HK J Paediatr (new series) 2010;**15**:52-63

Clinical Guideline

Clinical Guidelines on Management of Prolonged Seizures, Serial Seizures and Convulsive Status Epilepticus in Children

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Date of Endorsement

4 November, 2009

To be Reviewed

November, 2011

These guidelines only address the in-hospital management of prolonged seizures, serial seizures and convulsive status epilepticus in children. Treatment of neonatal seizures is not included.

Foreword

The publication is a project carried out under Hospital Authority Paediatric Coordinating Committee, Quality Assurance Subcommittee, Working Group on Guideline and Evidence Based Practice. The present guideline is endorsed by Paediatric Coordinating Committee.

Definition of level of evidence and grading recommendation is based on SIGN grading scheme.[1] This grading scheme has been widely used and is also recommended by Royal College of Paediatrics and Child Health.

Key to Evidence Statements and Grades of Recommendations

Levels of evidence

1++	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs) or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; orExtrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or Extrapolated evidence from studies rated as 2+

Good practice points (GPP)

√	Recommended best practice based on the clinical experience of the guideline development group

Summary of recommendations

Recommendations	
1.	Spontaneous cessation of generalised convulsive seizures is unlikely after 5-10 minutes and, therefore, acute treatment with anticonvulsants should be commenced. (Level 2)
2.	Treatment of prolonged (>5 minutes) or serial seizures must be started as soon as possible, preferably in pre-hospitalisation phase. (Level 1+, recommendation A)
3.	Rectal diazepam is safe and effective as first-line treatment of prolonged seizures in community setting or when intravenous access is not available. (Level 1+, recommendation A)
4.	Convulsive status epilepticus (CSE) is conventionally defined as epileptic activity persisting for 30 minutes, manifesting in a wide spectrum of clinical symptoms. Children who fail to respond to initial emergency medication should be managed according to CSE protocol. Treatment should be started without waiting till seizures last beyond 30 minutes. (GPP)
5.	All units admitting children with CSE are recommended to have a protocol for management of CSE with a clear structured time frame. (GPP)
6.	Cardio-respiratory function should be continuously monitored and managed. General emergency management is essential. Support of cardiovascular function and identification of complications of prolonged seizures are vital. General measures should be instituted along with drug therapy. (GPP)
7.	Intravenous lorazepam or diazepam is indicated for the treatment of initial CSE. (Level 1+, recommendation A)
8.	If benzodiazepines fail to control seizures, intravenous phenytoin (preferred) or phenobarbitone is indicated. (Level 1++, recommendation B)
9.	A trial of intravenous pyridoxine should be given to children under 3 years of age with a prior history of chronic active epilepsy or SE of unclear aetiology. (GPP)
10	Investigation into the cause of SE should be carried out without delaying initial treatment. The prompt identification and treatment of the cause of SE are important (GPP): • Antiepileptic drug levels should be checked for a child with epilepsy receiving treatment. (Level 2+, recommendation C) • Electroencephalogram is advisable to confirm diagnosis and monitor treatment response. (Level 3, recommendation D) • Neuroimaging and/or lumbar puncture may be considered if there is no contraindication. (Level 3, recommendation D)
11.	Refractory SE is defined as failure to respond to 2 or 3 antiepileptic drugs in combination with seizure duration of at least 60 minutes. Patient should be managed in the intensive care unit. Metabolic disturbances should be monitored closely and corrected. (GPP)
12.	General anaesthesia should be instituted for refractory SE as soon as possible. (GPP)
13.	EEG monitoring is required when managing refractory SE. (Level 3, recommendation D)
14.	Midazolam, propofol and pentobarbitone are the drugs of choice in controlling refractory SE. (Level 3, recommendation D)
15.	Intravenous sodium valproate can be an alternative to diazepam infusion in refractory SE. (Level 1-, recommendation B)
16.	CSE has a high risk of relapse. Antiepileptic drugs that can be titrated quickly to therapeutic range can be added to optimise seizure control. (Level 2+, recommendation C)

Introduction

Convulsive status epilepticus (CSE) is a life threatening emergency associated with serious mortality and morbidity. Incidence in developed countries is between 17-23/100,000 with a higher rate in younger children.[2] Outcome of **status epilepticus (SE)** is determined by its underlying aetiology and duration. Current mortality estimates ranges from 3 to 9%.[2-4] Neurological sequelae of CSE occurred in 6% of those older than 3 years but rose to 29% of those aged less than 1 year.[4] Acute mortality is often related to systemic disturbances of prolonged seizures. In addition, the longer the seizure lasts, the more difficult it is to terminate. Rapid and aggressive treatment is required to prevent neuronal damage, systemic complications and death. Standardised guidelines are believed to improve the quality of emergency care and outcome.[5] For practical purpose, the approach to a child who presented with a tonic-clonic seizure lasting for more than 5 minutes should be the same as a child with "established status" with the aim to stop the seizure early and prevent the development of status epilepticus.[6]

Definitions

The Commission on Classification and Terminology of International League Against Epilepsy (ILAE) defines SE as "a seizure [that] persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur".[7] Experimental studies have shown that irreversible neuronal damage was observed after 30 minutes of continuing epileptic activity.[8] Therefore, CSE is conventionally defined as epileptic activity persisting for 30 minutes, manifesting in a wide spectrum of clinical symptoms.[9,10]

Prolonged seizure is defined as a seizure lasting longer than 5 minutes but less than 30 minutes.[11-13] Children who have prolonged seizure (>5 minutes) or serial seizures (brief, repetitive seizures with recovery of consciousness between seizures) are more likely to progress to CSE.[14,15] ***(Level 2)***

Treatment

Prolonged Seizures/Serial Seizures

Prompt recognition of prolonged seizures and the need to treat cannot be over-emphasised. A common misconception for treatment interventions labeled "status epilepticus interventions" is that they begin only after the patient's seizures has reached the time indicated for SE (30 minutes). Clinical data indicate that spontaneous cessation of generalised convulsive seizures is unlikely after 5 to 10 minutes and progression to CSE is more likely. Therefore, acute treatment with anticonvulsants should be commenced.[12,14,15] ***(Level 2)***

Any patient experiencing a seizure on arriving at hospital can be considered as having a prolonged seizure. A pre-hospital trial showed that the time from seizure onset to initiation of treatment was inversely correlated with the percentage of patients who responded to first-line therapy. Patients receiving first-line therapy within 30 minutes had >80% response rate compared to 75% within 60 minutes and 63% within 90 minutes.[16] Early treatment before admission to hospital reduces the length of seizure and leads to the use of fewer drugs.[17] Treatment of prolonged or serial seizures must be started as soon as possible, preferably in pre-hospitalisation phase.[12,13,17,18] ***(Level 1+, recommendation A)***

Management of prolonged seizures and serial seizures are similar. Initial assessment should follow the ABC principle of resuscitation. High flow oxygen should be given and the blood glucose measured by finger-prick stick testing. A brief history and clinical examination (including pre-hospital treatment and assessing whether seizure was genuine) should be undertaken.[12,13,18,19] ***(GPP)***

Regarding the use of intravenous benzodiazepines, Alldredge et al published the results of a randomised, double-blind trial in an out-of-hospital setting comparing lorazepam, diazepam and placebo in 205 adults with continuous or repeated seizures lasting more than 5 minutes. Both lorazepam and diazepam were superior to placebo in termination of seizure (59.1%, 42.6% and 21.1% respectively).[17] ***(Level 1+, recommendation A)***

Administration of benzodiazepines compared to placebo did not result in more complications such as arterial hypotension or respiratory compromise. These side effects occurred in 10.6% of patients treated with lorazepam, 10.3% diazepam and 22.5% given placebo.[17] ***(Level 1+)***

Rectal diazepam is safe and effective as first-line treatment of prolonged seizures in community setting or when intravenous access is not available.[20,21] ***(Level 1+, recommendation A)*** Rectal lorazepam may be more effective than rectal diazepam.[22] Rectal administration may be difficult with wheel-chair users and larger patients. It can be socially unacceptable and there is increasing concern about risk of sexual abuse allegation.[12,23] Buccal or intranasal midazolam is as effective as rectal diazepam and

can be considered as a preferable alternative in community setting.[20,23-25] ***(Level 1+, recommendation A)*** Buccal use of midazolam should be used according to an agreed protocol drawn up by specialists and used after training.[13] ***(GPP)*** Prolonged seizures should be treated with either nasal or buccal midazolam or rectal diazepam or rectal lorazepam when intravenous line is not available or in the community setting. ***(Level 1+, recommendation A)*** For a small number of children, rectal paraldehyde is more useful.[13,26] ***(Level 2+, recommendation C)***

Recommendation *Spontaneous cessation of generalised convulsive seizures is unlikely after 5-10 minutes and, therefore, acute treatment with anticonvulsants should be commenced.* ***(Level 2)***

Recommendation *Treatment of prolonged (>5 minutes) or serial seizures must be started as soon as possible, preferably in pre-hospitalisation phase.* ***(Level 1+, recommendation A)***

Recommendation *Rectal diazepam is safe and effective as first-line treatment of prolonged seizures in community setting or when intravenous access is not available.* ***(Level 1+, recommendation A)***

Convulsive Status Epilepticus

Children who fail to respond to initial emergency medication should be managed as CSE. It is not necessary to wait till seizure lasts beyond 30 minutes.[6,12] It has been shown that provision of standardised guidelines or protocols improve the quality of emergency care and therefore outcome. All units admitting children with SE should have a protocol for management of convulsive SE with a clear structured time frame.[12,27] **(GPP)**

For practical purposes and basing on pathophysiological data, CSE is subdivided into stages according to temporal parameters and responsiveness to antiepileptic drugs. Treatment options are provided separately for different stages: (1) Initial/early SE (within 20-30 minutes); (2) established SE (30-60 minutes) and (3) refractory SE (>60/90 minutes).[18,19,28] There are some key principles of various treatment guidelines: (1) act upon an agreed treatment protocol, (2) serially provide antiepileptic drugs quickly and in maximal mg/kg dose, and (3) consider EEG when subtle or non-convulsive SE need to be excluded.[27] Evidence for management of early SE is well supported, whereas evidence for established and refractory SE is weak.[27] The drugs used in children are based largely on adult experience with weight and age adjustment in doses.[12]

Recommendation *CSE is conventionally defined as epileptic activity persisting for 30 minutes, manifesting in a wide spectrum of clinical symptoms. Children who fail to respond to initial emergency medication should be managed according to CSE protocol. Treatment should be started without waiting till seizures last beyond 30 minutes.* ***(GPP)***

Recommendation *All units admitting children with SE are recommended to have a protocol for management of convulsive SE with a clear structured time frame.* ***(GPP)***

Initial/early CSE (within 20-30 minutes)

Cardio-respiratory function should be continuously monitored and managed. General emergency management is essential. Support of cardiovascular function, which is often compromised, is vital. Systemic complications of prolonged seizures listed in Table 1 should be promptly identified. General measures should be instituted along with drug therapy. Investigation into the cause of SE must be carried out without delay of initial treatment.[18,19,27,29] ***(GPP)*** Core investigations will be further elaborated on pages 60 and 61.

Veterans Affairs Status Epilepticus Study (VA Status Study) compared intravenous lorazepam, phenobarbitone, diazepam followed by phenytoin and phenytoin alone in 384 patients who had generalised convulsive status epilepticus. Better result was observed for lorazapam than

Table 1 Complications of CSE

Cerebral	Hypoxia
	Excito-toxic cerebral damage
	Cerebral oedema and raised intracranial pressure
	Cerebral venous thrombosis
	Infarction
Cardio-respiratory	Hypotension/hypertension
	Cardiac failure
	Dysarrhythmia
	Respiratory failure and apnoea
	Pulmonary oedema
	Aspiration
Metabolic and systemic	Hyperpyrexia
	Dehydration and electrolyte disturbances
	Metabolic acidosis
	Acute renal failure
	Acute hepatic failure
	Rhabdomyolysis
	Fractures
	Disseminated intravascular coagulopathy

phenytoin alone.[30] ***(Level 1++)*** Other comparative studies suggested phenytoin, phenobarbitone, diazepam, lorazepam and midazolam were efficacious in treating initial and established generalised CSE and benzodiazepines were the first-line drugs.[30-33] Intravenous lorazepam or diazepam is indicated for the treatment of initial CSE. ***(Level 1+, recommendation A)*** There is at least one RCT and meta-analysis showing lorazepam is slightly superior to diazepam.[27] Because phenobarbitone had similar efficacy to the benzodiazepine arms in the VA Status Study, it should also be considered as an appropriate first-line therapy.[30] ***(Level 1++)***

There have been a total of 4 trials, randomised controlled or quasi-randomised controlled trials, providing evidence-based treatment guidelines in children. Intravenous lorazepam is at least as effective as intravenous diazepam and is associated with fewer adverse effects. Children receiving diazepam are likely to require additional antiepileptic drugs to control initial convulsion.[22] ***(Level 1+, recommendation A)*** In general, all three benzodiazepines (diazepam, lorazepam and midazolam) are well tolerated, and no clear superiority in efficacy or effectiveness is shown.[11]

Treatment with benzodiazepines can be repeated after 5-10 minutes if necessary.[6,13,19,27,28,31] In a study of 39 episodes of generalised CSE, 13 episodes responded to intravenous lorazepam after the first administration and three on the second administration when seizures continued or recurred after 10 minutes, whilst three did not respond. With diazepam, 14 responded to initial administration, two to the second whilst four did not respond.[31] ***(Level 1+)***

Efficacy of rectal paraldehyde in acute seizures was reported in a recent multi-center study. It terminated convulsion in 62.3% of patients and there was no recorded respiratory depression in any episode.[26] ***(Level 2+)***

Recommendation *Cardio-respiratory function should be continuously monitored and managed. General emergency management is essential. Support of cardiovascular function and identification of complications of prolonged seizures are vital. General measures should be instituted along with drug therapy.* ***(GPP)***

Recommendation *Investigation into the cause of SE should be carried out without delaying initial treatment. The prompt identification and treatment of the cause of SE are important.* ***(GPP)***

Recommendation *Intravenous lorazepam or diazepam is indicated for the treatment of initial CSE.* ***(Level 1+, recommendation A)***

Established CSE (30-60 minutes)

If benzodiazepines fail to control seizures, intravenous phenytoin (preferred) or phenobarbitone is indicated.[6,18] There have been no data reporting the superiority of one drug over the other. VA Status Study showed that phenobarbitone was equally efficacious as diazepam plus phenytoin.[30] In view that phenytoin causes less respiratory and central nervous system depression, it is the preferred drug.[27] ***(Level 1++, recommendation B)*** Phenobarbitone is recommended if patient is already on phenytoin.

Loading dose of phenytoin is 15-20 mg/kg intravenously at a rate not faster than 1 mg/kg/min. Dilution of phenytoin in glucose solution is to be avoided, because precipitation may occur. A large independent venous line for infusion is advisable to avoid phlebitis. Heart rate and blood pressure should be closely monitored. Phenytoin is contraindicated in patients with second-degree heart block or severe hypotension. Phenytoin may exacerbate cardiotoxicity in toxin-induced seizures, such as in poisoning due to tricyclic antidepressants. Use of phenytoin in Dravet syndrome should be cautious because of its potential in seizure exacerbation and induction of involuntary movements. It takes 20-25 minutes to attain its maximal anti-epileptic effect. Fosphenytoin can be used as an alternative.[18]

Some studies suggested that sodium valproate might also be a valuable option for established SE. In an adult randomised study, seizures were aborted in 66% of valproate group and 42% of phenytoin group. Side effects of the two groups did not differ.[34] ***(Level 1-)*** Although promising, safety profile for its use in children remained to be determined especially in view of the risk of unrecognised metabolic disease.

Children under 3 years of age with a prior history of chronic active epilepsy or SE of unclear aetiology should be given a trial of intravenous pyridoxine to exclude pyridoxine dependent or responsive seizures.[6,19,35,36] ***(GPP)***

Vital status of patient should be continuously monitored and managed. Metabolic disturbances should be identified and corrected. Admission to intensive care unit should be planned for subsequent treatment.[6,12,18,19]

Electroencephalogram (EEG) monitoring to confirm diagnosis and monitor treatment response is advisable.[6,18,19,37] ***(Level 3, recommendation D)*** When there is clinical suspicion that neuroimaging and/or lumbar puncture might be helpful in the management of CSE, they should be done in the absence of contraindication such as raised intracranial pressure. ***(Level 3, recommendation D)***

Recommendation *If benzodiazepines fail to control seizures, intravenous phenytoin (preferred) or phenobarbitone is indicated.* ***(Level 1++, recommendation B)***

Recommendation *A trial of intravenous pyridoxine should be given to children under 3 years of age with a prior history of chronic active epilepsy or SE of unclear aetiology.* ***(GPP)***

Refractory SE (>60/90 minutes)

Refractory SE is defined as seizure that fails to respond to two or three antiepileptic drugs in combination with duration of at least 60 minutes.[18,27,38]

It is associated with high mortality and morbidity. If initial first and second line antiepileptic agents fail to control seizure, a paediatric Fellow, preferably a paediatric neurologist, should be informed. Assistance of an anaesthesiologist or intensivist is advisable. Patient should be managed in the intensive care unit. Cardio-respiratory and metabolic disturbances should be monitored closely and corrected.[6,13,19] ***(GPP)***

There is no study comparing anaesthetic therapy with other anticonvulsants. The decision on further management is based on retrospective studies and expert opinions.[28] There is no recommendation of which anaesthetic agent should be administered first.[18,28]

EEG monitoring is required when managing refractory SE.[13,18,19,27] ***(Level 3, recommendation D)*** In a study that was conducted in a small group of patients with refractory SE, "EEG suppression pattern" appeared to be preferable to the "suppression-burst" pattern as the end point of treatment. Nevertheless, the former is associated with higher risk of hypotension.[39] There is no recommendation regarding EEG end-points.[18,40,41]

1. Continuous Intravenous Anaesthetic Agents for Refractory SE

Midazolam, propofol and barbiturates are indicated for the treatment of refractory SE only in ICU after evaluation of potential risks and benefits in individual patients. It has been recommended that when seizures have been controlled for 12 hours, the drug dosage should be slowly reduced over a further 12 hours. If seizure recurs, the general anaesthetic agent should be given again for 12 hours, and then withdrawal is attempted again.[27]

Midazolam

Only one randomised trial is available. An open-label randomised controlled study by Singhi et al including 40 children with refractory SE revealed that seizure activity was controlled in 85.7% of midazolam infusion group versus 89.5% of diazepam infusion group. The median time to reach seizure control was similar in both groups. Midazolam was observed to have a higher relapse rate.[42] ***(Level 1-)***

Gilbert et al reviewed efficacy of treatment in refractory SE in 111 children from 12 published articles including case reports, retrospective and prospective studies. Midazolam, pentobarbitone, thiopentone, isoflurane and diazepam were all effective in seizure control. However, mortality was less frequent in midazolam treated groups.[43] ***(Level 3, recommendation D)***

Igarta et al studied 8 children with refractory SE treated with midazolam bolus followed by infusion, 88% of cases had seizure terminated at a mean midazolam infusion rate at 14 microgram/kg/min (range 4-24 microgram/kg/min). In the majority of cases, cessation of seizures occurred before achievement of suppression-burst pattern in EEG. Cardiovascular instability was not associated with midazolam even at doses resulting in suppression-burst.[44] ***(Level 3, recommendation D)***

Morrison et al reported experience of using high-dose midazolam for refractory SE in children. A higher loading dose (0.5 mg/kg vs 0.15-0.2 mg/kg) led to more rapid seizure control. High infusion rate (mean 10.6 microgram/kg/min, maximum 32 microgram/kg/min) can safely be administered.[45] ***(Level 3, recommendation D)***

Propofol

Propofol acts on location other than the type A receptor of GABA. It has rapid action and is easily titratable. However, administration of propofol, particularly in children is associated with "Propofol infusion syndrome" characterised by rhabdomyolysis, cardiac arrhythmia, cardiac failure, metabolic acidosis, renal failure and death.

A retrospective study of 20 adults with refractory SE treated with propofol and midazolam showed that seizure control was observed in 64% of propofol group and 67% of midazolam group. Overall mortality was higher with propofol than midazolam treatment (57% vs 17%).[46] ***(Level 3, recommendation D)***

In a retrospective study of refractory SE in children, thiopentone was effective in 55% and propofol 64% of cases. Propofol was initiated at a bolus of 1-2 mg/kg followed by infusion of 1-2 mg/kg/hour, to a maximum of 5 mg/kg/hour. Complications, including rhabdomyolysis

and hypertriglyceridemia, prompted discontinuation in 18% of patients.[47]

Barbituates

Thiopentone (4-8 mg/kg bolus followed by infusion of up to 10 mg/kg/hr) and its metabolite pentobarbitone (5 mg/kg loading followed by 1-3 mg/kg/hr) have been used for refractory SE in children and adults. Adequate monitoring including drug level of thiopentone and critical life supports should be readily available. In a meta-analysis of adult patients with refractory SE, use of pentobarbitone was associated with less short term treatment failure and less breakthrough seizures but was associated with more hypotension than midazolam and propofol.[48] ***(Level 3, recommendation D)*** Studies of pentobarbitone for refractory SE in children reported an efficacy of 74-100%.[43,49,50]

Repeated boluses of intravenous phenobarbitone (10 mg/kg) every 30 minutes without reference to a predetermined maximal serum level or dose has been reported to be effective. A retrospective report of 50 children with refractory SE treated with high-dose phenobarbitone to attain serum level of up to 1481 micromol/L achieved seizure control in 94%. Intubations were common, but hypotension was mild and unusual.[51]

Other Anaesthetic Agents

Ketamine, lidocaine and inhaled anaesthetic drugs can be efficacious in some cases of refractory SE. These drugs should only be administered by physicians experienced in their use and they are only indicated when other drugs have failed. These drugs should be given only after thorough consideration of prognostic factors.[18,52] ***(Level 4, recommendation D)***

2. Non-anaesthetic Agents for Refractory SE

Sodium Valproate

In an open-label, randomised controlled study of 40 children with refractory SE, 80% of valproate group and 85% of diazepam group had seizures controlled and the mean time of seizure control was significantly shorter for valproate than diazepam.[53] (5 min vs 17 min) ***(Level 1-, recommendation B)*** It may be particularly useful when successful intubation is unlikely, because there is a lower risk of respiratory failure than other agents. The initial bolus may be 20-30 mg/kg, periodic dosing (twice per day) may be appropriate if seizures are terminated. If seizure continues, a continuous infusion of 5 mg/kg/hr may be effective.[51] Data from nine level 3 studies revealed that an inborn error of metabolism was diagnosed in 4.2% of children with SE.[37] Valproate should be used with caution in children whose refractory SE is of unclear aetiology.

Other Non-anaesthetic Agents

Topiramate, levetiracetam, paraldehyde, chlomethiazole infusion, ketogenic diet and epilepsy surgery have been reported to be effective in some cases of refractory SE.[51]

Corticosteroids, adrenocorticotropic hormone and plasmapheresis may be useful in the context of autoimmune aetiologies for refractory SE, such as Rasmussen's encephalitis or vasculitis. Trial of biotin and folinic acid is worthwhile in intractable status.[51]

One case series of three children with refractory SE successfully treated with hypothermia along with barbiturate coma.[54] Further data is necessary to determine its benefit.

Recommendation *Refractory SE is defined as failure to respond to 2 or 3 antiepileptic drugs in combination with seizure duration of at least 60 minutes. Patient should be managed in the intensive care unit. Metabolic disturbances should be monitored closely and corrected.* ***(GPP)***

Recommendation *General anaesthesia should be instituted for refractory SE as soon as possible.* ***(GPP)***

Recommendation *EEG monitoring is required when managing refractory SE.* ***(Level 3, recommendation D)***

Recommendation *Midazolam, propofol and pentobarbitone are drugs of choice in controlling refractory SE in children.* ***(Level 3, recommendation D)***

Recommendation *Intravenous sodium valproate is an alternative to diazepam infusion in refractory SE.* ***(Level 1-, recommendation B)***

Further Management of CSE

Sudden withdrawal of anticonvulsants may lead to SE and increased seizure frequency.[55] Chronic AED treatment should be continued during SE.[18] ***(Level 4)***

SE may induce cerebral oedema,[56] but there are no data demonstrating the benefit of specific anti-oedema treatment during SE. Specific treatments for cerebral oedema (e.g. mannitol or steroids) are indicated in selected cases only, depending on patient's clinical condition. These treatments require careful assessment of potential contraindications.[18] ***(Level 4)***

SE is associated with high relapse rate and subsequent

seizures.[10] Antiepileptic drug is generally required after resolution of SE to prevent relapses. The choice of different antiepileptic drugs and duration depends on aetiology, clinical status and individual patient's characteristics.[18] ***(Level 2+, recommendation C)***

Recommendation *CSE has a high risk of relapse. Antiepileptic drugs that can be titrated quickly to therapeutic range can be added to optimise seizure control.* ***(Level 2+, recommendation C)***

Protocol for in-hospital management and common drugs used in CSE are described in Tables 2 and 3.

Core investigations of Prolonged Seizure/CSE

Antiepileptic drug levels should be considered when a child with treated epilepsy develops SE.[37] ***(Level 2+, recommendation C)*** Low AED levels were detected in 32% of children on antiepileptic drugs. In one study it was reported that four of the nine children with low drug levels had the drugs acutely withdrawn or discontinued within one week.[55]

The following investigations are indicated for children not known to have epilepsy:[37] ***(Level 3, recommendation D)***

Table 2 Protocol for in-hospital management of CSE

	Antiepileptic drug	General measures	Investigations
Early SE (within 20/30 min)	IV access → Lorazepam or diazepam IVI* No IV access → Diazepam (rectal) Seizure continue 5-10 min Still no IV access → diazepam (rectal) or rectal paraldehyde *(If pre-hospital benzodiazepine has been given, early initiation of treatment for established SE is recommended)*	Airway: oxygen Cardio-respiratory function and regular monitoring: ECG, blood pressure and SaO_2 Intravenous access Physical examination and history	Glucostix Blood investigations: AED level (know epilepsy) Blood glucose, blood gas Urinalysis RFT/LFT Calcium and magnesium level (for child under 1 year old) Plasma ammonia Complete blood picture Blood culture 1-2 ml plasma, 1-2 ml serum and 10 ml urine saved for later analysis
Established SE (30/60 min)	Intravenous* phenytoin (preferred) or / and phenobarbitone (for patients already on phenytoin)	Cardio-respiratory function and monitoring Metbolic disturbances should be identified and corrected Arrange ICU admission Intravenous pyridoxine for children <3 yr with unknown aetioloty Call paediatric Fellow	Arrange EEG If no contraindication and clinically indicated: neuroimaging +/- CSF studies
Refractory SE (>60/90 min)	Midazolam infusion or Thiopentone infusion or Other medications (propofol, valprote, etc.) can be considered (see text)	ICU care Ventilatory and haemodynamic support Monitor metabolic disturbances and systemic complications	EEG monitoring Monitor electrolytes and blood gas

* Intraosseous route if intravenous route cannot be established

Table 3 Common drugs used in CSE

Drug	Dosage
Lorazepam	IVI: 0.1 mg/kg (max 4 mg)
Diazepam	IVI: 0.1-0.3 mg/kg (max 10 mg) Rectal: 0.5 mg/kg, 10-20 mg for adult
Midazolam	Buccal: 0.3 mg/kg IVI infusion: 0.1-0.5 mg IVI bolus followed by continuous infusion 1-2 microgram/kg/min and increased as needed to 30 microgram/kg/min
Phenytoin	IVI: 15-20 mg/kg not faster than 1 mg/kg/min under cardiac monitor
Phenobarbitone	IVI: 15-20 mg/kg at a maximum rate 1 mg/kg/min High dose phenobarbitone: 10 mg/kg IVI, repeated every 30 min
Thiopentone	IVI: 3-5 mg/kg bolus followed by infusion 3-5mg/kg/hr
Propofol	IVI: bolus of 1-2 mg/kg (max 10 mg/kg) followed by infusion of 1-2 mg/kg/hour, to a maximum of 5 mg/kg/hour.
Pentobarbitone	IVI: 5 mg/kg loading dose, followed by 1-3 mg/kg/hour
Sodium valproate	IVI: 20-30 mg/kg, periodic dosing (twice per day) may be appropriate if seizures are terminated. If seizure continue, a continuous infusion of 5 mg/kg/hr may be effective.
Pyridoxine	IVI: 50-100 mg
Paraldehyde	Rectal, 0.3-0.4 ml/kg, give with same volume of olive oil

- Blood glucose
- Blood gas
- Urinalysis
- Urea and electrolytes
- Calcium and magnesium level (for child under 1 year old)
- Liver function tests
- Plasma ammonia
- Complete blood picture
- Blood culture

It is also recommended to save 1-2 ml plasma, 1-2 ml serum and 10 ml urine for later analysis.

(*Serum lactate, urine for toxicology if cause of prolonged seizures remained unknown after reviewing the above core investigations)

Electroencephalogram abnormalities were observed in 43% of children with SE and helped to determine the nature and location of precipitating electroconvulsive events.[37] EEG is also useful in confirming the diagnosis of SE especially when pseudoseizure is suspected.[18,19,29] ***(Level 3, recommendation D)***

Provided that there was no contraindication and no clues to the cause of CSE, neuroimaging and/or lumbar puncture can be obtained.[37] One level 3 study identified bacterial meningitis in 8% of the entire group of children with CSE and 17% of those with febrile CSE.[57] Abnormalities on neuroimaging that may explain the aetiology of SE were observed in at least 8% of children.[37] ***(Level 3, recommendation D)***

Recommendation:

- Antiepileptic drug levels should be checked for a child with epilepsy receiving treatment. ***(Level 2+, recommendation C)***
- Electroencephalogram is advisable to confirm diagnosis and monitor treatment response ***(Level 3, recommendation D)***
- Neuroimaging and/or lumbar puncture may be considered if there is no contraindication ***(Level 3, recommendation D)***

Acknowledgement

We thank Pharmacy of Tuen Mun Hospital (represented by Miss YY Lam) on drug advice.

References

1. Scottish Intercollegiate Guideline Network. A guideline developer's handbook, SIGN. 50, 2000.
2. Neville BG, Chin RF, Scott RC. Childhood convulsive status epilepticus: epidemiology, management and outcome. Acta Neurol Scand Suppl 2007;186:21-4.
3. Aicardi J, Chevrie JJ. Consequences of status epilepticus in infants and children. Adv Neurol 1983;34:115-25.
4. Maytal J, Shinnar S, Moshe SL, Alvarez LA. Low morbidity and mortality of status epilepticus in children. Pediatrics 1989;83: 323-31.
5. Shepherd SM. Management of status epilepticus. Emerg Med Clin North Am 1994;12:941-61.
6. Appleton R, Choonara I, Martland T, Phillips B, Scott R, Whitehouse W. The treatment of convulsive status epilepticus in children. Arch Dis Child 2000;83:415-9.
7. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalopgraphic classification of epileptic seizures. Epilepsia 1981;22:489-501.
8. Meldrum BS, Horton RW. Physiology of status epilepticus in primates. Archives of Neurology 1973;28:1-9.
9. Shorvon S. Status epilepticus: its clinical features and treatment in children and adults. Cambridge: Cambridge Univesity Press, 1994.
10. Knake S, Rosenow R, Vescovi M, et al. Incidence of status epilepticus in adults in Germany: a prospective, population-based study. Epilepsia 2002;42:714-8.
11. Glauser TA. Designing practical evidence-based treatment plans for children with prolonged seizures and status epilepticus. J Child Neurol 2007;22(Suppl 5):S38-46.
12. SIGN guideline Diagnosis and Management of Epilepsy, 2003 www.sign.ac.uk/pdf/sign 70.pdf (zccessed October 15, 2007).
13. NICE guideline Epilepsy, 2004. www.nice.org.uk/CG020 (accessed October 15, 2007).
14. Theodore WH, Porter RJ, Albert P, et al. The secondarily generalized tonic-clonic seizure: a videotape analysis. Neurology 1994;44:1403-7.
15. Shinnar S, Berg AT, Moshe SL, Shinnar R. How long do new-onset seizures in children last? Ann Neurol 2001;49:659-64.
16. Lowenstein DH, Alldredge BK. Status epilepticus at an urban public hospital in the 1980s. Neurology 1993;43:483-8.
17. Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001;345:631-7.
18. Minicucci F, Muscas G, Perucca E, Capovilla G, Vigevano F, Tinuper P. Treatment of status epilepticus in adults: guidelines of the Italian League Against Epilepy. Epilepsia 2006;47 (Suppl 5):9-15.
19. Finnish national guidelines for the treatment of prolonged seizures and status epilepticus. Summary by Kalviainen R. In Evidence-Based Medicine Guidelines by Duodecim Medical Publications Editor-in-Chief Kunnamo I. Wiley. Cichester, West Sussex, England, 2005. Full test in Finnish in http://www.kaypahoito.fi.
20. Scott RC, Besag FM, Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomized trial. Lancet 1999;353:623-6.
21. Pellock JM. Safety of Diastat, a rectal gel formulation of diazepam for acute seizure treatment. Drug Saf 2004;27:383-92.
22. Appleton R, Macleod S, Martland T. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database Syst Rev 2008;3:CD001905.
23. Wilson MT, Macleod S, O'Regan ME. Nasal/buccal midazolam use in the community. Arch Dis Child 2004;89:50-1.
24. Lahat E, Goldman M, Barr J, Bistritzer T, Berkovitch M. Comparison of intranasal midazolam versus intravenous diazepam for treating febrile seizures in children: prospective randomized study. BMJ 2000;321:83-6.
25. Fisgin T, Gurer Y, Tezic T, et al. Effects of intranasal midazolam and rectal diazepam on acute convulsions in children: prospective randomized study. J Child Neurol 2002;17:123-6.
26. Rowland AG, Gill AM, Stewart AB, et al. Review of the efficacy of rectal paraldehyde in the management of acute and prolonged tonic-clonic convulsions. Arch Dis Child 2009;94:720-3.
27. Shorvon S, Baulac M, Cross H, Trinka E, Walker M; TaskForce on Status Epilepticus of the ILAE Commission for European Affairs. The drug treatment of status epilepticus in Europe: Consensus document from a workshop at the first London Colloquium on Status Epilepticus. Epilepsia 2008;7:1277-84.
28. Meierkord H, Boon P, Engelsen K, et al. EFNS guideline on the management of status epilepticus. Eu J Neurol 2006;13:445-50.
29. The management of a child with a decreased conscious level: A nationally developed evidence-based guideline for hospital practitioners, 2005. http://www.nottingham.ac.uk/paediatric-guideline/home2.htm.
30. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments of generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998;339:792-8.
31. Leppik IE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double-blind study of lorazepam and diazepam in status epilepticus. JAMA 1983;249:1452-4.
32. Shaner DM, McCurdy SA, Herring MO, Gabor AJ. Treatment of status epilepticus: a prospective comparison of diazepam and phenytoin versus Phenobarbital and optional phenytoin. Neurology 1988;38:202-7.
33. Appleton R, Sweeney A, Choonara I, Robson J, Molyneux E. Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus. Dev Med Child Neurol 1995;37: 682-8.
34. Misra UK, Kalita J, Pate R. Sodium valproate vs phenytoin in status epilepticus: a pilot study. Neurology 2006;67:340-2.
35. Scott RC, Fenella Kirkham FJ. Clinical update: childhood convulsive status epilepticus. Lancet 2007;370:724-6.
36. Chin RF, Verhulst L, Neville BG, Peters MJ, Scott RC. Inappropriate emergency management of status epilepticus in children contributes to need for Intensive Care. J Neurol Neurosurg Psychiatry 2004;75:1584-8.
37. Riviello JJ Jr, Ashwal S, Hirtz D, et al. Practice parameter: Diagnostic assessment of the child with status epilepticus (an evidence-based review) Report of the Quality Standards

Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2006;67:1542-50.
38. Lothman EW. The biochemical basis and pathophysiology of status epilepticus. Neurology 1990;40:13-23.
39. Krishnamurthy KB, Drislane FW. Depth of EEG suppression and outcome in barbiturate anesthetic treatment for refractory status epilepticus. Epilepsia 1999;40:759-62.
40. Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepitcus with pentobarbital, propofol, or midazolam. A systematic review. Epilepsia 2002;43:146-63.
41. Rossetti AO, Logroscino G, Bromfield EB. Refractory status epilepticus: Effect of treatment aggressiveness on prognosis. Arch Neurol 2005;62:1698-702.
42. Singhi S, Murthy A, Singhi P, Jayashree M. Continuous midazolam versus diazepam infusion for refractory convulsive status epilepticus. J Child Neurol 2002;17:106-10.
43. Gilbert DL, Gartside PS, Glauser TA. Efficacy and mortality in treatment of refractory generalized convulsive status epilepticus in children: a meta-analysis. J Child Neurol 1999;14:602-9.
44. Igartua J, Silver P, Maytal J, Sagy M. Midazolam coma for refractory status epilepticus in children. Crit Care Med 1999; 27:1982-5.
45. Morrison G, Gibbons E, Whitehouse WP. High-dose midazolam therapy for refractory status epilepticus in children. Intensive Care Med 2006;32:2070-6.
46. Prasad A, Worrall BB, Bertram EH, Bleck TP. Propofol and midazolam in the treatment of refractory status epilepticus. Epilepsia 2001;42:380-6.
47. van Gestel JP, Blussé van Oud-Alblas HJ, Malingré M, Ververs FF, Braun KP, van Nieuwenhuizen O. Propofol and thiopental for refractory status epilepticus in children. Neurology 2005; 65:591-2.
48. Claasen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: A systematic review. Epilepsia 2002;43:146-53.
49. Kim SJ, Lee DY, Kim JS. Neurologic outcomes of pediatric epileptic patients with pentobarbital coma. Pediatr Neurol 2001; 25:217-20.
50. Holmes GL, Rivello JJ Jr. Midazolam and pentobarbital for refractory epilepticus. Pediatr Neurol 1999;20:259-64.
51. Crawford TO, Mitchell WG, Fishman LS, Snodgrass SR. Very high-dose phenobarbital for refractory status epilepticus in children. Neurology 1988;38:1035-40.
52. Abend NS, Dlugos DJ. Treatment of refractory status epilepticus: Literature review and a proposed protocol. Pediatr Neurol 2008; 38:377-90.
53. Mehta V, Singhi P, Singhi S. Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children: a randomized controlled trial. J Child Neurol 2007; 22:1191-7.
54. Orlowski JP, Erenberg G, Lueders H, Cruse RP. Hypothermia and barbiturate coma for refractory status epilepticus. Crit Care Med 1984;12:367-72.
55. Maytal J, Novak G, Ascher C, Bienkowski R. Status epilepticus in children with epilepsy: the role of antiepileptic drug levels in prevention. Pediatrics 1996:1119-21.
56. Calistri V, Caramia F, Bianco F, Fattapposta F, Pauri F, Bozzao L. Visualization of evolving status epilepticus with diffusion and perfusion MR imaging. AJNR Am J Neuroradiol 2003;24: 671-3.
57. Chin RF, Neville BG, Scott RC. Meningitis is a common cause of convulsive status epilepticus with fever. Arch Dis Child 2005; 90:66-9.