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# Status Epilepticus – CPS Podcast

Developed by Drs. Larissa Shapka, Chris Novak and Kyle McKenzie for PedsCases.com.
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## Introduction:

*Larissa:* Hello, my name is Larissa Shapka and I'm a pediatric resident at the University of Toronto.

*Chris:* and I'm Dr. Chris Novak, a hospital pediatrician at Alberta Children's Hospital. After years of working together on PedsCases this is our first time recording together!

*Larissa:* This podcast was produced by PedsCases and the Canadian Paediatric Society (CPS). The goal of this podcast is to summarize the 2021 CPS practice point titled "Emergency management of the pediatric patient with convulsive status epilepticus." The podcast was developed with Dr. Kyle McKenzie, a pediatrician in Red Deer, Alberta, and one of the authors of the practice point. To view the complete practice point, please visit www.cps.ca. The script for this podcast can be accessed at www.pedscases.com

Prolonged seizures are a presentation that many health care practitioners will encounter, whether in the Emergency Department or inpatient setting. Pediatric status epilepticus is also a frequent indication for ICU admission. Status epilepticus is a neurological emergency, so it's important to have a practical and timely approach to it.

The current CPS position statement replaces a previous version from 2011, with an updated treatment algorithm and new medication recommendations. We'll cover all this in detail later in the podcast. It's important to remember that these guidelines apply to children and infants older than one month of age. Please refer to neonatal specific resources for any patients under 28 days.

### Objectives

*Chris:* After listening to this podcast, the learner should be able to:

1. Define convulsive status epilepticus
2. List common etiologies of convulsive status epilepticus (CSE) in the pediatric population
3. Initiate basic management of pediatric CSE as per the CPS algorithm including:
    - Maintain adequate airway, breathing, and circulation
    - Order appropriate medications to terminate the seizure
    - Diagnose life threatening causes of CSE

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For a review of seizure classification, epilepsy syndromes, and long-term antiepileptic therapy, please refer to the other podcasts and notes on PedsCases.com

## Clinical case

*Chris:* We will begin with a clinical case to provide some context and return to it throughout the podcast to apply what we learn. Let's get started!

You are working in the Emergency Department when Liam, a 3-year-old male, is brought in by EMS with concern for a prolonged seizure. His parents called 911 after finding him unresponsive with jerking movements of all his limbs. He was given one-dose of intranasal midazolam by EMS en route, but the movements have persisted, and it's now been 15 minutes. How do you manage the situation?

## Background

*Larissa:* To start, let's talk about what status epilepticus is and why it matters. When we say "status epilepticus" what do we even mean?

*Chris:* The International League Against Epilepsy defines status epilepticus as a single epileptic seizure lasting more than 30 minutes or a series of seizures where function is not regained in between within 30 minutes. However, the definition of status epilepticus and what we would treat in practice often differ, since we want to stop seizures earlier to prevent brain injury. Research has shown that early treatment is more effective, and delays can cause increased morbidity and mortality. You may hear the terms "early" or "impending" status epilepticus which refer to continuous or intermittent seizures lasting longer than 5 minutes without full recovery of consciousness in between. The CPS advises using the 5-10 minute mark as the threshold to treat for a prolonged seizure. From our clinical experience, most practitioners intervene at the 5-minute mark.

The annual incidence of pediatric convulsive status epilepticus is 10 to 73 episodes per 100 000 children, and CSE is associated with significant morbidity and mortality. The risk of mortality is between 2.7-8%, and for morbidity the risk is 10-20%. Morbidity includes hemodynamic instability, diagnosis of neurologic conditions, long-term neurologic deficits, cognitive impairment, and behavioural concerns. In general, these outcomes are determined by the underlying cause, but length of CSE also plays a role.

## Etiologies

*Larissa:* Now that we know what CSE is, let's talk about some of the common the causes.

*Chris:* One way to categorize etiology is by timeframe, ie. acute vs remote. The most common cause of CSE in children is a prolonged febrile seizure. Other acute causes include:

- CNS infection
- Trauma
- Metabolic and electrolyte disturbances like hypoglycemia, hyperglycemia, hyponatremia, and hypocalcemia
- Toxin or medication ingestions
- Subtherapeutic levels of anti-epileptic medications

Patients can also have remote pathologies lowering their seizure threshold, including:

- Perinatal hypoxic-ischemic encephalopathy
- Congenital brain anomalies like cerebral dysgenesis

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- Prior brain injury (such as from stroke, trauma, or meningitis)
- Progressive neurodegenerative disorders

CSE can also be idiopathic.

**Principles of management**

*Larissa:* Witnessing a patient having a seizure can be scary. What should be going through your mind when you're called to the bedside of a patient who is seizing?

*Chris:* You can break down acute management of CSE to 4 main parts:

1. Maintaining airway, breathing, and circulation
2. Stopping the seizure and preventing recurrence
3. Managing any refractory status epilepticus
4. Diagnosing life-threatening causes of CSE

While it can be easy to focus on trying to stop the seizure activity in CSE, your first and most important priority is maintaining the airway. It's all about the ABCs, and airway comes first for a reason- inadequate airway maintenance is the most critical immediate risk to patients with CSE. They can experience upper airway obstruction related to decreased tone and may require help with ventilation. Hypoxia is also common.

Maneuvers to help manage the airway initially include positioning. Chin lift and jaw thrust are helpful to open the upper airway and relieve obstruction. You can place the child on their side and suction any easily accessible secretions, before repositioning them on their back. Patients should be kept in a safe position for the duration of the seizure, but not restrained.

A patient with a prolonged seizure should be placed on cardiorespiratory and oxygen saturation monitors and receive 100% O2 via face mask. Watch closely for airway compromise, respiratory failure, hypotension, or cardiac arrythmias. Vital sign changes that usually accompany seizures include tachycardia and hypertension, but these should resolve once a seizure stops. If your patient is showing signs of respiratory depression or hypoxia (SpO2 < 90%) despite receiving 100% O2 via facemask, you should be thinking about assisted ventilation. Red flag signs concerning for severe hypoxia include bradycardia, hypotension, and poor perfusion. These should cue you to immediately secure the airway either by bag-valve-mask ventilation, intubation, or an alternative airway.

As with any emergency situation, make sure you're calling for help and mobilizing the appropriate resources for your situation – ICU should be consulted when there is respiratory and hemodynamic compromise associated with a seizure as well as in cases of refractory status epilepticus.

Remember, the priority is ABCs. For the next part, let's talk about what some of the other key principles are in managing CSE.

*Larissa:* As with other acute presentation, you should take a focused history and physical exam. This will help you identify possible life-threatening causes of CSE and may also yield information that could influence what medications you use to try to stop the seizure. Make sure you are asking about any associated symptoms, history of seizure disorder, medications, and drug allergies.

Don't forget to ask for a STAT glucose- point of care glucose testing is quick, easy, and can significantly change your management of CSE! You don't want to miss hypoglycemia – it's potentially life threatening, but reversible. A common mnemonic for emergencies in pediatrics is ABC DEFG: Airway, Breathing, Circulation, and Don't Ever Forget Glucose!

You'll also want to establish IV access ASAP for medication administration. As with any emergency situation, two large-bore IVs are ideal. If you have difficulties with getting access, you do have options for other routes of initial medication administration. However, you should think about escalating to placing an intraosseous line if you can't get IV access and the patient is decompensating, or if you get to the point where the seizure requires treatment with second-line medications. You can consider sending some blood work with this to investigate other potentially reversible causes of CSE (more on this to come) but obtaining these tests should not delay medication administration!

Continuous cardio-respiratory monitoring is also important if you end up giving any antiepileptic medications. Anti-epileptic medications can lead to loss of airway reflexes, respiratory depression, hypotension, and cardiac arrythmias, so it's important to monitor for these complications and be prepared to deal with them.

I know it sounds like a lot, but in real-time often many things can happen at once- for example someone can check a point-of-care glucose while you take your focused history, while another team-member draws up first-line medications to have on hand. Coordinating the medical team is key!

Let's move on to discussing how to stop the seizure. As mentioned earlier, you should think about giving anti-epileptic medication to prevent brain injury if the seizure is prolonged more than 5 minutes, or if your patient experiences recurrent seizures in a short period of time.

*Chris*: Yes, that's correct! Realistically you should start thinking about this even before the 5-minute mark. It takes time to draw up medications and get vascular access. If you suspect you could be moving towards status, it's very reasonable to ask a team member to start getting vascular access and drawing up medications.

**First-line medications**

*Larissa:* So which medication do you choose for first-line treatment?

*Chris:* In general, there is limited evidence for a "gold standard protocol" for pediatric CSE, and different guidelines have minor variations. Intervening quickly may be more important than specific medication selection. Remember this is a medical emergency! The CPS statement has a really helpful figure outlining their treatment algorithm, and a great table comparing the different antiepileptic drugs. We highly suggest saving it on your phone for quick access on the go. Let's delve into these recommendations.

Your first-line medications for treatment of CSE are benzodiazepines.

For pre-hospital management, midazolam is the preferred benzodiazepine and can be given a variety of routes- intranasal, intramuscular, and buccal. Please refer to the CPS statement for full details of dosing. Alternatives to midazolam include buccal lorazepam.

Once in hospital, the preferred route of benzodiazepine administration is IV. However, medication administration should not be delayed while vascular access is being secured, and other routes such as intramuscular, intranasal, and buccal can be used in the interim.

Your options for IV benzodiazepines are midazolam, lorazepam and diazepam. Lorazepam IV and midazolam IV or IM all have similar efficacy and are the recommended first-line options for treatment. These have been shown to be more effective than diazepam and phenytoin.

We suggest you pick one of these and memorize the dosing as your go to! For example, I have the dosing of Lorazepam: 0.1mg/kg to a max of 4mg IV as my go to.

Side effects of benzodiazepines include hypotension, respiratory depression, and sedation. Typically, these are seen after more than 2 doses, but it's important to be aware and prepared to manage them.

*Larissa:* Okay so you've given a benzodiazepine as your first-line medication for CSE. You reassess your patient after and they are still seizing. What do you do next?

*Chris:* If your patient is still having a seizure 5 minutes after the first dose of benzodiazepine, administer another dose of a benzodiazepine. If you didn't give the first dose via IV, switch to IV route for this second dose if possible.

If more than 2 doses of benzodiazepines have been given, including pre-hospital medications, and seizure is still ongoing 5 minutes after the last dose, it's time to move onto second-line mediations.

And as a general rule, if you are moving on to second-line anti-epileptic medications and you don't have IV access yet, you should be thinking about an IO for medication administration and contingency planning.

**Second-line mediations**

*Larissa:* Second-line treatment consists of loading doses of antiepileptic drugs such as fosphenytoin/phenytoin, phenobarbital, levetiracetam, or valproate. How do you choose between these options?

*Chris:* Efficacy, availability, side effects, and the individual clinical scenario all play into your decision making. Current evidence suggests that for benzodiazepine refractory seizures, fosphenytoin/phenytoin, levetiracetam, and valproate are all equally effective.

Fosphenytoin/phenytoin and phenobarbital have been the two most used second-line agents in Canada because of familiarity and availability. However, IV levetiracetam came to the Canadian market in 2019 and is changing things- it's a nice option in patients whom you are worried about respiratory and hemodynamic stability. IV valproate is in short supply and as of July 2020 is only available through Health Canada's Special Access Program. One other consideration is route of administration- all of these second-line mediations require vascular accesses except fosphenytoin which can be given IM as well. We'll review each of those medications in details.

**Phenytoin and fosphenytoin**

*Larissa:* Phenytoin and fosphenytoin are sodium channel blockers, with fosphenytoin being the water-soluble prodrug of phenytoin. Phenytoin has a high pH, so can cause severe

subcutaneous extravasation injuries. This risk doesn't exist with fosphenytoin, so fosphenytoin also has the flexibility of being administered IM. But fosphenytoin is more expensive and not as widely available as phenytoin.

Evidence suggests that phenytoin stops about 50-80% of prolonged seizures. In addition to broad availability, it also has less respiratory effects then phenobarbital. Potential effects of phenytoin/fosphenytoin include bradycardia, arrythmias, and hypotension. You should also avoid phenytoin/fosphenytoin if you suspect the seizure is caused by toxin ingestion or drug withdrawal as it could be harmful in theophylline or tricyclic antidepressants ingestions.

The dosing of phenytoin/fosphenytoin is 20mg/kg to a maximum of 1000mg. Of note, fosphenytoin should always be ordered as mg of phenytoin equivalents. This should be common practice in hospital pharmacies, but essentially dosing of phenytoin and fosphenytoin is 1:1 equivalent. An additional 5mg/kg can be given if the initial dose is ineffective. But if a patient is already on phenytoin for maintenance anti-epileptic therapy, this initial dose should be lower- 5mg/kg only, with further dosing guided by drug levels. Always remember that phenytoin and fosphenytoin should not be used in combination with each other. They are considered equivalent, so if one has already been given, don't give the other. Practically speaking, it's also helpful to know that it takes 5-10 minutes to infuse this medication.

**Phenobarbital**
*Chris:* The efficacy of phenobarbital is similar to phenytoin, but phenobarbital has a higher risk of respiratory depression, especially when benzodiazepines have already been given. Phenobarbital also has a similar mechanism of action to benzodiazepines, so it also might actually be less effective in treating seizures that failed to respond to first-line treatment. Potential side effects of phenobarbital include hypotension and sedation. Given all of this, you should be cautious about using it in patients with respiratory depression or hemodynamic instability, and probably pick a different medication.

That being said, there are instances in which it may be a good choice. Phenobarbital may be the best second-line option for: infants < 6 months, febrile status epilepticus, seizures caused by toxin ingestion or drug withdrawal, or in cases where your patient is already on phenytoin maintenance. Another benefit of phenobarbital is that it tends to be widely accessible. If you are giving phenobarbital the dose is 20mg/kg to a max of 1000 mg. This infusion must be run over 20 minutes. Next let's talk about the new additions to the CPS treatment algorithm!

**Levetiracetam**
*Larissa*: First is levetiracetam, more commonly known by its trade name of Keppra. IV levetiracetam has been available in Canada for the past couple of years. Data suggests it has similar efficacy to other anti-epileptics such as phenytoin, phenobarbital, and valproate and overall, it seems to be better tolerated, with fewer respiratory and cardiovascular side effects than phenytoin and phenobarbital. It's a really good choice in children who are unstable. Another benefit is that it also has relatively fewer medication interactions than some of the other anti-epileptic medications. In terms of side effects of levetiracetam, post-ictal psychosis has been reported, but the overall the risk of this is low. The dosing for levetiracetam recommended by CPS is 60 mg/kg to a max of 3000 mg.

**Valproate**
*Chris:* IV valproate has similar efficacy to phenytoin, phenobarbital, and levetiracetam, with potentially less respiratory and cardiovascular side effects. It is also a useful second-line agent

in children who are already on valproate for maintenance antiepileptic therapy but have had poor adherence to this. Dosing is 30mg/kg to a maximum of 3000mg, with an additional 10mg/kg top-up which can be given if initially ineffective. However, the availability of IV valproate in Canada is a limiting factor, as it is currently only accessible through Health Canada's Special Access Program.

It's also important to know that valproate is strictly contraindicated in those with mitochondrial disease (suspected or confirmed), including children under 2 years of age with unexplained developmental delays. You should also be cautious in patients with pre-existing liver disease.

**Other medications**
Paraldehyde does not appear in the CPS algorithm as it is no longer available in Canada. Lacosamide may have potential as a second-line agent, however right now there is insufficient evidence to recommend routine use.

*Larissa:* So what happens if you give one of these second-line agents and it doesn't stop the seizure? Are there any recommendations for what to pick next?

*Chris*: If your patient has received 1 second-line medication and the seizures is still ongoing 5 minutes after the medication has been fully delivered, give a different second-line mediation.

If your patient is less than 18 months of age, you can consider giving pyridoxine (vitamin B6) in case the seizures are caused by an undiagnosed metabolic disorder.

**Refractory status epilepticus**
*Larissa:* What if you are in a situation where you've given two doses of first-line anti-epileptic medications (benzodiazepines) and two doses of the second-line drugs, and still the seizure has not stopped?

*Chris:* If a patient is still seizing after two second-line antiepileptic medications, this would generally be considered refractory status epilepticus (though some definitions require a duration of 1 hour.)

For any case of refractory status epilepticus, you should be consulting specialty services including intensive care and Neurology. Second-line medications for CSE are less likely to be effective after the first hour of seizure activity, and other treatments may be required, such as continuous midazolam infusion, propofol, high-dose phenobarbital, or pentobarbital. These can have significant respiratory and hemodynamic effects and they require escalation of care to the ICU setting.

**Medication Summary**
*Larissa:* That was a lot of information! To recap:

- The CPS algorithm advises that convulsive seizures lasting longer than 5 minutes be treated with antiepileptic medications. Benzodiazepines are the first-line medication for CSE.
- You would give a dose of benzodiazepine, then repeat again 5 minutes later if ineffective.
- Once two doses of benzodiazepine have been given, it's time to escalate to second line antiepileptic drugs if the seizure persists for more than 5 minutes.

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- Your second-line medication choices are fosphenytoin/phenytoin, phenobarbital, levetiracetam, and valproate. Availability, efficacy, and side effect profile will help you tailor your selection.
- If one second-line medication is ineffective, try a different one. However, if the seizure continues after this, the patient is in refractory status epilepticus and it's time to consult ICU to discuss escalation of care.
- The whole time you are managing a patient with CSE you should be providing supportive care and monitoring for respiratory depression, hypotension, and arrythmias, which would necessitate earlier consultation with intensive care.

*Chris:* Yes, that about sums it up! Of course, these are just guidelines. Patients with complex epilepsy histories may have individual seizure management plans, but the same general principles apply.

**Investigations**

*Larissa:* We've spent a lot of time talking about management and medication algorithm for CSE. What about investigating for potential causes of it? What tests should be considered?

*Chris:* This will vary depending on your individual patient's clinical scenario.

All patients should have history and physical exam performed to assess for precipitating causes with special attention to signs of infection, intoxication, trauma, and focal neurological deficits.

Investigations should be tailored to a patient's clinical scenario. Remember that the most common cause of CSE is prolonged febrile seizure, in which case an extensive work-up is usually not required. Similarly, if children have known epilepsy, then extensive work-up may not be indicated.

Lab tests should be considered when the etiology of CSE is unclear. In addition to the initial glucose measurement, these include: CBC, electrolytes, blood gas, blood cultures if sepsis is suspected, and anti-epileptic drug levels if a patient is already on maintenance therapy. Extended electrolytes including calcium, magnesium, liver enzymes, lactate, and ammonia can also be considered depending on your clinical suspicion for metabolic derangements.

If you suspect meningitis or encephalitis, IV antibiotics and antivirals should be urgently administered. Do not delay treatment to draw cultures. The LP should be deferred until the patient has stable vital signs, has stopped seizing, and there is no concern for raised-intracranial pressure (ICP).

Head CT should be performed if there is a history of trauma, signs of raised ICP or cerebral herniation, focal neurologic deficits, or unexplained loss of consciousness. MRI may be helpful for more detailed assessment but is not always readily available.

It is key to remember that if there are signs of increased ICP/herniation, your priority is managing this. Elevated ICP must be treated immediately before any further investigation or imaging. Also keep in mind that a normal CT does not exclude raised ICP, and that a LP is contraindicated if there are signs of raised ICP.

Always have intoxication on your differential diagnosis. When there is strong suspicion for it, consider using activated charcoal once the seizure has stopped and the airway is protected.

**Non-Convulsive Status Epilepticus**

*Larissa:* We've spent the podcast discussing convulsive status epilepticus, now a quick word on non-convulsive status epilepticus. Non-convulsive status epilepticus refers to a persistent change in a patient's baseline level of consciousness and accompanying continuous epileptiform changes on EEG, but no clinical motor manifestations. You would want to get an EEG to rule out non-CSE if your patient does not recover level of consciousness as expected once a convulsive seizure has stopped, or when neuromuscular paralytic agents have been given. If EEG isn't available, you should discuss with Neurology and start empiric treatment for non-CSE.

**Clinical Case**

Now let's return to our case to apply what we've learned before we wrap up the podcast.

You begin your assessment of Liam as your team attaches heart rate and oxygen saturation monitors. His airway appears patent, he is breathing spontaneously and receiving O2 via facemask as started by EMS. He is tachycardic and mildly hypertensive, but peripheral perfusion is still maintained. Liam is unresponsive on exam with tonic-clonic movements of his extremities. His mother worriedly tells you that while he had a fever and cold the past day, she didn't think it was anything serious. She was shocked and scared when he started to seize today; he had been his usual self-up until this. He is normally healthy and has no regular medications or allergies. There is no history of trauma and or known substance ingestion.

You ask for a point of care blood glucose, which is normal, IV insert, and administer a dose of IV lorazepam 0.1mg/kg. Unfortunately, despite this, the seizure continues. Given that Liam has already received a total of two doses of benzodiazepines including the dose of midazolam with EMS, you escalate to your second-line agents. You choose phenobarbital as this drug may be more effective in febrile status epilepticus, you have it readily on hand, Liam has remained stable from hemodynamic and respiratory perspectives. His seizure continues and 5 minutes later you give a dose of IV levetiracetam, which quickly stops the seizure with no significant cardiorespiratory compromise. You suspect that the etiology of Liam's CSE was prolonged febrile seizure and continue on with your assessment.

**Summary**

*Chris:* We've made it to the end of the podcast, so let's end by reviewing a few key points:

1. CSE is a neurologic emergency. Your most important priority in CSE is maintaining respiratory and hemodynamic stability.
2. Anti-epileptic medications should be given promptly for prolonged seizure greater than 5 minutes recurrent seizures in a short period of time.
3. First-line medications to terminate CSE are benzodiazepines. If your first dose doesn't work, try one more! Then move on to second-line medications. Second-line medications are fosphenytoin/phenytoin, phenobarbital, levetiracetam, or valproate. Your choice between these will depend on availability, side effect profile, and efficacy. If you've tried one of these second-line medications and it is ineffective, try a different one. Also consider giving pyridoxine in those less than 18 months of age.
4. If you've given two second-line medications with no response, this is considered refractory status epilepticus. In this situation, you should be consulting ICU for consideration for transfer care, as well as Neurology.

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5. Keep in mind the potentially life-threatening causes of CSE. Investigations should be guided by clinical suspicion but remember your first priority is stabilizing the patient.

That concludes our podcast reviewing the CPS practice point on “Emergency management of the pediatric patient with convulsive status epilepticus.” We hope you found it helpful, and thanks for listening!

**References**

McKenzie KC, Hahn CD, Friedman JN. Emergency management of the paediatric patient with convulsive status epilepticus. *Paediatr Child Health*. 2021;26(1):50-66. Published 2021 Jan 21. doi:10.1093/pch/pxaa127