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Guideline for the management of convulsive status epilepticus in infants and children

Children treated more aggressively and those with shorter episodes of status epilepticus have been found less likely to develop neurological deficits.

ABSTRACT: Convulsive status epilepticus is a medical emergency requiring early and effective treatment. Airway, respiratory, and circulatory support should be provided immediately. Initial investigations should then focus on possible metabolic derangements and conditions that require immediate treatment, such as meningitis. The recommended first-line therapy includes a fast-acting benzodiazepine followed by a longer-acting antiepileptic. In cases of refractory status epilepticus, further treatment will depend on the setting. When pediatric intensive care is not available, phenobarbital or paraldehyde might be used. When pediatric intensive care is available, midazolam, barbiturates, and propofol are options. Neuroimaging by either CT or MRI should be undertaken only after the patient has been stabilized and the convulsive seizure activity controlled.

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Convulsive status epilepticus accounts for 70% of episodes of status epilepticus (SE) occurring in infants and children.[1] Status epilepticus, whether convulsive or nonconvulsive, is "an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition."[2] Early studies used a definition of continuous seizure activity lasting for 30 minutes or recurrent seizures without any intervening recovery of full consciousness.[3] However, most seizures in children that last for longer than 7 minutes will last for at least 30 minutes.[4] Consequently, it is generally recommended that seizures lasting for more than 5 minutes should be treated as for status epilepticus.[5] Because of the significant morbidity and mortality associated with SE, early and effective treatment is essential.

Morbidity and mortality

More effective treatment of status epilepticus has reduced the mortality rate in children to between 1% and 5%.[6-9] However, status epilepticus can be associated with significant morbidity, including epilepsy, motor disorders, and cognitive abnormalities. The underlying cause is considered to be the most important determinant of outcome, and the morbidity appears to be less in those with febrile and unprovoked status epilepticus.[6] Studies of status epilepticus in primates have demonstrated a direct relationship between the duration of the seizure and the development of permanent brain injury that probably occurs as a result of the depletion of energy substrate.[10] In addition, children treated more aggressively and those with shorter episodes of SE are less likely to develop subsequent neurological deficits or epilepsy.[9] Similarly, resistance to first- and second-line treatments for SE is directly related to the duration of seizures prior to treatment.[11,12] These studies demonstrate that a prolonged seizure per se can result in brain injury and emphasize

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the importance of early and effective treatment of SE.

Causes of status epilepticus in children

It is important to consider the underlying cause of status epilepticus. The cause will guide the investigations, may require immediate treatment, and has a major influence on the prognosis. In approximately one-quarter of children affected, status epilepticus is the sign of an underlying acute brain disorder, such as traumatic brain injury or meningitis. Approximately one-third of children affected will have a history of previous epileptic seizures, developmental delay, or other neurological abnormality. One-quarter of children affected will have a prolonged febrile convulsion and no other cause will be demonstrated. An underlying cause will not be found in the remaining children.

Initial management and investigations

The accompanying **Figure** describes the organized approach to managing convulsive status epilepticus in infants and children recommended by physicians at BC Children's Hospital (BCCH). The initial management involves stabilization of the airway, maintenance of adequate ventilation (with oxygen administered as necessary), and circulatory support. Intravenous access should then be established as this permits the most rapid delivery of a drug to the brain. If difficulty is encountered achieving intravenous access within 3 minutes, then intraosseous access should be established if possible. During the management of the patient, it is important to consider the duration of the seizure both prior to and during treatment.

The initial laboratory studies should focus on the possible causes of status epilepticus, particularly those that require immediate treatment, such as meningitis and reversible derangements of metabolism.[13] Investigations should include complete blood count, blood culture (in febrile children), serum electrolytes, and blood glucose. Blood glucose should also be checked at the bedside and 5 mL/kg 10% dextrose administered if blood glucose is less than 3 mmol/L. Antiepileptic drug levels should be determined if the patient is receiving phenobarbital, phenytoin, carbamazepine, or valproic acid.

A computed tomography or magnetic resonance imaging scan of the head should be considered if there are clinical indications, such as a focal neurological abnormality, or if the cause is unknown. If neuroimaging is done, it should be undertaken only after the patient has been stabilized and the convulsive seizure activity controlled.[13]

Table 1. Drugs for initial treatment of convulsive status epilepticus.

Drug	Dose and route	Notes
Lorazepam	0.1 mg/kg (max 4 mg) IV	• Can be repeated once after 5 min
Diazepam	0.3 mg/kg (max 5 mg in infants and 10 mg in children) IV, IO 0.5 mg/kg (max 10 mg) PR	• IV dose should be given over 2 to 5 min to avoid respiratory depression • Can be repeated once after 5 min
Midazolam	0.2 mg/kg (max 10 mg) IN or 0.5 mg/kg (max 10 mg) buccal	• Can be repeated once after 5 min
Phenytoin	18–20 mg/kg IV, IO	• Should be given over 20 min • Monitor for bradycardia, hypotension, cardiac arrhythmia
Fosphenytoin	18–20 mg/kg of phenytoin equivalents IV or IM	• IV 1.5–3.0 mg/kg/min (max 150 mg/min) • IM in single or divided doses
Phenobarbital	15–20 mg/kg IV	• Monitor for respiratory depression, hypotension
Paraldehyde	0.3–0.4 mL/kg (max total volume 10 mL) mixed in an equal amount of mineral or olive oil PR	

IV = intravenous; IO = intraosseous; PR = per rectal; IN = intranasal; IM = intramuscular

Drugs

Physicians are generally aware of the doses of anticonvulsant medications used in adults, but unfamiliarity with the doses and routes used in children sometimes results in administration of inappropriate doses.[14,15] **Table 1** describes the doses for initial treatment in children based on their weight.

Benzodiazepines

Benzodiazepines act rapidly and are the medications for first-line treatment of convulsive status epilepticus. The dose of whichever benzodiazepine is used should be repeated after 5 minutes if the seizure continues.

Lorazepam. Intravenous lorazepam is the treatment of choice for status epilepticus. It has a longer duration of action and fewer adverse effects than diazepam,[15,16] and has been reported to be associated with more rapid seizure control than IV diazepam.[17] Peak concentrations of sublingual lorazepam may not occur for 60 minutes[18] and rectal absorption is erratic.[19] Consequently, sublingual and rectal lorazepam are not recommended for the treatment of status epilepticus.

Diazepam. Intravenous diazepam should be administered over 2 minutes because the risk of respiratory depression is increased with more

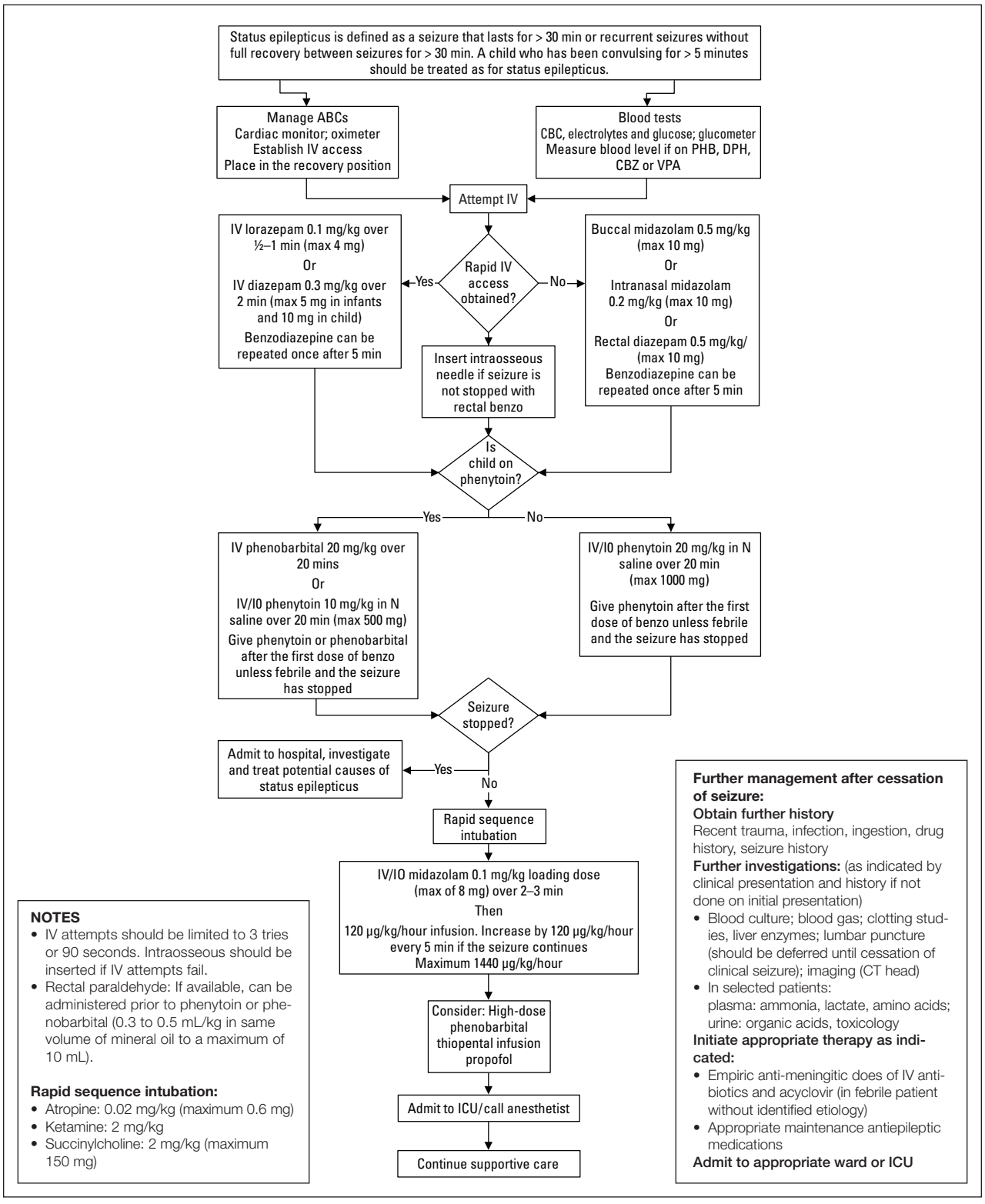

Figure. Management of convulsive status epilepticus in infants and children.

rapid administration and with more than two doses.[15] Rectal diazepam is absorbed rapidly and attains a therapeutic level in 10 minutes.[20]

Midazolam. Midazolam is a fast-acting, water-soluble benzodiazepine that can be administered intravenously and is rapidly absorbed via both the nasal and buccal mucosa.[21,22] Studies in children have shown both buccal and intranasal midazolam to be more effective than rectal diazepam in children with acute convulsions.[21,23] The absence of studies comparing the efficacy of IV midazolam with that of lorazepam or diazepam limits our ability to recommend midazolam for first-line treatment of status epilepticus in children. However, it is considered to be of particular value in refractory status epilepticus.[24,25]

Longer-acting antiepileptic medications

A longer-acting antiepileptic drug should also be administered because of the relatively short duration of action of benzodiazepines. At BCCH, it is our practice not to do this in febrile children with a seizure lasting less than 15 minutes who respond immediately to a benzodiazepine. Phenytoin is preferred over phenobarbital, which is more likely to cause respiratory depression and to alter the child's level of consciousness. Drugs that alter consciousness complicate the assessment of the child when the convulsion has stopped.

Phenytoin. Phenytoin is administered at a dose of 18 to 20 mg/kg intravenously or by the intraosseous route[26] over 20 minutes (with a maximum infusion rate of 50 mg/min). Administration should start *immediately* after the first dose of a benzodiazepine. Intravenous phenytoin treatment may be complicated by bradycardia, hypotension, and cardiac arrhythmia, so cardiorespiratory monitoring is recommended. In children who are receiving phenytoin prior to the onset of status epilepticus, we recommend the use of a smaller dose of phenytoin (5 mg/kg over 5 min), while awaiting the results of a blood phenytoin level. When IV access cannot be achieved promptly, intramuscular (IM) fosphenytoin or rectal paraldehyde can be used.

Fosphenytoin. Fosphenytoin is a water-soluble phenytoin prodrug that can also be administered by either intravenous or intramuscular routes.[27-29] Peak plasma concentration of fosphenytoin is observed at the end of IV infusion and 20 to 39 minutes after IM administration.[30] Intravenous fosphenytoin can be administered at a rate of up to 1.5 mg/kg/min (maximum 150 mg/min).[27,28] When IV access is not possible, IM fosphenytoin (18 to 20 mg/kg of phenytoin equivalents) should be given as a single dose.

If the child is not in a hospital that is able to provide pediatric intensive care including respiratory support, either intravenous phenobarbital or rectal paraldehyde can be used.

What to do when first-line treatment fails

Convulsive status epilepticus that is refractory to a benzodiazepine and an appropriate longer-acting anticonvulsant occurs in approximately 40% of cases[9] and is associated with higher morbidity and mortality.[31,32] The management of the child in that situation depends partly on the setting.

When pediatric intensive care and respiratory support are not available

If the child is not in a hospital that is able to provide pediatric intensive care including respiratory support, either intravenous phenobarbital or rectal paraldehyde can be used. However, consultation with a pediatric intensivist at BCCH is recommended.

Phenobarbital. IV phenobarbital is administered in a loading dose of 15 to 20 mg/kg.[33] It is highly effective but has a long duration of action. Phenobarbital is more likely than phenytoin to cause sedation, respiratory depression, and hypotension, particularly if a benzodiazpine has also been administered.

Paraldehyde. Rectal paraldehyde is administered mixed in an equal amount of mineral or olive oil. It is effective in 66% to 74% of children with convulsive status epilepticus and respiratory depression is uncommon.[34] The restricted availability of paraldehyde in recent years has limited its use.

When pediatric intensive care is available

There have been no controlled trials on the management of refractory status epilepticus in children. However, midazolam, a barbiturate (thiopental, pentobarbital, or phenobarbital), and propofol are the most commonly used drugs. **Table 2** describes the doses used for refractory SE. However, because these drugs can cause cardiorespiratory compromise and intubation may be necessary, they should be administered only in centres with appropriate facilities. Overtreatment of refractory status epilepticus is associated with significant mortality and the management of refractory status epilepticus in children should be performed in consultation with the staff of a pediatric intensive care unit.

Table 2. Drugs used for refractory convulsive status epilepticus.

Drug	Dose and route	Notes
Midazolam	Bolus: 0.1 mg/kg IV Initial infusion: 2 µg/kg/min IV; titrate to effect (maximum 24 µg/kg/min)	• Prolonged infusion may result in accumulation in peripheral tissues
Thiopental	Bolus: 3–5 mg/kg IV; additional boluses of 1–2 mg/kg every 3 to 5 min to response (max total dose 10 mg/kg) Infusion: 3–5 mg/kg/h IV	
Pentobarbital	Bolus: 10 mg/kg IV Infusion: 0.5–1.0 mg/kg/h IV	• Prolonged infusion may result in accumulation in peripheral tissues
Propofol	Bolus: 1 mg/kg IV loading dose; additional 1–2 mg/kg boluses every 3–5 min to response (max 10 mg/kg) Infusion: 2–4 mg/kg/h IV	• Use with caution in patients <16 years • Risk of propofol infusion syndrome

We recommend midazolam for first-line treatment because of its relative ease of use and because treatment can be initiated once the airway is appropriately secured. When midazolam fails to achieve seizure control, a barbiturate or propofol can be used. Treatment with these requires prior rapid sequence induction, intubation, and ventilatory support.

Midazolam. Several authors have recommended the use of midazolam for first-line treatment in refractory SE, citing the high response rate and low complication rate.[9,32,35] One meta-analysis comparing treatments of refractory SE in children found that midazolam was associated with better efficacy and less mortality than diazepam, isoflurane, pentobarbital, and thiopental.[32]

The short elimination half-life (1.5–3.0 hours) and large volume of distribution of midazolam make it suitable for continuous IV infusion[32] but result in an increased risk of breakthrough seizures if not administered as an infusion or as multiple boluses.[33] We recommend a loading dose of 0.1 mg/kg, followed by a 2 µg/kg/min infusion. This initial infusion rate can be titrated to effect, up to a maximum of 24 µg/kg/min. After prolonged infusion, midazolam may accumulate in peripheral tissues and result in a prolonged half-life of up to 50 hours.[36,37]

Barbiturates (thiopental, pentobarbital). Thiopental can be administered as a 3 to 5 mg/kg bolus, followed by additional boluses of 1 to 2 mg/kg every 3 to 5 minutes until a clinical response is achieved, up to a maximum total dose of 10 mg/kg. Thereafter, it can be infused at a rate of 3 to 5 mg/kg/h.[33] Pentobarbital is administered as a 10 mg/kg bolus, followed by a continuous infusion at a rate of 0.5 to 1.0 mg/kg/h. After continuous administration, there is a tendency toward accumulation in body tissues, resulting in the need for prolonged ventilatory support even after the withdrawal of medication. Hypotension is a common adverse effect of barbiturates. At BCCH it is our practice to use barbiturate doses that achieve burst suppression on EEG.

Propofol. Propofol has a rapid onset of action and a short half-life (between 1 and 2 hours), which permits rapid titration. One study found propofol infusion more efficacious than thiopental in children with refractory status epilepticus.[38] Prolonged use in children (beyond 48 hours) is associated with an increased risk of propofol infusion syndrome, which is heralded by metabolic acidosis and is characterized by circulatory collapse, rhabdomyolysis, and cardiac arrhythmias.[37] It is considered to be relatively safe when used at infusion rates up to 4 mg/kg/h for short duration and when the dose is reduced if the child develops side effects.[38,39] We recommend that it be used with caution in children under the age of 16 years and only by specialists with experience in its use. The loading dose is 1 mg/kg; additional 1 to 2 mg/kg boluses can be administered every 3 to 5 minutes until a clinical response is achieved, up to a maximum dose of 10 mg/kg. Continuous infusion, started at an initial rate of 2 to 4 mg/kg/h, can be titrated to achieve burst suppression on EEG. The infusion rate should not exceed 4 mg/kg/h; if seizure control is not achieved rapidly, another agent should be used.[33] Acid-base imbalance, increased serum creatine phosphokinase, and increased serum triglycerides are markers of propofol infusion syndrome and should be monitored carefully. Propofol should be avoided in

Key points for management of convulsive status epilepticus

- Convulsive status epilepticus is a medical emergency requiring early treatment.
- Seizures lasting longer than 5 minutes should be treated as for status epilepticus.
- Benzodiazepines are the first-line pharmacological treatment.
- Treatment with phenytoin should be initiated immediately following benzodiazepines.
- Initial investigations should be undertaken to identify causes that require immediate treatment and metabolic derangements.
- Management of refractory convulsive status epilepticus in children may be associated with cardiac and respiratory complications and consultation with the staff of a pediatric intensive care unit is recommended.

children on the ketogenic diet because of its interference with fatty acid oxidation.[40]

Has the seizure really stopped?

Nonconvulsive status epilepticus may exist when clinical seizure activity has stopped. It occurs in up to approximately 20% of children after treatment of refractory convulsive status epilepticus.[9] Nonconvulsive status epilepticus should be suspected if the child has subtle muscle jerks, eye deviation, or abnormal eye movements.[41] Although impaired consciousness after convulsive status epilepticus can be caused by other factors, such as medications, and the postictal state, an EEG should be obtained if there is persistent impairment of consciousness. Neuromuscular paralysis, which may be used to facilitate respiratory support, prevents detection of clinical seizures, and an EEG should be obtained if neuromuscular paralysis is being used to manage the child.[42]

Summary

Convulsive status epilepticus in children is a medical emergency that is handled most effectively with an organized approach. Drugs for initial treatment include benzodiazepines and longer-acting antiepileptics. The treatment of refractory status epilepticus will depend on the setting. Updates in the approach described in this article will be posted on the guidelines section of the Child Health BC website: www.childhealthbc.ca.

Competing interests

None declared.

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