hypertension

Also consider another additional **antiseizure medication** from **Phase 3***, ketogenic diet, epilepsy surgery.

ELSEVIER

Pediatric Neurology

Volume 158, September 2024, Pages 41-48

Research Paper

Enteral Ketamine for Status Epilepticus in Children with Epilepsy

Laura DiDomenico MD, MS (Trainee Author) [a b], Lisa C. Garrity SM, PharmD, BCPS [a], Kelsey E. Poisson MD [a c], Eileen Broomall MD [a]

Show more

https://doi.org/10.1016/j.pediatrneurol.2024.05.006

Ketamine

an ***N-methyl-D-*ASPARTATE receptor antagonist**,

is an anesthetic growing in use for the treatment of SE.

There is a plausible mechanism for ketamine's therapeutic effect on refractory seizures given the proposed pathophysiology of SE, which involves **involution** of **GABA type A receptors** and **upregulation of excitatory NMDA** and **α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors**.

Intravenous ketamine has been reported to be effective in the treatment of SE in children, preventing intubation in some clinical circumstances.

Enteral ketamine :

has been utilized less often in the treatment of SE.

5 pediatric patients with epilepsy presenting in **NCSE** were successfully treated with enteral ketamine with **seizure resolution within 48 hours**, corroborated by clinical **improvement and EEG** characteristics.

This observational study presents **9** pediatric patients with epilepsy treated with enteral ketamine for **approximately 3 to 5 days** for **both NCSE and CSE** at a pediatric tertiary care center.

The study highlights the potential efficacy and safety of enteral ketamine in the treatment of SE and its potential benefits for treatment in specific pediatric patients with epilepsy.

KETAMINE DOSE:

1.5 mg/kg/day

divided twice daily for approximately

3 to 5 days with initial doses initiated in the PICU

Neurocrit Care (2024) 40:45–47
https://doi.org/10.1007/s12028-023-01881-4

NEUROCRITICAL CARE SOCIETY

INVITED COMMENTARY

Ketamine for Status Epilepticus in Children: Searching for the Right Drug for the Right Patient

Kristin P. Guilliams[1*] and Dana Harrar[2]

In this issue, Jacobwitz et al. report their experience using ketamine, an NMDA receptor antagonist, as a first-line anesthetic infusion in pediatric patients with SE.

In "**A Comparison of Ketamine Versus Midazolam** as First-Line Anesthetic Infusions for Pediatric SE:

117 children with refractory SE cared for at a large children's hospital over **a 5-year period, 79 (68%)** of whom received **midazolam** as the frst-line anesthetic infusion and **38 (32%)** of whom received **ketamine.**

seizures were more likely to terminate with ketamine than midazolam.

adverse efects occurring during or **within 12 h of the last** anesthetic administration were **more frequently** observed with **midazolam** than ketamine.

DMCN Developmental Medicine & Child Neurology

ORIGINAL ARTICLE

Efficacy of intravenous clonazepam for paediatric convulsive status epilepticus

Maxime Colmard, François Rivier, Gaëlle de Barry, Agathe Roubertie, Sarai Urtiaga-Valle, Blanca Mercedes-Alvarez, Clementine Combes, Gilles Cambonie, Christophe Milesi, Pierre Meyer

First published: 23 January 2024 | https://doi.org/10.1111/dmcn.15859 | Citations: 1

This original article is commented by Mifsud on pages 968–969 of this issue.

Aim

To compare the efficacy of **IV clonazepam** (CLZ) for the initial management of CSE in children as a function of the first-line in-hospital dose used.

Method

This monocentric **retrospective** study included children who received a first dose of CLZ for **CSE** at Montpellier University Hospital, France, between January 2016 and June 2019.

Data from medical records (clinical, treatment, course) were collected and compared as a function of the first CLZ dose used.

Results

Among the **310** children treated for CSE, **105** received at least one CLZ dose

Among these 105 patients, **24 (22%)** received a **dose less than 0.03 mg/kg (low dose)** and **69 (65%)** received a **dose of at least 0.03 mg/kg (high dose)**.

Seizure cessation rate was not different between the **low- and high-dose** groups (62.5% vs 76%; odds ratio 0.53, 95% confidence interval [CI] 0.19–1.44, p = 0.29)

The administration of a **second dose of CLZ** was **more frequent** in the **low**- than the high-dose group (37.5% vs 16%; odds ratio 3.2, 95% CI 1.1–9.1, p = 0.04).

Interpretation

Our study **did not** find any difference in seizure termination rate as a function of CLZ dose in children with CSE.

However, a **second CLZ dose** was more frequently needed in the group receiving **low** (less than 0.03 mg/kg) CLZ.

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اقلیم بلند اختر ِشعر و ادب و راز!

گسترده به دامان چمن، بید و صنوبر
سر بر زده سرو تو به گردون، زسر ناز

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خنیا گر افسانه سرا، موطن ممتاز

ای شعر تو را، ورد زبان عالِم و عامی
صد لشکر احساس، تو را حامی و سرباز

دامان تو معراج ادیبانه‌ی **حافظ**
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خفته ست بدامان پر از مهر تو **سعدی**
بر درگه تو، **خواجوی ِ کرمان** ِغزل باز!

ای شهر سخن پرور ِمن دیر بمانی
همواره چو بستان و گلستان ِسرافراز

گیراتر از این خاک نبودست و نباشد
ای هستی من! شهر غزل پرور شیراز!

مرضیه اوجی
"