

Review of the new APLS guideline (2021): Management of the Convulsing Child

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ABSTRACT

Convulsive status epilepticus (CSE) is the most common childhood medical neurological emergency. A convulsion lasting more than 5 minutes is considered prolonged and will often require treatment to aid termination. If a convulsion persists beyond 30 minutes, it is associated with increased risk of death and long-term neurological consequences. However, the main predictor of outcome is the underlying aetiology. The duration of the convulsion is also important with medical treatments, particularly benzodiazepines, becoming less effective with increasing duration. Effective early intervention is crucial to outcome. The proposed guideline is set to provide an updated evidence-based structured approach on how to manage the convulsing child in the United Kingdom.

BACKGROUND

Convulsive status epilepticus (see box 1) is the most common childhood medical neurological emergency, with an incidence of approximately 20 per 100,000 per year in the developed world.¹⁻⁴

Box 1 Definition of Status Epilepticus

Status Epilepticus is a condition resulting either from failure of the mechanism responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t_1 at 5 minutes).

It is a condition, which can have long-term consequences (after time point t_2 after 30 minutes) including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.

CSE can be fatal, but mortality is lower in children than in adults – at about 2-7%.^{5,6}

Adverse neurological consequences following CSE consist of subsequent epilepsy, motor deficits, learning and behavioural difficulties.

The main determinant of outcome is the underlying aetiology. There are many different causes of CSE in children. The International League Against Epilepsy (ILAE) currently divides these into two main categories known (i.e. symptomatic) or unknown (i.e. cryptogenic) causes. The symptomatic category can also be further divided in relation to time; acute, remote, progressive.^{2,7} Box 2 provides a summary of some of the common causes of CSE in children.

Box 2 Common Causes of Status Epilepticus

Known (i.e. symptomatic)

Structural: intracranial tumour, cerebrovascular disease, head injury, cortical dysplasia

Infectious: CNS infection (meningitis, encephalitis), tuberculosis, cerebral malaria

Metabolic: metabolic disturbance (electrolyte imbalance, glucose imbalance, organ failure...etc), metabolic disorders, anoxic injury, mitochondrial disorders

Toxicity or drug-related: low or high level of anti-seizure medication, withdrawal of anti-seizure medication, other drug/alcohol overdose, neurotoxins and poisons

Inflammatory: autoimmune disorders, neurocutaneous disorders

Genetic: Dravet syndrome, ring chromosome 20, Angelman syndrome, fragile X syndrome, Rett syndrome, trisomy 21

Unknown (i.e. cryptogenic)

Although morbidity and mortality may be considerable after CSE, it is primarily seen in those with symptomatic causes and/or delay to treatment. The risk of adverse outcome in unprovoked and febrile CSE is low.^{5,6}

Any child who has had an episode of CSE that lasted longer than 30-minutes is at greater risk of future episodes of CSE. The risk is mainly determined by the underlying aetiology and it is highest in those with pre-existing neurological abnormalities.^{1,5,6}

INFORMATION ABOUT THE CURRENT GUIDELINE

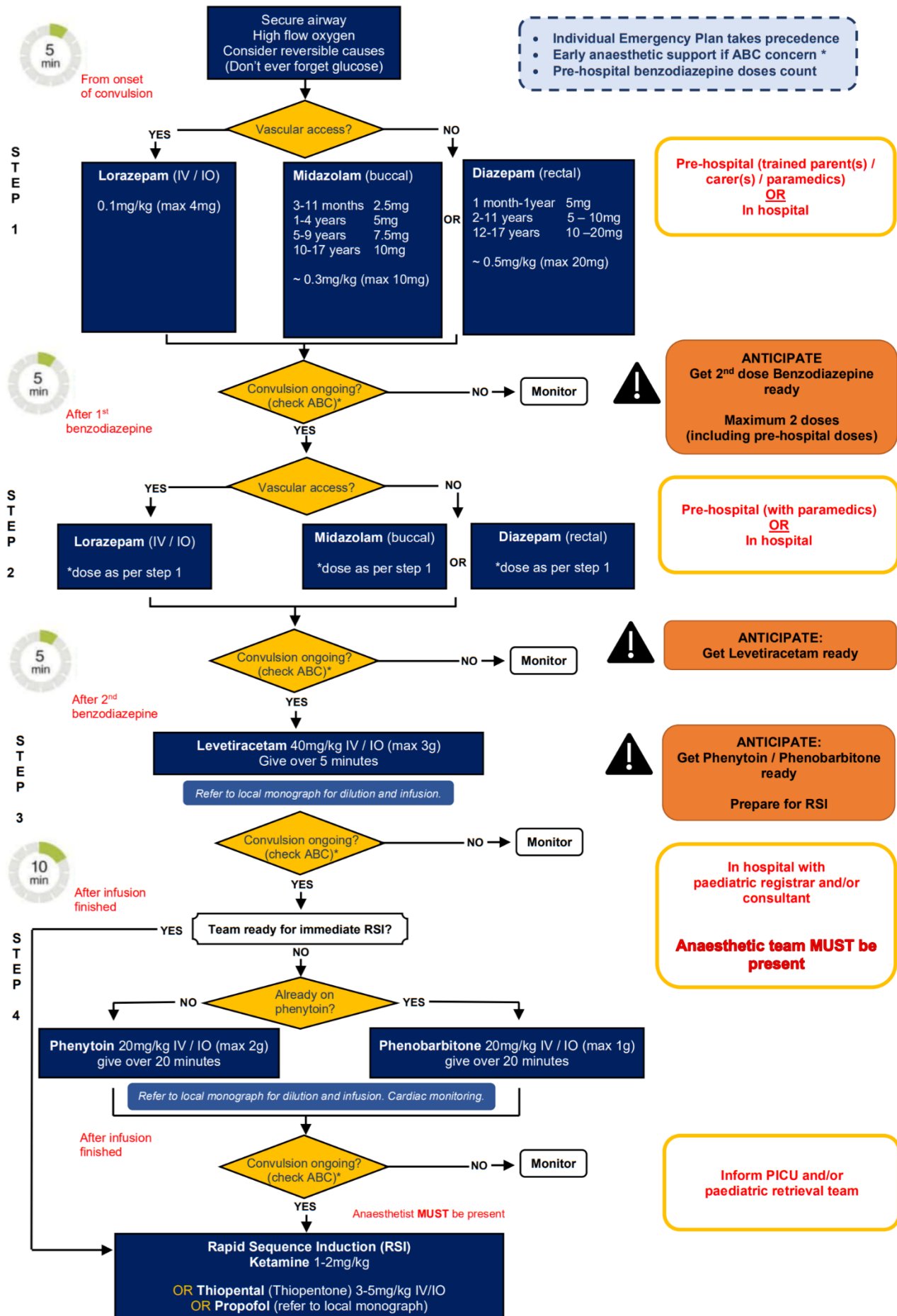
The Advanced Life Support Group (ALSG) who run the Advanced Paediatric Life Support (APLS) programme provides internationally renowned guidance on the emergency management of common childhood emergencies. The APLS programme is also endorsed by the Royal College of Paediatric Child Health (RCPCH). Together, a professional working group consisting of members of the ALSG, British Paediatric Neurology Association, Paediatric Intensive Care Unit, Royal College of Emergency Medicine, ambulance representatives, pharmacists and a parent representative worked collaboratively to review and update the emergency management for generalised convulsive status epilepticus (CSE) in children aged 1 month old to 18 years old (see image 1).

This guideline is not intended for the use of the management of non-convulsive status epilepticus or super refractory status epilepticus. In certain circumstances, a child may have an individual emergency care plan which supersedes this guideline.

PREVIOUS GUIDELINE

The first APLS manual was published in 1997 and the material contained within the manual is updated on a 5-yearly cycle. The current version is the sixth edition published in 2016.⁸ Since then there have been some significant changes in practice observed around the world on how to manage the convulsing child based on most recent research. Hence, this review aims to summarise the key updates which will feature in the upcoming APLS seventh edition.

Image 1: NEW Advanced Paediatric Life Support (APLS) algorithm on management of the convulsing child



WHAT CAN I CONTINUE TO DO AS BEFORE?

Principles of treatment

It is well established that most (90%) convulsions will spontaneously terminate within four minutes, with no intervention required. However, should the convulsion continue beyond t1(5-minutes) there is a greater chance (70-80%) of it lasting longer than 30-minutes.^{2,9}

Beyond this time point, it is unknown when exactly brain injury occurs and the longer the duration of the convulsion the harder it is to terminate. Together with effective resuscitation early recognition and treatment of ongoing convulsion may affect outcome.¹⁰

► The aims of acute treatment are summarised in box 3.

Box 3 Aims for acute treatment

- Support airway, breathing, circulation (ABC)
- Identify and treat life-threatening causes
- Termination of the convulsion
- Prevent re-occurrence of the convulsion
- Reduce risk of associated mortality and morbidity
- Avoid admission to intensive care

Primary assessment and resuscitation

► It is important to obtain a brief history of events, current medication and allergies. A focused physical examination will also help identify the underlying cause. Simultaneously, acute resuscitation must be undertaken.

► The approach to resuscitation remains the same as for any seriously unwell child. Treatment of the convulsion should be assessed and treated only after the Airway, Breathing, Circulation, Disability (ABCD) have been assessed and managed (see box 4).⁸

Box 4 Features specific for the convulsing

Airway – maintain airway, manage secretions

Breathing – give high-flow oxygen, consider intubation and ventilation

Circulation – establish IV/IO access, check vital signs

Disability – assess conscious level, check pupils, don't forget the glucose!

To aid the diagnostic work up of a child presenting with ongoing convulsion consider the follow investigations (see box 5).³

Box 5 Investigations to consider

- Blood tests – FBC, bone profile, magnesium, glucose, U&Es, LFT, blood gas, CRP
- Blood culture (if febrile)
- Brain imaging – CT, MRI
- Lumbar puncture CSF analysis (when stable)
- Toxicology – blood, urine
- Metabolic screen – serum ammonia, lactate, plasma amino acids, urine organic acids
- Anti-seizure medication levels (if on treatment)
- EEG

WHAT DO I NEED TO KNOW?

Emergency treatment of convulsion

- ▶ The updated medical algorithm will continue to be provided in four steps however with different time intervals. The new time intervals reflect current pharmacological understanding that allows enough time for treatment effect.
- ▶ There is an emphasis that whilst completing a step, the team should continually re-assess ABCD and get ready for the next step to avoid any delays in treatment.
- ▶ Anti-seizure medication doses are based on recommended dosing as per the British National Formulary for children and/or the most current available evidence.¹¹

Box 6 Key Updates

Step 1 & 2

- ▶ Shorter 5-minute interval between benzodiazepine doses.
- ▶ Pre-hospital treatment is endorsed.

Step 3

- ▶ Second line drug is levetiracetam

Step 4

- ▶ If the team are ready, they should proceed to RSI with either ketamine, thiopental or propofol.
- ▶ If the team are not ready either phenytoin or phenobarbital can be given and if immediately after completing this the child is still convulsing the team should proceed to RSI.

WHAT SHOULD I START DOING?

First-line treatment

Step 1

After 5 minutes of the start of the convulsion administer the first dose of benzodiazepine.

- ▶ If no IV/IO access is available, then give either buccal midazolam or rectal diazepam.
- ▶ If IV/IO access is available, give lorazepam

Benzodiazepines (BDZ) remain the first-line anti-seizure medication of choice. The fact that BDZ can be given quickly and have a rapid onset of action supports their use as first-line. There are also time-dependent GABA receptor changes that result in pharmaco-resistance to BDZ, further supporting its early use.¹² If the first dose of benzodiazepines is given early (within 20 minutes of the convulsion) trials have shown 70–86% seizure termination, but this decreases significantly as the convulsion progresses.^{13–15} Studies have shown that the time from BDZ administration to seizure termination is between 2 and 10 minutes.^{14–17}

Respiratory depression is the most common and most clinically relevant side effect, the frequency of this adverse event is observed up to 18% of children.^{11,14,18}

The choice of BDZ will vary depending on local practices and availability the options include the following: If no IV/IO access is available buccal or intramuscular (IM) midazolam, rectal diazepam or intranasal lorazepam are all acceptable options. However, if IV/IO access is available then lorazepam, midazolam, clonazepam or diazepam are all reasonable options. There is limited high quality evidence comparing the different BDZ. A recent metanalysis comparing different BDZ did show that buccal or IM midazolam and IV lorazepam are superior to IV or PR diazepam and that IV lorazepam is at least as effective as buccal or IM midazolam.^{14,19}

In the UK, the BDZ readily available are buccal midazolam, rectal diazepam and intravenous lorazepam. The main reasons for the use of these is that they are licensed for use in children, are readily available and easy to administer.

Buccal midazolam may also be regarded as the least invasive option and more socially acceptable. From a practical perspective, the BDZ that can be given the quickest should be considered the BDZ of choice.

Given that a large proportion of convulsions occur pre-hospital a trained carer or paramedic is empowered to administer first-line treatment to avoid delays in initiating treatment.

Step 2

After 5 minutes of administering the first dose of benzodiazepine and if the convulsion is still ongoing.

- ▶ If no IV/IO access is available, then give a second dose of either buccal midazolam or rectal diazepam
- ▶ If IV/IO access is available, give lorazepam

It is common practice to administer a second dose of benzodiazepine if the convulsion has not stopped after 5-minutes from the first dose. However, the evidence to support this practice is very limited and one paper was suggestive that repeat doses are much less likely to be effective (17% versus 85% after the first dose).^{4,12,14,15,19,20}

The risk of respiratory depression increases if more than two doses of benzodiazepines are administered.^{4,5,14-17} For this reason, the second dose of BDZ should be given in the presence of a trained health professional in either a hospital or pre-hospital setting.

The main rationale for this step is that establishing IV/IO access may invariably take time to establish and thus a second dose BDZ is commonly considered better than no treatment.¹⁴⁻¹⁷

Any pre-hospital doses should be counted and no more than two doses of benzodiazepine administered as this significantly increases the risk of respiratory depression and is unlikely to be effective.

The team should continuously monitor and support the child's airway and breathing.

Summary of first-line benzodiazepines available in UK are provided in Table 1.

Table 1: First-line anti-seizure medication^{4,11,21}

Drug	Route	Dose	Directions for Administration	Pharmacokinetics	Adverse effects
Midazolam	Buccal	0.3mg/kg (max 10mg) 3–11 months 2.5mg 1–4 years 5mg 5–9 years 7.5mg 10–17 years 10mg	Pre-filled syringe Administer liquid into the buccal cavity	Time to peak 30 minutes Plasma half-life 2 to 5 hours	Respiratory depression
Diazepam	PR	0.5mg/kg (max 20mg) 1month– 1 year 5mg 2–11 years 5-10mg 12–17 years 10-20mg	Pre-filled rectal tube Administer liquid into the rectum	Time to peak 10 to 30 minutes Plasma half-life initially rapid distribution phase followed by a prolonged terminal elimination phase of 1 to 2 days	Sedation Hypotension
Lorazepam	IV / IO	0.1mg/kg (max 4mg)	Dilute with an equal volume of sodium chloride 0.9% give over 3 to 5 minutes Max. rate 50micrograms/kg over 3 minutes	Time to peak: IV unknown. IM 60 to 90 minutes Plasma half-life 12 to 18 hours	

Second-line treatment

Step 3

After 5 minutes of administering the second dose of benzodiazepine and if the convulsion is still ongoing administer IV/IO levetiracetam.

Levetiracetam, phenytoin, fosphenytoin, phenobarbital, and sodium valproate are all considered to be equally effective second-line treatment for managing a convulsion that have not responded to initial benzodiazepines.^{13,16,22,23}

Levetiracetam is now considered the second-line anti-seizure medication of choice. With careful consideration, the professional working group felt it is the safest and most appropriate second line anti-seizure medication.

Levetiracetam is licensed for paediatric use although not yet for CSE and is readily available in the UK. Two recent randomised control trials have shown that levetiracetam is of comparable efficacy to phenytoin.^{22,24} One of several advantages of giving levetiracetam is that it can be given to any convulsing child without any contraindications. It can also be administered in a timely manner, as it is easy to prepare and it can be given over 5-minutes rather than the 20-minutes recommended for phenytoin or phenobarbitone, and it does not require any specific monitoring. It also has the added benefit that it has few adverse effects and none that alter the haemodynamic state of the child.

Although sodium valproate is a viable option there is a risk of exacerbating undiagnosed mitochondrial disease and the risk of teratogenicity in pregnancy or in females of child-bearing potential. It should also be used with caution in children with pre-existing liver disease. Hence, it is not recommended as a second-line treatment in an emergency.

Step 4

After 10 minutes of administering IV/IO levetiracetam and if the convulsion is still ongoing:

▶ *If the team are ready, proceed to rapid sequence induction*

▶ *If the team are not ready, administer IV/IO phenytoin or if the child is already on phenytoin administer phenobarbital. At the end of the infusion if the convulsion is still ongoing immediately proceed to rapid sequence induction.*

At this stage of management there is no clear evidence that outlines what the next best step is. The treatment options are limited to either trying a further second line anti-seizure medication or to proceed with rapid sequence induction (RSI) with anaesthesia. The professional working group came to the consensus that a second line anti-seizure medication is a suitable interim step should the team not be ready to do an immediate RSI after step 3.

This decision is largely based on evidence from the ConSEPT open label randomised controlled trial conducted in Australia and New Zealand.²² In the trial, 64% of patients who were given phenytoin and then levetiracetam had their seizures stop and 52% had levetiracetam then phenytoin had their seizures stop without the need for RSI. This implies giving a further anti-seizure medication can reduce the need for RSI and intubation by 50% at the cost of an additional 20-minutes of treatment is given before RSI. In addition, recent research has shown that there is no significant difference between outcomes when a convulsion continues beyond 30-minutes whilst the patient is receiving emergency anti-seizure medication and airway management, suggesting that the risk of substantial short-term harm from this approach is low.^{5,6} The working group also considered the morbidity and resource implications of intubation and admission to intensive care unit.

Although fosphenytoin has some theoretical advantages over phenytoin, fosphenytoin is not readily available in the UK. Phenytoin is licensed in UK for paediatric use and therefore recommended. Phenytoin solution is very alkaline it can cause serious extravasation injury. Common side effects of phenytoin are that it can cause arrhythmia, bradycardia, hypotension and more rarely respiratory arrest.¹¹ These side effects are more likely if the infusion is given too quickly. Continuous cardiac monitoring is recommended during its administration. If the child is already on oral phenytoin then phenobarbitone should be given instead.

Phenobarbital is licensed for use in the UK and is a reasonable alternative to phenytoin. Phenobarbital is associated with a greater incidence of adverse reactions.²⁰ Phenobarbital is a cytochrome P450 inducer, it interacts with many medications and has a worse side effect profile, with a propensity to cause hypotension, sedation, and respiratory depression, particularly with rapid infusion.²³ Continuous cardiac monitoring is recommended during its administration.

Ketamine, propofol, thiopental, and midazolam are all anaesthetic drugs that can be used for RSI in the convulsing child failing to respond to second line drugs. There is little to no evidence which suggests one is superior to another when managing ongoing convulsion at this stage. The management of super-refractory CSE is beyond the scope of this guideline. The drug of choice for RSI is largely influenced by the underlying aetiology, pharmacological evidence and the experience of the anaesthetic team. To reflect this the new guidance recommends use of either ketamine, thiopentone or propofol to induce anaesthesia. These anaesthetic drugs are familiar, readily available and licensed for the use in children. The main advantage of ketamine is it can be given in a haemodynamically unstable child who is not catecholamine deplete unlike thiopentone and propofol which may cause hypotension. In addition, there is rationale for using ketamine (with NMDA receptor antagonist action), in BDZ-resistant CSE.

Paralysing drugs should be avoided when possible as it will make it difficult to detect clinical seizures. When the child is stable, they should be transferred to a paediatric intensive care unit for ongoing care. At this stage, a paediatric neurologist should be consulted to provide clinical advice and support.

See below (Table 2) a summary of the currently recommended second-line anti-seizure medication.

Medication	Route	Dose	Directions for Administration	Pharmacokinetics	Adverse effects	Special considerations
Levetiracetam	IV/IO	40mg/kg (max 3g)	Dilute 1:1 with 0.9% sodium chloride (max 50mg in 1mL) and infused over 5 minutes	Time to peak 15 minutes Plasma half-life 7+/- 1 hour	Somnolence, dizziness, possible psychosis (low risk)	None
Phenytoin	IV/IO	20mg/kg (max 2g)	Dilute 1:1 with 0.9% sodium chloride to a minimum volume of 20mLs (maximum concentration 10mg in 1mL) and infused over 20 minutes Give through an in-line filter Rate of infusion should be no greater than 1mg/kg/minute (max. 50mg/minute)	Time to peak 30 to 60 minutes Plasma half-life 10 to 15 hours	Hypotension, arrhythmia, bradycardia, respiratory arrest Risk of IV extravasation injury	Do not use this if the child is on regular phenytoin Requires cardiac monitoring (ECG and blood pressure) Avoid if underlying cause is toxicity due to the increased risk of dysrhythmia
Phenobarbital	IV/IO	20mg/kg (max 1g)	Dilute 1:1 with 0.9% sodium chloride to a minimum volume of 20mLs (max. 20mg in 1mL) and infused over 20 minutes Rate of infusion should be no greater than 1mg/kg/minute	Time to peak 30mins Plasma half-life 21 to 75 hours	Respiratory depression, hypotension, sedation	Requires cardiac monitoring (ECG and blood pressure)

Other medications to consider

Paraldehyde

The use of paraldehyde should not delay giving a second-line anti-seizure medication and only be considered in circumstances when there are difficulties obtaining IV/IO access that would delay treatment.⁸ The dose is 0.8mL/kg (maximum per dose 20mLs) per rectum, the dose is based on the use of premixed solution of paraldehyde in olive oil in equal volumes.¹¹ Paraldehyde takes 10-15 minutes to act and its action is sustained for 2-4 hours. Paraldehyde causes little respiratory depression and should not be given to children with liver disease. Its main disadvantages include its variable availability in the UK and its irritant effect on the rectal mucosa.

HOW DO I IMPLEMENT THESE GUIDELINES INTO MY PRACTICE?

- ▶ In order to deliver this, health care professionals need the appropriate training and easy access to clear guidelines. In the UK, the APLS training provided by the ALSG delivers this to a high standard.
- ▶ Consider simulation practice scenarios with local teams to become familiar the new treatment algorithm.
- ▶ The algorithm should be easily accessible during an emergency.

CONCLUSION

CSE is a medical emergency associated with significant morbidity and mortality. Management of CSE is time critical. It is important that any recommendations on the emergency management of CSE in children and young people is regularly reviewed and reflects the emerging new evidence and medications available.

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