An update in the initial management of paediatric status epilepticus

Ben Lawton[a,b,c], *Tessa Davis*[d], *Henry Goldstein*[a,b], *and Andrew Tagg*[e]

Purpose of review
Over the last 2 years, algorithms for the optimal management of status epilepticus have changed, as the medical community has recognized the need to terminate seizures in status in a timely manner. Recent research has evaluated the different choices of benzodiazepine and has given consideration to second-line treatment options.

Recent findings
There has been a move to examine alternatives to phenytoin (such as levetiracetam and lacosamide) as second-line agents. Valproate should be used cautiously in view of the potential side effects. Three ongoing trials [Established Staus Epilepticus Treatment Trial (ESETT), Convulsive Status Epilepticus Paediatric Trial (ConSEPT), and emergency treatment with levetiracetam or phenytoin in status epilepticus in children (EcLiPSE)] are comparing the efficacy of levetiracetam and phenytoin.

Summary
Benzodiazepines remain the first-line agent of choice, although there is ongoing discussion about the mode of administration and the best drug to choose. The results of ESETT, ConSEPT, and EcLiPSE will affect our future management of status, as we give consideration to levetiracetam as an alternative to phenytoin. Other medications such as lacosamide may emerge in future algorithms too.

Keywords
benzodiazepines, levetiracetam, status epilepticus

INTRODUCTION

> '..his neck turns left, his hands and feet are tense and his eyes wide open, and from his mouth froth is flowing without having any consciousness'.

First described in ancient Mesopotamia [1], status epilepticus and its management have undergone many iterations through the millenia. This article will focus on the most recent developments in both the definition of and treatment of what is the most common paediatric neurologic emergency. Status epilepticus has an incidence of 17–23 per 100 000 per year and a case fatality of around 3%; [2] it is the most common paediatric 'category 1' presentation under the Australasian Triage Scale [3] guideline system.

DEFINITIONS AND DEMOGRAPHICS

In 2015, the International League Against Epilepsy redefined status epilepticus as 'a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures' [4].

Within this definition, newly agreed specific time points identify the progression from 'seizure' to 'prolonged seizure' to 'seizures with consequences'. Timing differs for particular seizure types, with generalized tonic clonic convulsions having the shortest duration. Longer than 5 min is considered prolonged, whilst more than 30 min is associated

[a]Emergency Department, Lady Cilento Children's Hospital, South Brisbane, [b]Emergency Department, School of Medicine, University of Queensland, St Lucia, [c]Emergency Department, Logan Hospital, Meadowbrook, Queensland, Australia, [d]Emergency Department, Royal London Hospital, London, UK and [e]Emergency Department, Footscray Hospital, Melbourne, Victoria, Australia

Correspondence to Ben Lawton, BSc (Hons), MBChB, FRACP (PEM), Emergency Department, Logan Hospital, Armstrong Rd. & Loganlea Rd., Meadowbrook 4131, QLD, Australia. E-mail: ben.lawton@yahoo.com

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KEY POINTS

- The goal in the management of status epilepticus is to terminate seizures as early as possible to ensure the best outcome.
- The latest treatment algorithms all focus on moving through treatment options in a timely manner to achieve seizure cessation.
- Benzodiazepines remain first-line treatment in status epilepticus. Studies have shown little difference in the efficacy when using intravenous lorazapem, intravenous diazepam, or midazolam (via the intravenous, buccal, intranasal, or intramuscular routes).
- ESETT, ConSEPT, and EcLiPSE are ongoing trials assessing the difference between intravenous phenytoin and intravenous leviteracetam as second-line agents in status.
- Lacosamide may also emerge as a potential second-line agents.

with long-term morbidity [5]. The duration of a seizure is also interpreted within a new diagnostic classification system for seizures considering four axes: semiology, cause, electroencephalography correlates, and age [4].

Older definitions of status epilepticus used seizures lasting longer than 30 min [6]. Consequently, current knowledge must be considered in the context of the former definition. It is likely that with a broadened definition of status epilepticus, so too will there be a broadening of causes and a potential shift in the demographics.

The current epidemiologic data cite the risk factors for status epilepticus as being men, a neonate, having an intercurrent febrile illness, having a developmental impairment, and having structural brain anomalies [2,7]. The majority of status epilepticus presentations (up to 75%) are children with their first seizure [6]. Significant underlying causes worthy of early consideration include abnormal electrolytes, intracranial infection [2], space occupying lesions, and intracranial haemorrhage.

IMMEDIATE MANAGEMENT AND POINT OF CARE TESTING

It has become clear that early recognition of status epilepticus and implementing early treatment have a positive impact on clinical outcome. Therefore, it is also important to note the time of the start of the seizure, in order for the team to keep track of the length of the seizure and the timing of the medications.

Initial management should follow the same pathway as for any emergency. Ensure the airway is patent; nasopharyngeal airways are often helpful in this context. Check the breathing and measure oxygen saturations. Use a bag and mask for ventilation if required, otherwise apply oxygen via a facemask. Assess the circulation including heart rate, capillary refill time, and blood pressure.

Ideally intravenous access should be obtained (although there are initial options for giving per rectum, buccal, or intramuscular medications to treat status epilepticus). As with any paediatric emergency, if initial attempts at peripheral cannulation are not successful, then consider intraosseous access early. Immediate investigative priorities are to exclude hypoglycaemia, hyponatraemia, and hypocalcaemia all of which can be achieved on venous blood gas analysis. Measuring serum antiepileptic medication levels is helpful only in the context of specific medications (e.g., phenytoin/phenobarbitone) being used as maintenance therapy, or concerns about compliance. Remember that a sample from an intraosseous device cannot be run through a blood gas machine as the marrow will damage the machine. Point of care testing equipment using cartridges may be able to accept marrow samples.

Treat with a fluid bolus if there are signs of shock or sepsis and treat with glucose if the patient is hypoglycaemic. Also consider broad spectrum antibiotics if indicated.

By the time these steps have been worked through, most simple seizures will have stopped. If the patient is still seizing, it is time to initiate some medical management to terminate the seizures.

ALGORITHMS

There are a number of key algorithms for the management of status epilepticus. In the United Kingdom, the National Institute for Clinical Excellence (NICE) (2011) [8] guidelines and the Advanced Paediatric Life Support algorithms [9] are the most widely used. In the United States, the American Epilepsy Society (AES) proposed an algorithm in 2016 [10]. In Australia, there is no nationally agreed guidance, but there is statewide guidance – for example, New South Wales (NSW) Health has a 2016 management algorithm [11]. A recent Australian study by PREDICT showed a broad variation of practice across Australian institutions for second-line and third-line treatments [12].

All the major algorithms make similar recommendations; however, in the more recent guidelines (NICE, AES, and NSW Health), there is an emphasis on the timing of the treatment. The treatment pathway will be split into the stabilization phase (the first

5 min) in which the Airway, Breathing, Circulation pathway is followed and ideally venous access is obtained; the initializing treatment phase (approximately 5–20 min) in which benzodiazepines are given; the second therapy stage (approximately 20–40 min) in which second-line medications are considered; and then the final emergency phase (up to 45 min) when the patient will have rapid sequence induction using anaesthetic agents for intubation. The aim of these timings is to ensure that treatment is delivered expediently, and that by 45 min from the start of the seizure, the treating team should be at the point of intubation.

BENZODIAZEPINES

The benzodiazepines are widely used as first-line therapy for status epilepticus and achieve lasting seizure control in up to 80% of patients [13]. Their place at the top of the treatment algorithm is agreed by consensus guidelines from around the world [9,10,14] with controversy beginning once the specific medication, dose, and route of administration enter the discussion. Midazolam (intravenous, intramuscular, buccal, or intranasal), lorazepam (intravenous), and diazepam (intravenous or per rectum) are variously recommended. All benzodiazepines work by potentiating the neuroinhibitory effects of gamma-aminobutyric acid (GABA).

The major differences between the three commonly used benzodiazepines lie in their pharmacokinetics, though differences in their relative affinities for various receptor subtypes explain the small pharmacodynamic variance [15]. With an elimination half-life of 1–4 h [15], midazolam is the quickest to be removed. Metabolism of all these drugs is via cytochrome P450-dependent isoenzymes, the activity of which is low at birth, increases to supranormal adult levels at 2–3 years and then declines to adult levels by age 4 years [15]. Consequently, repeat dosing should be undertaken cautiously in infants.

The range of comparisons made in available randomized controlled trials (RCTs) make a firm evidence-based recommendation for benzodiazepine choice difficult. A 2016 network meta-analysis included 1821 patients from 16 RCTs involving seven different drug regimens and found midazolam to be more effective than diazepam in achieving seizure cessation (odds ratio 1.91 95% confidence interval: 1.42–2.57) [16]. The same meta-analysis was unable to demonstrate a difference in efficacy between midazolam and lorazepam or between lorazepam and diazepam, findings which suggest the question is not definitively answered. A 2008 Cochrane review found a higher rate of adverse events with intravenous diazepam than intravenous lorazepam [17], whereas a 2015 RCT comparing intramuscular midazolam with intravenous lorazepam in children was insufficiently powered to comment on their relative safety or efficacy [18].

When including adult and paediatric populations, no difference has been found in time to seizure cessation when comparing intravenous with nonintravenous routes of benzodiazepine administration [19]. The exception to this was the largest and highest quality trial conducted addressing this question to date which found intramuscular midazolam led to faster seizure cessation than intravenous lorazepam in the prehospital environment [20], though subgroup analysis of the paediatric patients in this trial failed to show any difference in this group [18].

A 2016 systematic review showed that when comparing routes of administration, intravenous leads to the shortest time to seizure cessation from the point of drug delivery but is consistently the slowest to achieve drug delivery itself [20]. When taking this into account, intramuscular, buccal, and intranasal routes of administration all have similar times to seizure cessation as the intravenous route. Rectal drug administration had a slower time to achieve drug delivery than intramuscular or buccal routes, and also had a longer delay between drug delivery and seizure cessation than all other routes. Significantly, the rectal route was also associated with lower patient and caregiver satisfaction [21]. Intraosseous delivery was not included and this remains a valid option in which available, particularly when a second benzodiazepine dose is required.

Based on available data midazolam via the intravenous, buccal, intranasal, or intramuscular routes, or lorazepam or diazepam via the intravenous route are equally acceptable choices for the first dose of benzodiazepine, depending on the resources available to the clinician or caregiver at the time. Where a second dose is required, any of these agents given intravenous or intraosseous is ideal, but any of the above delivery options remain reasonable. We would advocate against rectal drug delivery in status epilepticus if any other option is available given the slower time to onset and decreased social acceptability [21] outlined above.

SECOND-LINE AGENTS

The traditional choices of phenobarbitone in infants and phenytoin (or fosphenytoin) in those over 1 year of age [9] are being jostled from position by newer antiepileptic drugs. Leading the charge of novel agents are sodium valproate and levetiracetam with lacosamide peaking over the therapeutic horizon.

Levetiracetam has a broad spectrum of activity against all seizure types, a very low adverse event rate and its minimal protein binding and lack of hepatic metabolism render it low risk for drug interactions [22▪▪]. Though recommended for oral or intravenous use, levetiracetam can be given intramuscularly with no muscle damage and complete bioavailability [23]. Despite a time to peak onset of 2 h via the intramuscular route, the ease and reliability of delivery may lead to a role for levetiracetam in the prehospital management of status epilepticus in the future.

Sodium valproate is a broad spectrum antiseizure medication which modulates sodium channels, potassium channels, and the metabolism of GABA [22▪▪]. A recent meta-analysis, not restricted to paediatric patients, found sodium valproate to be more effective than phenobarbitone, levetiracetam, and phenytoin in terminating status epilepticus though 95% confidence intervals did overlap [24]. The main concerns regarding valproate use in children are its rare but devastating reported adverse events including hepatotoxicity resulting in liver failure [25], and various haematologic complications including pancytopaenia and hyperammonaemia. It is of particular concern in infants and those with suspected mitochondrial disorders [26].

These second-line agents are currently being evaluated by three RCTs which will provide the most authoritative information to date about the safety and efficacy of commonly used second-line medications in paediatric status epilepticus.

In November 2017, the Convulsive Status Epilepticus Paediatric Trial (ConSEPT) finished recruiting 200 children aged between 3 months and 16 years to compare the efficacy of 20 mg/kg of phenytoin with 40 mg/kg of levetiracetam in stopping benzodiazepine resistant seizures [27▪]. Emergency treatment with levetiracetam or phenytoin in status epilepticus in children (EcLiPSE) is currently aiming to recruit 308 children in the United Kingdom aged between 6 months and 18 years [28▪], comparing phenytoin and levetiracetam in the same doses as ConSEPT. The North American-based Established Staus Epilepticus Treatment Trial (ESETT) trial is aiming to recruit 795 adult and paediatric patients (over 2 years of age) before the end of 2019 [29▪]. Using the same primary outcome measure as ConSEPT and EcLiPSE, ESETT has three arms comparing 20 mg/kg of fosphenytoin with 40 mg/kg of sodium valproate and 60 mg/kg of levetiracetam. The exclusion of below 2 years old reflects the increased risk posed by valproate in these younger patients. Note also the higher dose of levetiracetam being evaluated in ESETT.

Lacosamide is beginning to enter practice, with a 2017 systematic review of 522 patients (including 36 children) finding it to be effective in terminating 57% of seizures overall and 92% of focal seizures [30▪]. Lacosamide is well tolerated, available in oral and intravenous preparations, and, significantly, shows no clinically relevant drug interactions [31].

INDUCTION AGENTS

The final common pathway in the management of status epilepticus is intubation and ventilation. The provision of supplemental oxygen via humidified high-flow nasal cannulae may extend the well tolerated apnoea period, reducing the likelihood of critical hypoxia and ensuing neuronal damage [32]. Most children requiring intubation already have an impaired level of consciousness, either due to the underlying disease process or aggressive use of benzodiazepines, and so care must be taken with choice and dosing of induction medication.

With the exception of ketamine, most standard agents in use act at the $GABA_A$ receptor. These drugs cause further sedation and respiratory depression as well as hypotension with consequent cerebral hypoperfusion. These cardiovascular effects can be ameliorated by the use of ketamine [33]. There have only been a handful of underpowered, head-to-head studies comparing agents. They tend to favour the safety profile of midazolam over alternates such as thiopentone (causing hypotension) or propofol [34] Routine use of a paralytic agent is recommended to optimize first pass success. Whilst the use of short acting agents, such as suxamethonium, may allow ongoing seizure activity to be visualized in the post-intubation phase, its use is not without risk. Prolonged seizures can lead to an increase serum potassium levels. Coupled with the potential hyperkalaemic properties of the depolarising agent [35] in a patient who is acidaemic, it may lead to life threatening cardiac arrhythmias. With this in mind, a nondepolarizing muscle-relaxant-like rocuronium may be a better choice, with the awareness that it might mask ongoing seizures.

CONCLUSION

Robust, evidence-based algorithms will continue to form the backbone of the management of status epilepticus. Benzodiazepines are firmly established as first-line therapy, and whereas further research may finesse choices of drug and routes of administration, several reasonable alternatives will remain. Recommendations for second-line antiepileptic drugs will be heavily influenced by the outcomes of the ConSEPT, EcLiPSE, and ESETT trials. The

tolerability and lack of significant drug interactions associated with leviteracetam and lacosamide will encourage clinicians to use combinations of second-line agents, and thus practice will continue to vary around those core recommendations. The availability, currently experimental, of intravenous topiramate, lamotrigine, and carbamazepine [31] will further complicate the next generation of guideline recommendations and trial design. The development of status epilepticus registries (already underway in Australia) will play a key role in determining which drugs or drug combinations should be included in the RCTs performed to further refine the management of paediatric status epilepticus in the 2020s.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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