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Review Article

Japanese guidelines for treatment of pediatric status epilepticus – 2023

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ABSTRACT

The updated definition of status epilepticus (SE) by the International League Against Epilepsy in 2015 included two critical time points (t_1: at which the seizure should be regarded as an "abnormally prolonged seizure"; and t_2: beyond which the ongoing seizure activity can pose risk of long-term consequences) to aid in diagnosis and management and highlights the importance of early treatment of SE more clearly than ever before. Although Japan has witnessed an increasing number of pre-hospital drug treatment as well as first- and second-line treatments, clinical issues have emerged regarding which drugs are appropriate. To address these clinical concerns, a revised version of the "Japanese Guidelines for the Treatment of Pediatric Status Epilepticus 2023" (GL2023) was published. For pre-hospital treatment, buccal midazolam is recommended. For in-hospital treatment, if an intravenous route is unobtainable, buccal midazolam is also recommended. If an intravenous route can be obtained, intravenous benzodiazepines such as midazolam, lorazepam, and diazepam are recommended. However, the rates of seizure cessation were reported to be the same among the three drugs, but respiratory depression was less frequent with lorazepam than with diazepam. For established SE, phenytoin/fosphenytoin and phenobarbital can be used for pediatric SE, and levetiracetam can be used in only adults in Japan. Coma therapy is recommended for refractory SE, with no recommended treatment for super-refractory SE. GL2023 lacks adequate recommendations for the treatment of nonconvulsive status epilepticus (NCSE). Although electrographic seizure and electrographic SE may lead to brain damages, it remains unclear whether treatment of NCSE improves outcomes in children. We plan to address this issue in an upcoming edition of the guideline.

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1. Introduction

Status epilepticus (SE) is frequently encountered critical condition in pediatric emergency medicine, requiring rapid and appropriate treatment to prevent serious neurological sequelae. Although treatment strategies for pediatric SE are largely similar worldwide, accessible medications vary depending on the medical scenarios in each country. Furthermore, because SE requires immediate treatment, conducting high-level evidence-based clinical research on its management, such as randomized controlled trials (RCT), is extremely challenging.

In Japan, "Draft Guidelines for the Treatment of Status Epilepticus in Children" [1] was first released in 2005. Subsequently, phenobarbital (PB) in 2008, fosphenytoin (fPHT) in 2011, and midazolam (MDL) in 2014 received insurance coverage for SE in Japan, and the Japanese Society of Child Neurology (JSCN) issued the "Guidelines for the Treatment of Pediatric Status Epilepticus 2017" in June 2017 [2]. Subsequently, lorazepam (LZP) was covered by insurance in 2018, followed by buccal MDL in 2020, and levetiracetam (LEV) in 2023, but only for adults. Although the expansion in treatment options for SE in Japan is encouraging, clinical issues have arisen as to which drugs are appropriate. To develop a new guideline for these clinical concerns, the "Guidelines for the Treatment of Pediatric Status Epilepticus 2023" (GL2023) was published as a revised version. Recommendations from GL2023 are described in Table 1.

In GL2023, the target population for treatment was defined as children aged 1 month to 18 years. The rationales are as follows: 1) the causes of SE in the neonatal period are distinct, 2) treatment in the neonatal period is mostly performed in the Neonatal Intensive Care Unit, 3) the underlying conditions in adult SE differ from those in pediatric SE, and 4) treatment options differ from those in later age groups.

Although the GL2023 was already published in 2023 in Japanese, we decided to publish this review in English for several reasons. The first is we wanted to share Japan's pediatric SE treatment with the international community, since available medications and medical systems vary among countries, as already mentioned. Second, we sought to compare the epidemiological results of SE in Japan with those in other countries.

2. Definition of SE

The 2015 International League Against Epilepsy (ILAE) definition of SE emphasizes early recognition and treatment, introducing two critical time points [3]. The first time point (t_1), the duration at which the seizure should be considered "abnormally prolonged seizure", and the second time point (t_2), the duration beyond which the ongoing seizure activity is associated with a significant risk of long-term consequences. These time points differ according to the SE seizure type (Fig. 1). In the tonic-clonic SE, which is synonymous with convulsive SE (CSE), t_1 is specified to be 5 min and t_2 30 min. As for the nonconvulsive SE (NCSE) types, in the focal SE with impaired consciousness, t_1 is defined as 10 min and $t_2 > 60$ min, whereas in the absence SE, t_1 is 10–15 min and t_2 remains unknown.

In terms of clinical time course and drug response, the following terms were adopted in GL2023.

2.1. Early SE

Early SE is defined as the initial phase with the seizure duration of 5–10 min, to which immediate first-line treatment (benzodiazepines [BZDs]) should be initiated.

2.2. Established SE

This is the phase with a seizure duration of 10–30 min, following failure of the first-line treatment (one or two adequate doses of BZDs), and requiring second-line treatment. In Japan, initiation of second-line treatment may be possible for in-hospital SE; however, it may be

Table 1
Recommendations from Guidelines for the Treatment of Pediatric Status Epilepticus 2023.

CQ1: What are the early treatments for prolonged seizures?
1. If a seizure continues for more than 5 min, it is difficult to stop spontaneously and rapidly progresses to SE. Thus, early treatments is recommended.
2. Buccal MDL is suitable as an initial treatment for prolonged seizures occurring outside hospital as pre-hospital treatment.
3. There is no clear evidence that DZP suppositories and chloral hydrate are effective in discontinuing prolonged seizures early.
4. Nasal MDL and rectal DZP gel are recommended as pre-hospital treatment in European and American guidelines, but these medications are not available in Japan.

CQ2: What is the first treatment for persistent convulsive seizure on arrival at hospital?
1. Perform the initial assessment within 5 min of arrival at the hospital, secure the airway, and stabilize cardio-respiratory conditions. Check blood glucose levels, and administer glucose if hypoglycemia is present.
2. The first-line treatment of BZDs, such as MDL, LZP, and DZP, should be administered intravenously.
3. Non-intravenous (intrabuccal, intranasal, and intramuscular administration) MDL can be expected to have the same effect of discontinuing seizures as intravenous DZP.
4. It is important to administer medications with appropriate and sufficient dosages.

CQ3: What can be administered for convulsive pediatric SE when an intravenous route cannot be obtained?
1. Buccal MDL, non-intravenous (intrabuccal, intranasal, and intramuscular administration) MDL intravenous formulation, and intrarectal DZP intravenous formulation are recommended as alternative treatments. These treatments are effective and highly safe.

CQ4: What are the indications for hospitalization or transportation?
1. The following conditions may be considered for hospitalization or transportation. In clinical practice, these indications depend on the region and facility.
(1) SE or seizures in cluster
(2) Persistent impaired consciousness or new neurological signs
(3) Signs of increased intracranial pressure or meningeal irritation, or instability of respiratory and circulatory conditions
(4) A situation when the physician deems hospitalization necessary

CQ5: When seizures are discontinued by BZDs, is it effective to add additional medication to prevent seizure recurrence?
1. There is no clear evidence on the effectiveness of adding additional medication to prevent recurrence of seizures.

CQ6–1: When seizures do not discontinue by BZDs, what are the next treatment as second-line?
1. Phenytoin/fosphenytoin and phenobarbital are recommended to be administered in Japan.
2. Continuous intravenous MDL is not recommended as the second-line treatment.

CQ6–2: Are intravenous LEV and LCM effective for pediatric SE?
1. Intravenous LEV has been reported to be effective for SE in other countries. However, its use is off-label for SE in children, not adults, in Japan.
2. There are reports showing the effectiveness of intravenous LCM for SE. However, it is off-label use for SE in children and adult in Japan.

CQ7: Does treatment for NCSE improve outcomes?
1. Electrographic seizures and electrographic SE in children are seen in 3–45 % of cases in ICU and 8–17 % of cases in emergency departments.
2. Electrographic seizures/electrographic SE are independent factors associated with outcomes.
3. There is no consensus on whether treatment for NCSE improves outcomes.

CQ8: What are the indications for ICU admission in SE?
1. The following conditions may be considered for ICU admission. In clinical practice, these indications depend on the region and facility.
(1) The condition of impaired consciousness, poor respiratory and circulatory status caused by underlying diseases, such as acute encephalopathy or metabolic disorders
(2) The condition of respiratory and circulatory disorders caused by SE or its treatment
(3) The conditions of continuing seizures even after second-line treatment

CQ9: Is coma therapy effective for refractory SE?
1. Coma therapy induced by continuous intravenous MDL or barbiturates as the third-line treatment is effective.
2. In barbiturate coma therapy, the treatment goal is to achieve burst suppression on EEG in which seizure activity is considered to be controlled. However, as it is difficult to achieve burst suppression with continuous intravenous MDL, the treatment goal is to end the state of NCSE.
3. The use of propofol for SE in children is contraindicated in Japan.

(*continued on next page*)

Table 1 (*continued*)

CQ10: What treatments are available for super-refractory SE?
1. There are no recommended treatments for super-refractory SE. However, ketamine, general anesthesia, antiseizure medications, steroid and immunotherapy, epilepsy surgery, ketogenic diet, and therapeutic hypothermia are considered as fourth-line treatment.

CQ11: Is therapeutic hypothermia effective for refractory SE?
1. Therapeutic hypothermia may be attempted for refractory SE in children.
2. There is no evidence that therapeutic hypothermia improves the neurological outcomes for refractory SE in children.

CQ12: What are the investigations required for SE?
1. The following examinations should be considered for SE.
(1) Monitoring vital signs (respiratory rate, percutaneous arterial oxygen saturation, heart rate, blood pressure, monitoring electrocardiogram, level of consciousness, and body temperature)
(2) Rapid blood glucose test, blood gas analysis, and electrolytes (including calcium)
(3) Complete blood count, liver and kidney function, and ammonia
(4) Blood concentration of anti-seizure medication (if taking)
(5) Brain CT scan (see CQ14)
2. Brain MRI, EEG, additional blood tests, blood cultures, and cerebrospinal fluid tests depending on medical history, physical examination, and suspected causative disease.

CQ13–1: Is continuous EEG monitoring useful after initial treatment for SE?
1. If consciousness does not return for a long time after clinical cessation of seizures by treatment for SE, continuous EEG monitoring is useful for evaluating NCSE.
2. Continuous EEG monitoring is useful for evaluating the therapeutic effect of intravenous or continuous intravenous treatment in the case of refractory SE.
3. Continuous EEG monitoring with a reduced number of recording electrodes is relatively easy to perform and is useful for detecting non-convulsive seizures. However, it is necessary to keep in mind that the detection sensitivity may be reduced compared to the condition of monitoring EEG covered the entire head.

CQ13–2: Is amplitude-integrated EEG useful after initial treatment for SE?
1. Amplitude-integrated EEG may be useful as an alternative evaluation to regular EEG monitoring on continuous EEG monitoring in SE.

CQ14: Is emergency imaging (CT, MRI) necessary for SE?
1. Emergency imaging is useful when clinical symptoms and medical history suggest structural brain lesions, or when the cause is unknown at the first onset of SE.
2. Brain CT can be performed in most emergency departments and is useful in Japan when brain MRI cannot be performed immediately.
3. Brain MRI is required when clinical symptoms and medical history suggest hyperacute ischemic stroke or acute encephalitis/encephalopathy.

CQ15: What are the factors associated with poor outcomes in SE?
1. The factors that most influences poor outcomes in SE are the causes of SE.
2. Acute encephalopathy is the most common cause of poor outcomes in SE in Japan.
3. Younger age and seizure duration may be associated with poor outcomes.

BZDs, benzodiazepines; CT, computed tomography; DZP, diazepam; EEG, electroencephalogram; ICU, intensive care unit; LCM, lacosamide; LEV, levetiracetam; LZP, lorazepam; MDL, midazolam; MRI, magnetic resonance imaging; NCSE, nonconvulsive statue epilepticus; SE, status epilepticus.

challenging for out-of-hospital SE since it takes approximately 40–60 min from the commencement of the seizure to transfer to the emergency room [4,5]. In actual clinical practice in Japan, the first-line treatment for out-of-hospital SE is initiated at this time.

2.3. Refractory SE

This is the time point when the seizure duration is 30–60 min. Refractory SE is generally defined as the persistence of clinical or electrical seizures despite administration of one or more first-line (BZDs) as well as second-line treatment [6–8], and some reports define it as the phase when the seizure duration exceeds 60 min [9–15]. Third-line treatment is required for refractory SE. Although we considered 30–60 min as the reference standard for treatment timing, this time may have already been exceeded upon arrival at the hospital in the actual clinical practice of out-of-hospital SE.

2.4. Super-refractory SE

Super-refractory SE is a condition refractory to third- and fourth-line drugs and is generally defined as "SE that continues or is repeated for ≥24 h even after initiation of anesthetic therapy, including those that relapse when coma therapy is gradually withdrawn or discontinued" [16–19].

2.5. BZD-resistant SE

Unlike the preceding four types, BZD-resistant SE is identified based on drug response. It is the condition in which seizures do not stop when first-line BZD is administered, and is almost synonymous with established SE [17,20].

3. Epidemiology

3.1. Incidence

The incidence of pediatric SE is reported to be 3–42 children per 100,000 person-year [21–27]. The incidence varies with age and is reported to be highest in children under 1 year of age at 50–135 per 100,000 person-year [21,23]. The incidences also vary according to the era reported, region, racial composition of the reported cases, and the definition of SE. The incidence of pediatric SE in Japan is estimated to be 38.8–41.0 children per 100,000 person-year [28,29]. The recurrence rate of SE is approximately 20 % within 4 years of the first SE episode, and most of them would have occurred within the first 2 years [30]. It is reported that in 16 % of patients, recurrence occurs within 1 year after the first CSE regardless of the etiologies [31]. The incidence of refractory SE has been reported to be 10–40 % of SE [32–34], with super-refractory SE being 5–17 % of SE and 11–14 % of refractory SE [32–40]. In children, 7–20 % of SE [9,40,41], and 11 % of refractory SE progress to super-refractory SE [42], respectively. The etiology plays a major role in the progression from SE to refractory SE or super-refractory SE.

3.2. Etiology

The etiology of SE varies widely, and SE is classified into two major groups: the known category and the unknown category according to ILAE recommendation [3]. Furthermore, the known category is subdivided into four subtypes as follows: A) acute symptomatic, B) remote symptomatic, C) progressive, and D) electroclinical syndromes (Table 2).

The reason for the wide range in the proportion of causative diseases among each etiology is assumed to be (1) different definitions of SE depending on the time period to be reported, (2) different patient characteristics among the study, such as out-of-hospital SE cases or SE cases admitted to intensive care unit (ICU), (3) different concepts and classifications of causative diseases, and (4) different regions and medical environments.

3.2.1. Known etiology group

A) Acute symptomatic.
Acute symptomatic SE is generally caused by an acute disease. The percentage of SE is 10–40 % in other countries [3,21,23,24,27,43–51], and 8–45 % in Japan, which is almost comparable [28,29,52–57]. Particularly in Japan, acute encephalopathy accounted for 15–18 % of SE [28,29,55–57], which is much higher than the 1.9 % reported in other countries [49]. Bacterial meningitis accounted for 1.7–10 % of SE in other countries [9,21,44,45,47,49,50], whereas it is 2–12 % in Japan [28,29]. Cerebrovascular and metabolic disorders account for a small percentage of SE in Japan and other countries [9,29,47,49,50,57,58].

B) Remote symptomatic.
The remote symptomatic SE is caused by central nervous system disorders such as cerebral malformation, cortical dysplasia,

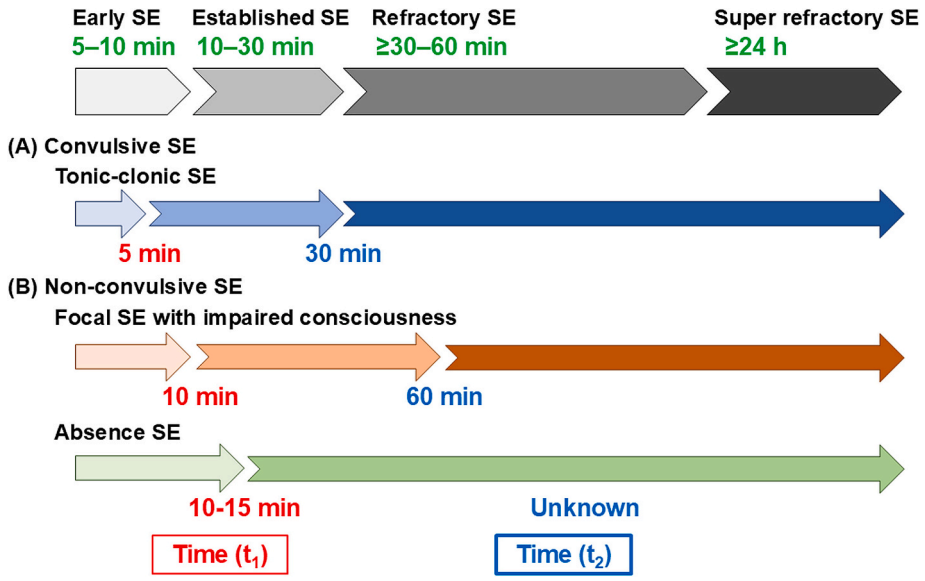

Fig. 1. The definition of status epilepticus.
SE, status epilepticus.

posttraumatic brain injury, and post-encephalitis and accounts for 15–28 % of SE in other countries [21,23,24,27,43–51] and 6.8–53 % in Japan [28,29,52–57].

C) Progressive.

Progressive SE is caused by progressive diseases, such as inborn errors of metabolism, brain tumors, and autoimmune encephalitis. The proportion of this subtypes accounts for 17–28 % of SE in other countries [9,43,47,48] and 0.9 % in Japan [52], which is extremely lower compared to that in other countries.

D) Electroclinical syndromes.

SE appearing in the setting of specific electroclinical syndromes is caused febrile seizures and epileptic syndromes. This etiological classification was proposed by ILAE in 2015 [3], and its proportion among total SE is still unclear, with future research results awaited. The proportion of electroclinical symptoms in pediatric SE reclassified according to the new ILAE proposal 2015 was reported as 4.6 % (8/173 patients) [48].

In previous reports, epilepsy accounted for 33–48 % of SE in other countries [45–47,49] and 12–54 % in Japan [29,53–57]. It is unclear if the current ILAE proposal accurately classifies epilepsy disorders among patients.

Febrile SE is the most common during childhood and has been classified as an independent etiology. In the new proposal, febrile SE is classified as electroclinical syndrome [3]. Febrile SE accounts for 15–40 % of SE in other countries [3,21,23,24,27,43–51], and 25–63 % in Japan [28,29,52–57], which is higher than that in other countries.

3.2.2. *Unknown etiology group*

The cause of SE in this group is unknown and this group was previously classified as “unclassified” or “idiopathic”. The proportion of this group accounts for 5–20 % in other countries [3,21,23,24,27,43–51] and 2–14 % in Japan [29,58]. According to Specchio et al. [48], 16.2 % (28/173) of pediatric SE cases were reclassified based on a revised ILAE proposal in 2015.

3.3. *Outcomes*

Acute complications of SE include tachycardia, hypertension, respiratory disorders, metabolic and respiratory acidosis, intracranial hypertension, cerebral edema, electrolyte abnormalities, rhabdomyolysis, renal failure, and other multiorgan damages [59]. Neurological sequelae include motor, cognitive and behavioral disorders, and epilepsy [30,44,59,60]. The mortality rate is estimated to be 3–11 %, with the cause of death primarily related to the etiology of SE and its causative disease [30,44,59,60]. The causes of SE have the greatest influence on poor outcomes, although they vary greatly depending on the study participants, methodologies, follow-up period, race, and medical conditions. In Japan, acute encephalopathy is the most common cause of poor outcome in SE [28,56,61,62], but younger age and seizure duration are also associated with adverse outcomes [63].

4. Pathophysiology

The inclusion of seizure duration in the definition of CSE is based on the outcomes of animal studies, in which systemic physiological changes, serum metabolic changes, and central nervous system (CNS) metabolic kinetics were examined in SE model generated by intravenous administration of bicuculline to *Papio papio* (baboons) [64–66]. In terms of physiological changes, within 30 min of the seizure, blood pressure increased, oxygen partial pressure in arterial blood decreased, carbon dioxide partial pressure in arterial blood increased, and body temperature increased (Table 3) [1]. In terms of serum metabolic changes, pH decreased, whereas lactate, blood glucose, and potassium levels increased. Cerebral oxygen consumption and blood flow increased by 300 and 900 %, respectively, compared with the pre-ictal state, which was classified as “energy compensatory state” at the time point. When the seizure lasted >30 min, blood pressure decreased, body temperature increased as the physiological changes, and creatine kinase levels were elevated owing to serum metabolic alterations. Cerebral oxygen consumption remained unchanged at 300 %, whereas cerebral blood flow decreased to 200 %, which was considered as “energy insufficient state” at this time point. Furthermore, as the seizure persisted for >60 min, physiological changes such as hypotension, hypoxemia, hypercarbia, pulmonary edema, and hyperthermia were observed, whereas serum metabolic changes included lactic and respiratory acidosis, hypoglycemia, hyperkalemia, and renal failure. Additionally, cerebral ischemia and cerebral edema were detected in the CNS circulatory and metabolic kinetics, indicating a “energy depletive state” at this time point. Human CSE has been observed to exhibit traits comparable to these experimental findings [67]. These data indicate that stabilizing of respiratory circulation, maintaining body temperature, and preventing

Table 2
Etiologies of status epileptics in children.

1. **Known**
   - 1.1. **Acute symptomatic**
     1. Cerebrovascular diseases
        Ischemic stroke, intracerebral bleeding, subarachnoid bleeding, subdural hematoma, epidural hematoma, sinus venous thrombosis, cortical venous thrombosis, Moya-Moya disease
     2. Central nervous system infections
        Acute bacterial meningitis, acute viral meningitis, tuberculous meningitis, acute fungal meningitis, acute viral encephalitis (influenza encephalitis, herpes encephalitis, HHV-6 encephalitis, etc.), brain abscess, subacute sclerosing panencephalitis
     3. Acute encephalitis/encephalopathy
        AESD, AERRPS (FIRES), ANE, HSES
     4. Acute disseminated encephalomyelitis
     5. Metabolic disturbances
        Electrolyte imbalances, hypoglycemia, acute renal failure, acute hepatic failure
     6. Hypoxia
        Hypoxic ischemic encephalopathy, asphyxia, drowning, nitric oxide poisoning
     7. Intoxication
        Aminophylline, ginkgo, ASMs, heavy metals, alcohol
     8. Others
        Adjustment/self-discontinuation/less adherence of ASMs, hypertensive encephalopathy, head trauma (including abuse), malignant hyperthermia
   - 1.2. **Remote symptomatic**
     1. Cerebral malformations
        Holoprosencephaly, congenital hydrocephalus
     2. Neurocutaneous syndromes
        Sturge-Weber syndrome, tuberous sclerosis complex, Neurocutaneous melanoma
     3. Cortical dysplasias
        Focal cortical dysplasia, hemimegalencephaly, heterotopic gray matter, subcortical band heterotopia, lissencephaly, polymicrogyria, schizencephaly
   - 1.3. **Progressive**
     1. Inborn errors of metabolism and neurodegenerative diseases
        Mitochondrial diseases (Alpers disease, MELAS, Leigh syndrome, MERRF), Menkes disease, adrenoleukodystrophy, Alexander disease, ornithine transcarbamylase deficiency, hyperprolinemia, maple syrup urine disease, metachromatic leukodystrophy, neuronal ceroid lipofuscinosis, Lafora disease, Unverricht-Lundborg disease, sialidosis, Gaucher disease, DRPLA, carnitine palmitoyl transferase deficiency
     2. Intracranial tumors
        Glioma, meningioma, metastases, lymphoma, carcinomatous meningiomas, ependymoma, embryonal tumors (atypical teratoid/rhabdoid tumor, medulloblastoma), LEATs (ganglioglioma, dysembryoplastic neuroepithelial tumors (DNET), diffuse glioma
     3. Autoimmune disorders
        Autoimmune encephalitis (anti-NMDA receptor encephalitis, anti-VGKC complex antibody encephalitis/LGI-1 encephalitis), anti-GAD antibody-associated encephalitis, anti-AMPA receptor encephalitis, seronegative autoimmune encephalitis), paraneoplastic encephalitis, Hashimoto's encephalopathy, Rasmussen's encephalitis, NPSLE, multiple sclerosis
   - 1.4. **Electroclinical syndromes**
     1. Febrile seizures
     2. Epilepsy
        Dravet syndrome, Lennox-Gastaut syndrome, SeLEAS, Ring Chromosome 20 syndrome, Angelman syndrome, Wolf-Hirschhorn syndrome
2. **Unknown**
   1. Epilepsy (unknown etiologies)
   2. Others

AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; AERRPS, acute encephalitis with refractory, repetitive partial seizures; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANE, acute necrotizing encephalopathy; ASMs, anti-seizure medications; DRPLA, dentatorubral-pallidoluysian atrophy; FIRES, febrile infection related epilepsy syndrome; GAD, glutamic acid decarboxylase; HHV-6, human herpesvirus-6; HSES, hemorrhagic shock and encephalopathy syndrome; LEATs, long-term epilepsy-associated tumors; LGI-1, leucine-rich glioma-inactivated 1 protein; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonus epilepsy associated with ragged-red fibers; NMDA, N–methyl–D–aspartate–type glutamate receptor; NPSLE, neuropsychiatric systemic lupus erythematosus; SeLEAS, self-limited epilepsy with autonomic seizures; VGKC, voltage-gated potassium channel.

hypoglycemia during the treatment of CSE might delay the onset of CNS damage in addition to reducing seizures.

Alterations in neurotransmitter receptors during prolonged seizures have been reported as a molecular pathogenesis [30,67] (Fig. 2). In mature neurons, γ-aminobutyric acid $(GABA)_A$ receptors migrate from the postsynaptic surface to the intracellular space during prolonged seizures, resulting in "internalization" that decreases the number of receptors on the postsynaptic surface. This is expected to minimize the inhibitory effects [68–70]. In contrast, *N*-methyl-D-aspartate (NMDA) receptors, which have excitatory effects, are upregulated on the postsynaptic membrane during prolonged seizures, which is hypothesized to increase neuronal excitability [71]. Furthermore, the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor is thought to maintain its plasticity during convulsive seizures, resulting in a seizure-sustained effect [72,73]. Alterations in these receptors have been reported to reduce the efficacy of BZD [30,67,72–74]. Based on these pathological conditions, a multi-combination therapy combining BZDs, $GABA_A$ receptor agonist, and ketamine, as NMDA receptor inhibitor, has been reported to be effective as early treatment in animal models of CSE [75–78] and may be clinically implemented in human patients in the future.

5. Management (Fig. 3)

5.1. Early SE

The goal at this stage is to terminate the seizures as early as possible. Outside of the hospital, rescue medications are administered non-intravenously as the pre-hospital management. In the hospital, it is important to first secure the airway and stabilize the respiratory circulation [79–85], before attempting to acquire a venous channel.

Table 3
Physiological changes during convulsive seizures.

Seizure duration	<30 min	≥30 min	>60 min
Systemic physiological changes			
Blood pressure	↑	↓	Hypotension
PaO_2	↓	↓	Hypoxemia
$PaCO_2$	↑	↑	Hypercarbonemia
Lung water content	↑	↑	Pulmonary edema
Body temperature	↑ (+1 °C)	↑ (+2 °C)	Hyperthermia
Metabolic changes			
pH	↓	↓	Acidosis
Lactate	↑	↑	Lactic acidosis
Glucose	↑	→	Hypoglycemia
K^+	↑	↑	Hyperkalemia
CK	→	↑	Renal failure
Cerebral metabolic kinetics			
Cerebral oxygen consumption	↑ (+300 %)	↑ (+300 %)	Cerebral ischemia
Cerebral blood flow	↑ (+900 %)	↑ (+200 %)	Cerebral edema
Energic state	Compensatory	Insufficient	Depletive

CK, creatine kinase; CO_2, carbon dioxide; K, potassium; O_2, oxygen; $PaCO_2$, arterial carbon dioxide pressure; PaO_2, arterial oxgen pressure.

5.1.1. *Pre-hospital treatment*

A) Buccal midazolam (MDL) (Bucolam®).

The dosage of buccal MDL is determined by the patient's age. However, depending on the patient's body size and co-morbidities such as airway and respiratory disorders, it may be appropriate to prescribe a lower dosage than that based on age.

Scott et al. [86] reported that when buccal MDL and rectal liquid diazepam (DZP) were administered for seizures lasting more than 5 min, seizures stopped in 75 % of the patients in the buccal MDL group (40 occasions) and 59 % patients in the rectal DZP group (39 occasions), with no significant difference between the two groups ($p = 0.16$) [86]. Furthermore, the mean time from drug administration to seizure cessation was 6 and 8 min in the buccal MDL and the rectal DZP groups, respectively, with no significantly difference ($p = 0.31$). Moretti et al. [87] reported that seizure duration was significantly shorter in buccal MDL group than in the rectal liquid DZP group ($p = 0.0004$) among children in outpatient setting.

B) Diazepam (DZP) suppositories.

As rectal DZP gel is not available in Japan, DZP suppositories have been used in clinical practice and buccal MDL was not in use until 2020. However, DZP suppositories are not indicated for SE treatment since they take longer to reach the maximum blood concentration than rectal DZP gel and do not achieve the optimal therapeutic range quickly. In addition, there are no evidence that DZP suppositories are effective for SE.

C) Chloral hydrate.

There have been a few reports the effectiveness of chloral hydrate against acute seizures and SE [88–91]; however, no high level evidence exist.

Current Issues and Future Prospects.

According to studies comparing family and caregiver satisfaction with pre-hospital medications, buccal and intranasal MDL were more favorable than rectal DZP in terms of perceived efficacy and ease of administration [92–95]. DZP nasal spray, MDL auto-intramuscular injector, MDL intranasal spray, and oral alprazolam inhaler are currently used in countries other than Japan [96,97], and we hope that these drugs will be available in Japan in near future.

It is difficult to make universal decisions regarding the administration of rescue medications as pre-hospital treatment not only in Japan but also in other countries owing to variability of patients' severities, their comorbidities, and emergency medical care systems. In addition, multiple issues must be addressed, such as recognizing the pre-existing condition that caused SE and establishing systematic first-aid training for caregivers and teachers in schools.

5.1.2. *In-hospital treatment*

If an intravenous route can be obtained, BZDs are administered intravenously; otherwise, the drug is administered via a non-intravenous route such as intramuscular, intranasal, or buccal [98]. If the blood glucose level is <60 mg/dL, 0.5 g/kg of glucose (max 25 g) should be

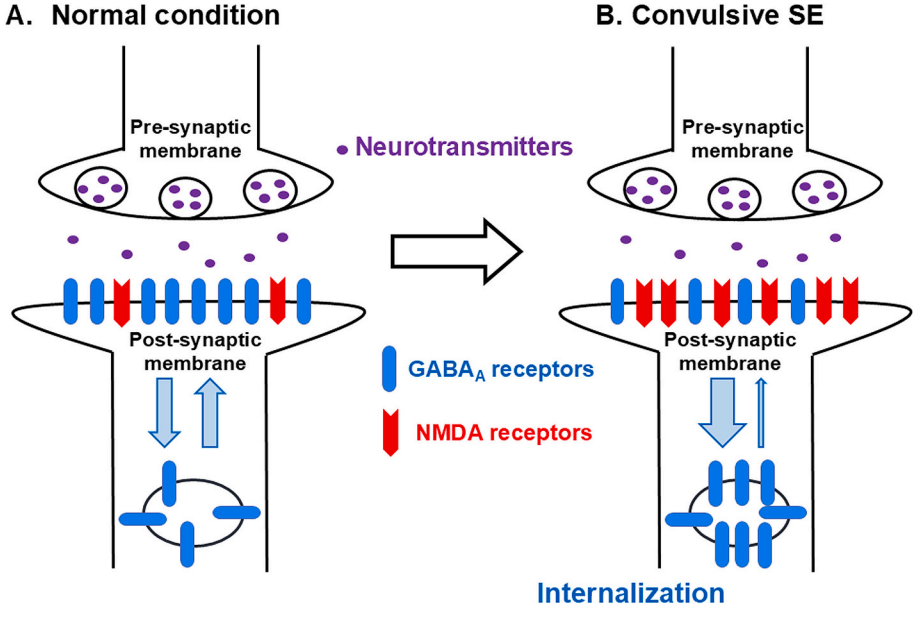

Fig. 2. Alterations in neurotransmitter receptors.
In normal condition, γ-aminobutyric acid $(GABA)_A$ receptors move between the postsynaptic surface and the intracellular space. During convulsive status epilepticus, $GABA_A$ receptors migrate from the postsynaptic surface to the intracellular space, resulting in "internalization" that decreases the number of receptors on the postsynaptic surface. In contrast, *N*-methyl-D-aspartate (NMDA) receptors, which have excitatory effects, are upregulated on the postsynaptic membrane.

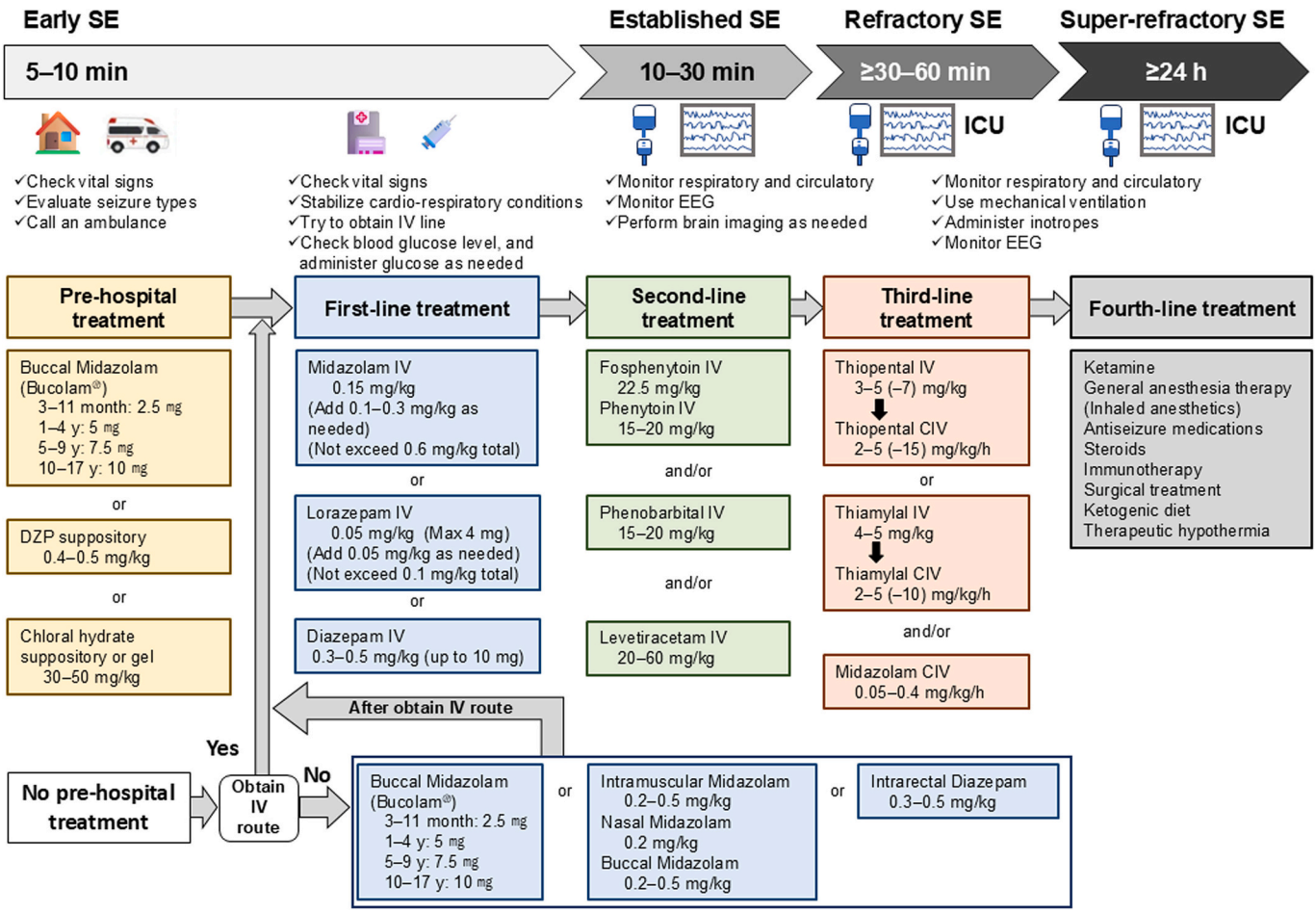

Fig. 3. Management for convulsive pediatric status epilepticus.
CIV, continuous intravenous; EEG, electroencephalogram; ICU, intensive cate unit; IV, intravenous; SE, status epilepticus.

administered intravenously as soon as possible [85]. Intramuscular administration of glucagon 0.02 mg/kg (maximum 1 mg) is also an option [85].

5.1.2.1. When intravenous route can be obtained. If a venous route is available, MDL, LZP, and DZP are first-line treatments. The intravenous administration of all three drugs is likely to have similar effects on SE cessation [99], as is the frequency of adverse events also being similar for them. However, for respiratory depression as adverse effects, LZP is less frequently found than DZP [98]. In this GL2023, systematic reviews and meta-analysis were performed on the efficacy of three types of BZDs (MDL, LZP, and DZP). As in another review [98], the rates of seizure cessation were the same among the three drugs, but respiratory depression was less frequent with LZP than with DZP. It is important to administer a sufficient dose of BZDs, since there have been reports that lower initial doses of BZDs than recommended have resulted in lower rates of seizure cessation [100]. If the initial dose is ineffective, one additional dose equivalent to the initial dose is administered 5–10 min later [79,82,84], and if that is ineffective, the second-line treatment should be initiated.

1) Intravenous MDL.

In a prospective study of 34 patients aged ≤16 years with SE (defined seizure duration >15 min or repeated seizures >5 min) at 26 centers in Japan, a bolus dose of 0.15 mg/kg of MDL and an additional dose of 0.1–0.3 mg/kg (total dose ≤0.6 mg/kg) resulted in a seizure cessation rate of 88.2 % within 10 min after last MDL administration [58]. In terms of dose, the seizure cessation rate was 52.9 % at a total dose of ≤0.15 mg/kg, and 82.4 % at a dose of ≤0.3 mg/kg, respectively. Adverse events were observed in three patients, with one case each of elevated liver enzymes, rash, and respiratory depression. Patients with respiratory depression required oxygen administration and bag-valve mask ventilation. In a retrospective study of 82 SE occasions, the seizure cessation rate was 45.9 % after the first MDL administration (mean dose; 0.173 mg/kg) [101]. Adverse events such as wheezing and mild respiratory depression were observed in three occasions. Yoshikawa et al. [102] reported that the first MDL dose (0.1–0.3 mg/kg) was administered for 16 occasions in 10 patients, and seizures ceased within 1 min except for one occasion and respiratory depression was not observed. In a multicenter study by Hayashi et al. [53], the seizure cessation rate was 74.3 % in 70 occasions when MDL was first administered, and respiratory depression was observed in 17.3 % of 52 occasions.

In another report, among 40 patients aged 6 months–14 years who received an initial 0.1 mg/kg and an additional 0.1 mg/kg of intravenous MDL, the efficacy rate was 97.5 % and respiratory depression was 0 % [99]. In a study using maximum five bolus doses of intravenous MDL (0.1 mg/kg) at 5-min intervals as the first treatment in 76 CSE occasions in patients aged 1–15 years found that 89 % of seizures stopped after up to three doses (mean dose until seizure cessation was 0.17 ± 0.09 mg/kg), and 91 % even stopped after up to five doses [103]. Concerning respiratory depression as the adverse effects, transient respiratory depression was reported in 13.1 % and ventilatory management was required in 3 % cases.

2) Intravenous lorazepam (LZP).

The recommended initial dose of LZP is 0.1 mg/kg (maximumly up

to 0.2 mg/kg) in Europe and the United States [79,82,84], whereas the initial dose in Japan is 0.05 mg/kg (maximum 0.1 mg/kg).

In reports on intravenous LZP for SE from other countries, a first bolus dose of 0.1 mg/kg was most common and the seizure cessation rate ranged from 70.4 to 100 % [99,104–107]. There was considerable variation in the seizure recurrence rates; 39.2 % (38/97) within 4 h [104], 5.0 % (2/40) within 12 h [99], and 0 % within 18 h [107]. As for adverse events, respiratory depression requiring ICU admission was reported in 3.7 % [105], and some degree of respiratory depression was observed in 36.5 %, with requirement of respiratory support in 17.6 % [104].

3) Intravenous diazepam (DZP).

In prospective studies on intravenous DZP for SE, the most common first bolus dose was 0.2–0.3 mg/kg, and the seizure cessation rate ranged from 64.7 to 100 % [99,104,105,108–113]. One study on patients with febrile seizures found DZP to be effective in 92.3 % (24/26 patients) [112]. As for adverse events, respiratory depression requiring ICU admission was reported in 23.5 % [105], and mild respiratory depression in 45.7 %, and in 16 % cases, respiratory support was required [104]. Additionally, Tonekaboni et al. [108] reported moderate hypotension and apnea in 21.7 % cases.

5.1.2.2. When intravenous route is not obtained. If an intravenous route cannot be obtained, administration of buccal MDL is recommended. According to the GL2023 results of the systematic reviews and meta-analysis on the efficacy between buccal MDL and intravenous DZP, the rates of seizure cessation and frequency of adverse effects, such as respiratory depression, were not different between the two drugs. Additionally, the results on the efficacy between buccal MDL and rectal gel DZP showed that buccal MDL had a higher seizure cessation rate, lower need for additional drugs, and a lower seizure recurrence rate within 1 h of administration compared with rectal gel DZP. MDL intravenous formulation, which is safe and effective when injected intramuscularly, nasally, or buccally, or DZP intravenous formulation, which is delivered rectally, is used off-label in Japan [98].

A) Non-intravenous MDL.

In a phase III multicenter, randomized, open-label study conducted in Japan on buccal MDL for CSE, 25 patients younger than 18 years (median age 2.8 years) were included, and seizures halted in 21 patients (84 %) within 10 min [114]. Fujita et al. [115] reported that seizure cessation was achieved within 3 min on three out of five occasions (60 %) for generalized clonic convulsions in patients with refractory epilepsy, whereas Kuki et al. [116] reported seizure cessation in 65 % (21/32 occasions in 14 patients) and no respiratory depression.

For intramuscular administration of MDL intravenous formulation, MDL dose at 0.2 mg/kg was administered to 48 children (69 seizure events), and seizure cessation was achieved on 64 occasions (93 %) with no adverse effects including respiratory depression nor hypotension [117]. MDL dose at 0.2 mg/kg was administered nasally to 20 children (20 occasions), with seizure cessation achieved within 5 min (mean 3.5 min) on 19 occasions (95 %), with no seizure recurrence within 60 min [118].

Alansari et al. [119] compared seizure cessation rates within 5 min between buccal and intramuscular MDL administration. The seizure cessation rates were 46 % (32/70) in buccal MDL group and 61 % (41/67) in intramuscular MDL group and they showed that intramuscular MDL administration was more likely to halt the seizures. Furthermore, some reports suggest that non-intravenous administration of intravenous MDL formulation is as effective and safe as intravenous or intrarectal administration of DZP for cessation of seizures [120,121].

B) Intrarectal DZP administration.

Since rectal DZP gel is not available in Japan, intravenous DZP formulation can be rectally administered as an off-label and alternative treatment.

5.2. Established SE

Established SE is synonymous with BZD-resistant SE, and the frequency is reported to be approximately 20–50 % [9,104,122–126]. For this condition, the drugs as the second-line treatment that differs from the pharmacological action of BZDs, should be administered. Although there is no clear definition of timing for evaluation of the efficacy of BZDs, it reported to be evaluated at 10–20 min after BZDs administration [9,104,122–125]. In GL2023, if seizures do not stop within 5–10 min of intravenous BZD injection, it should be deemed as “established SE”.

In Japan, as the second-line treatment, PHT/fPHT and PB can be used for pediatric SE and LEV can be used in adults only. Lacosamide (LCM) is not covered for SE by health insurance, and intravenous valproate (VPA) and clonazepam (CZP) are not available in Japan.

A) Phenytoin (PHT) and fosphenytoin (fPHT).

Because fPHT and PHT have a weak sedative effect and little influence on consciousness evaluation, they may be administered instead of PB in cases of SE with fever to differentiate between febrile SE and acute encephalitis/encephalopathy. PHT may cause inflammatory conditions such as pain, redness, and swelling at the site of intravenous administration, as well as tissue necrosis owing to extravascular leakage and “purple glove syndrome”. In contrast, compared to PHT, fPHT is water-soluble and slightly alkaline, with a lower osmotic pressure compared to saline solution, which can reduce tissue damage. Both drugs have the potential to alter cardiovascular functions, hence an electrocardiogram should be performed during administration. These drugs are contraindicated in the presence of sinus bradycardia or severe stimulated conduction disorders.

B) Phenobarbital (PB).

PB has a strong sedative effect, and it is often difficult to assess the level of consciousness. If patients have febrile SE, fPHT/PHT may be preferred over PB.

C) Levetiracetam (LEV).

Because LEV has fewer side effects such as increased secretions and respiratory depression, and has a weaker sedative effect, it may be preferred in children with severe mental and physical disabilities and those with febrile SE.

D) Lacosamide (LCM).

The suggested dose of LCM for SE in adults is 200–400 mg over 15 min, although there are no clear recommendations for children [81]. A systematic review on LCM use for BZD and non-BZD-resistant SE reported 57 % efficacy in children and adults, and 45–78 % efficacy in children alone (initial dose 2.0–10.0 mg/kg) [127]. Poddar et al. [128] conducted a cohort study on LCM use in BZD- or non-BZD-resistant pediatric SE (mean initial dose 8.7 mg/kg [3.3–10.0 mg/kg]) and found that seizure cessation rate was 44.4 % (4/9 patients) and 50 % responder rate was 33.3 % (3/9patients). In a retrospective study on LCM (initial dose 2.0 mg/kg) in BZD- or non-BZD-resistant pediatric SE conducted by Welch et al. [129], the efficacy rate was found to be 18.9 % (7/37 patients) [129]. More research outcomes are expected in the future.

5.2.1. Drug selection for BZD-resistant SE

The pharmacologic effects of second-line BZD-resistant SE medications differ, making it challenging to prioritize them owing to their efficacy varying among reports.

A double-blind RCT of fPHT, LEV, and VPA in pediatric BZD-resistant SE also reported efficacy of 49.3, 51.8, and 52.2 % for fPHT, LEV, and VPA, respectively, with no significant difference between drugs, and concluded that fPHT was as effective as LEV and VPA [130]. In a double-blind RCT on the efficacy of the three drugs (fPHT, LEV, and VPA) for BZD-resistant SE comprising adults and children, efficacy rates were 44.9, 46.9, and 46.3 % in fPHT, LEV, and VPA, respectively, with no significant differences among them [131]. In another report, the efficacy of three drugs (fPHT/PHT, LEV, and PB) was examined retrospectively. The effective rate was 22.2 % (6/27 patients) for fPHT/PHT, 77.8 % (7/9 patients) for LEV, and 89.5 % (17/19 patients) for PB with PB being more effective than fPHT/PHT [125].

Two open-label RCT of PHT and LEV for BZD-resistant pediatric CSE reported efficacy of 64.2 % for PHT vs 69.7 % for LEV and 59.6 % for PHT vs 50.4 % for LEV, respectively, with no significant difference in efficacy between PHT and LEV [132,133]. A retrospective study on the efficacy of LEV and PB for BZD-resistant pediatric SE reported 33.3 % for LEV and 100 % for PB concluding that PB was more effective than LEV [134]. Furthermore, a double-blind RCT of PB and VPA in pediatric BZD-resistant CSE reported no significant difference in efficacy of PB (76.7 %; 23/30 patients) and VPA (90 %; 27/30 patients) [135]. A retrospective study on the efficacy of PHT and LCM for refractory SE, resistant against BZD and LEV in adult found no significant difference in efficacy, with 40.0 % (6/15 patients) for PHT and 33.3 % (7/21 patients) for LCM, respectively [136].

In comparative studies of four or more anti-seizure medications (ASMs), a double-blind RCT for CSE in adult demonstrated that the efficacy rate was 43.6 % for PHT, 55.8 % for DZP + PHT, 64.9 % for LZP, and 58.2 % for PB, and PHT was less effective than LZP and PB [123]. A network meta-analysis of efficacy of the six drugs (VPA, PHT, DZP, PB, LCM, and LEV) for BZD-resistant CSE in adults demonstrated that: 1) PB was more effective than VPA, PHT, DZP, LCM, and LEV at 1 h after intravenous administration; 2) PB had higher seizure cessation rate than that of VPA, DZP, and LCM at 24 h after intravenous administration; and 3) LCM was less effective than PB, but did not differ significantly in efficacy among the other drugs [137].

5.3. Refractory SE

The goals of treatment in refractory SE are seizure control, cerebral protection, and reduction of complications [17]. In Japan, coma therapy induced by continuous intravenous MDL, thiopental (TPL), and thiamylal is recommended as the third-line treatment. In barbiturate coma therapy, the treatment goal is to achieve burst suppression on electroencephalogram (EEG), which means seizure activity is deemed to be controlled.

However, as it is difficult to achieve burst suppression with continuous intravenous MDL, the treatment goal is to end the state of NCSE. Propofol is not recommended for pediatric SE because propofol is contraindicated for sedation during ventilatory management in pediatric intensive care in Japan.

Coma therapy was first reported by Young et al. [138], who reported that continuous intravenous barbiturates for refractory SE was effective in terminating seizures, consistent with burst suppression on EEG. Currently, coma therapy refers to treatment in which brain function is suppressed by continuous intravenous anesthetics such as MDL and propofol, in addition to barbiturates. Furthermore, there is no clear definition of anesthetic depth, such as the presence or absence of burst suppression on EEG. Because coma therapy with barbiturates results in circulatory failure owing to decreased cardiac function and peripheral vascular resistance, management in an ICU should be considered. If high-dose catecholamines are required, maintaining circulation by reducing or discontinuing barbiturates should be a priority.

The goals of coma therapy are seizure control and suppression of EEG background activity, including burst suppression. Maintenance therapy is continued for 24–48 h for continuous intravenous MDL and 12–48 h for barbiturates [80,81,139]. Continuous intravenous MDL or barbiturates achieved seizure cessation in 94 % (51/54 patients) of refractory pediatric SE, thus, coma therapy with these drugs is considered as the vital treatment [140]. Regarding superiority of continuous intravenous MDL and barbiturates for refractory SE, previous studies have shown that 1) both drugs were equally effective in controlling seizures; 2) seizure recurrence rate, including seizures on EEG, was higher with continuous intravenous MDL than with barbiturates; and 3) the incidence of circulatory depression was higher with barbiturates than with continuous intravenous MDL [141–143]. The neurological prognosis is not conclusive because of variation in findings among reports [141–145]. Although there is no clear indicator of when to start coma therapy, refractory SE in adults has been found to improve within 48 h after the commencement of seizure [146]. Some studies suggest that coma therapy is less likely to cause complications or have a poor prognosis; thus, though coma therapy should be initiated without delay, it should not be continued indefinitely [147].

A) Continuous intravenous MDL.

In a systematic review of coma therapy for pediatric SE, continuous intravenous MDL controlled clinical seizures in 76 % patients [145]. In a study comparing fPHT and continuous intravenous MDL for BZD-resistant CSE in children, the percentage of patients requiring barbiturates coma therapy was 48.7 % (20/41patients) in fPHT and 35.3 % (29/82 patients) in continuous intravenous MDL, respectively, with no significant difference [148]. However, the percentage of patients who required ventilators was higher for continuous intravenous MDL than for fPHT, and the percentage of patients who did not show improvement in the level of consciousness at 12 h after treatment was also higher for continuous intravenous MDL compared to that for fPHT. In a study comparing continuous intravenous MDL and continuous intravenous DZP for refractory pediatric SE, it was reported that 1) the mean dose of continuous intravenous MDL was 0.22 ± 0.11 (0.12–0.48) mg/kg/h, 2) the seizure cessation rate was 86 % in MDL and 89 % in DZP; and 3) the seizure recurrence rate during continuous intravenous MDL was 57 % in MDL and 16 % in DZP [149]. This report included many cases of meningitis/meningoencephalitis as the causative disease, requiring ventilatory management in about half of the cases and hypotension in 40 %, with death in 10/40 cases.

Until now, intravenous bolus MDL and subsequent continuous intravenous MDL (0.1–0.5 mg/kg/h) have been widely used for SE in Japan. Although the frequency of respiratory and circulatory depression is not high with this dosage in Japan [53,101,102], it has been reported that ventilatory management was necessary in more than half of the cases with the same dosage in other countries [149,150]. Therefore, continuous intravenous MDL for refractory SE requires careful observation of respiratory and circulatory status, taking into consideration the causative disease and comorbidities. Regarding neurological prognosis, Nagase et al. [141] compared the barbiturates group with EEG monitoring and the continuous intravenous MDL group without EEG monitoring in febrile refractory SE in children. They found that the continuous intravenous MDL group was much less successful than the barbiturates group at preventing neurological sequelae.

Therefore, when continuous intravenous MDL is administered for Refractory pediatric SE, it is important to perform EEG as well as respiratory and circulation monitoring in the ICU.

B) Barbiturates (TPL/thiamylal).

TPL is also recommended for refractory SE in other countries

[79–84,151]. The barbiturates therapy usually requires ventilatory management for respiratory depression and blood pressure maintenance for hypotension and cardiac failure. Guidelines of other countries do not mention thiamylal. Animal studies indicate that its anesthetic effect is approximately 1.5 times more potent than that of TPL, with a faster anesthetic effect, reduced excitability, and faster recovery from anesthesia [152]. In reports on thiamylal for refractory SE in children and adult, there was cessation of seizures in almost all cases [141,153,154].

5.4. Super-refractory SE

There is no recommended treatment for super-refractory SE. Ketamine, general anesthesia, ASMs, steroid and immunotherapy, epilepsy surgery, ketogenic diet, therapeutic hypothermia, magnesium, pyridoxine, transcranial magnetic stimulation, electroconvulsive therapy, vagus nerve stimulation (VNS), deep brain stimulation (DBS), and cannabidiol are considered as the treatment options [17,155].

A) Ketamine.

Ketamine has NMDA receptor antagonist activity. It is reported that ketamine is administered for super-refractory SE and is relatively fast-acting with few serious adverse effects [155–157]. In 67 cases in which ketamine was combined with propofol, seizures ceased in 91 % patients [158]. In a study of 68 adults with super-refractory SE who were refractory to high-dose intravenous MDL, seizures discontinued in 63 % within 24 h after initiating ketamine and seizure frequency reduced by half in 18 % [19]. In another observational study, 27/42 patients (64 %) showed cessation of convulsive seizures after ketamine administration [159]. As for dosage and duration of treatment of ketamine, the dosage of continuous intravenous ketamine is 0.06–7.5 mg/kg/h and the duration of treatment is from 24 h to 10 days [19,159–162]. Regarding adverse effects, elevated blood pressure has been reported. Continuous intravenous ketamine was reported to stabilize blood pressure as the dosage increased and to be able to discontinue inotropic medications; however, barbiturates coma therapy for super-refractory SE required the inotropic drugs to prevent hypotension [19]. Furthermore, it has been reported that there was no difference in cerebral pressure, cerebral blood flow, or cerebral perfusion pressure regardless of the amount of ketamine administered [19]. On the other hand, secondary hypothermia was observed in 36/63 patients treated with ketamine for super-refractory SE in adults, thus body temperature needs to be monitored [163].

B) General anesthesia therapy (Inhaled anesthetics).

According to a systematic review, seizures were terminated in all 27 individuals; however, there was recurrence in 41 % patients after anesthetic therapy was withdrawn [155]. The time to discontinue seizures was just a few minutes following the start of anesthetic therapy, demonstrating an extraordinarily rapid onset of action [164–166]. Regarding complications of this therapy, hypotension, atelectasis, infection, paralytic ileus, and deep vein thrombosis are reported [164].

C) Anti-seizure medications (ASMs).

ASMs are often newly added to the treatment of super-refractory SE. Efficacy rates of ASMs were reported as follows: topiramate, 57 % (40/70 cases) [167–176]; LCM, 6 % (1/18) [177–179]; pregabalin, 0 % (0/2) [180]; LEV, 53 % (20/38) [181–189]; perampanel, 33 % (22/66) [190–194]; stiripentol, 60 % (3/5) [194–196]; high-dose PB therapy, 50 % (5/10) [197]; zonisamide, 14 % (1/7) [198]; and rufinamide 100 %, (1/1) [199]. When evaluating the efficacy of these ASMs, it is important to keep in mind the following: 1) they are used in combination with general anesthesia and other ASMs; 2) the time taken to evaluate the efficacy of each ASM will be as long as days; and 3) the efficacy evaluation criteria vary among studies.

D) Steroids and immunotherapy.

There are reports of immunotherapy including steroids, immunoglobulin, and plasma exchange for super-refractory SE caused by encephalitis/encephalopathy, such as acute encephalitis with refractory, repetitive partial seizures (AERRPS); febrile infection-related epilepsy syndrome (FIRES); among others. In a systematic review of 21 patients, seizures discontinued in 5 % (1/21) [155]. In addition, there are only a few case reports about plasma exchange being effective such as in a child with super-refractory SE caused by encephalitis [200] and another child with refractory SE caused by $GABA_B$ receptor limbic encephalitis being treated with rituximab [201]. Corticosteroids in adult super-refractory SE were effective in 20 % (1/5 patients) [202]. The efficacy of allopregnanolone, a $GABA_A$-receptor agonist neurosteroid, has been reported in some studies [203–206], and it was reported that 68 % (17/25) of adults with super-refractory SE successfully weaned from coma therapy [204].

E) Surgical treatment.

Focal resection may be performed in cases in which epileptic onset zone is evident on CNS imaging and electrophysiology. In a systematic review of 36 cases, seizures discontinued in 33 cases treated with various surgical interventions: focal resection in 21; hemispherotomy in eight; combination of focal resection and multiple subpial transection in three; combination of focal resection and corpus callosotomy in two; and combination of multiple subpial transection and corpus callosotomy in one [158].

F) Ketogenic diet.

In a systematic review of super-refractory SE, where 12 of 14 patients were FIRES, the ketogenic diet was beneficial in 12/14 cases [155]. Other studies also indicate that ketogenic diet was effective: for example, in 90 % (9/10 adult patients including 7 cases of encephalitis) [207], and it was effective (seizures terminated or reduced by less than 50 %) for 54 out of 67 people with super-refractory SE largely caused by FIRES [208–219]. In seven of these 54 cases ketogenic diet was administered intravenously [208,212,214–216]. In children, the time from the start of ketogenic diet to improvement of super-refractory SE was reported to be within one week [214], five days [215], and 1–19 days (mean 8.3 days) [216]. Early complications of ketogenic diet such as gastrointestinal disorders including diarrhea, lipid aspiration pneumonia, hyperlipidemia, and elevated hepatic enzymes are reported [213–215].

G) Therapeutic hypothermia.

Therapeutic hypothermia may be tried for pediatric patients with refractory/super-refractory SE, however, there is no evidence that hypothermia improves neurological outcome.

Hyperthermia in early stages of CNS injury, like post-resuscitation encephalopathy or head trauma, is associated with poor neurological prognosis. Therapeutic hypothermia may be neuroprotective by preventing apoptosis, reducing mitochondrial dysfunction, inhibiting free radical production, suppressing edema by reducing vascular permeability of blood-brain barrier, suppressing metabolism and immune response, and finally suppressing epileptic activity and seizures [220]. Recently, the term “targeted temperature management (TTM)” has been adopted to describe the controlled regulation of body temperature to a specified target level and it is being used in place of the term hypothermia [221].

One RCT of adults with SE (138 patients in the TTM group vs 130 in the non-TTM group) showed the association between TTM (hypothermia with 32–34 °C) and neurological outcomes in refractory SE [222]. The rate of controlling electrographic status epilepticus (ESE) on day 1 was 11 % in the TTM group and 22 %

in the non-TTM group, with a significant difference. On the other hand, there was no significant difference in the proportion of patients with a good neurological outcomes or death at day 90. The odds ratios of neurologically better outcome were higher for patients older than 65 years in the control group (odds ratio 0.49 [0.19–1.25]) and for patients younger than 65 years in the TTM treatment group (odds ratio 1.75 [0.98–3.16]). In reports on children, seizure recurrence rate and neurological prognosis in the TTM group were better than those in the non-TTM group [223]. In a report on acute encephalopathy in Japan, 4/10 patients treated with steroid pulse alone showed neurological sequelae, however, no patients with treated with steroid and TTM showed any sequelae [224].

In reports on cerebral hypothermia [141,222–239], cooling blanket was commonly used with various drugs such as barbiturates, MDL, and inhalation anesthetics. Target body temperature was ranged from 30 to 36 °C, most commonly 33 °C, and bladder temperature was commonly used for temperature monitoring. Cooling duration ranged from 11 h to 2 weeks (commonly 48 h). The rate of return of temperature was 0.5–1 °C every 3–24 h. Seizure cessation or burst suppression was obtained in 41/193 (21 %) cases by summarization of previous reports [141,222–239]. In addition, these reports show that number of patients with sequelae owing to encephalitis/encephalopathy or other causative diseases was high and that 81/203 (40 %) patients recovered to their pre-onset condition and 24/203 (12 %) patients died [141,222–239].

6. Limitations and future directions

GL2023 cited literature published between 1983 and 2021, therefore new findings from the last two years were not included. Furthermore, there are limitations to SE treatment because the choice of therapeutic drugs differs according to social factors in every country, and the urgency of SE makes it difficult to perform high-level evidence-based research.

Also, GL2023 does not provide sufficient recommendations for the treatment of NCSE. It is inconclusive whether treating NCSE improves outcomes, though electrographic seizure and ESE are factors associated with outcome in children. We hope to be able to address this issue in future versions of the guideline.

Author contribution

KK organized this review article. IK, MN, YU, RM, TS, HN, TA, and YM drafted the proposal. IK, MN, YU, RM, TS, HN, TA, YM, KS, KH, KM, HY, TF, and MK provided final review of the article. All authors meet the above ICMJE authorship criteria.

Declaration of competing interest

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