REVIEW ARTICLE

# Management of acute seizures in children: A review with special consideration of care in resource-limited settings

Ornella Ciccone[a,b], Manoj Mathews[b], Gretchen L. Birbeck[c,d,*]

[a] *The University of Zambia, School of Medicine, Lusaka, Zambia*
[b] *University Teaching Hospital, 1 Nationalist Road, P.O. Box 50440, Ridgeway, Lusaka, Zambia*
[c] *Chikankata Epilepsy Care Team, Chikankata Hospital, Private Bag S2, Mazabuka, Zambia*
[d] *Strong Epilepsy Center, Department of Neurology, University of Rochester, 265 Crittenden Blvd, Rochester, NY 14641, United States*

## ARTICLE INFO

## ABSTRACT

*Introduction:* We sought to review recent evidence-based guidelines and where applicable, primary data to extrapolate insights into the appropriate management of acute seizures in children in resource-limited settings.
*Methods:* PubMed and Google scholar searches were conducted with attention to publications from the last three to five years, including a focused search for acute seizure management guidelines relevant to resource limited settings. Since all guidelines to date, except the World Health Organization's, assume ready access to invasive ventilation and advanced diagnostic testing, guidelines and primary data were used to propose management appropriate for resource-limited settings where respiratory suppression from treatment presents a major challenge in management.
*Results:* Acute seizures are among the commonest medical emergencies encountered in the African settings. Seizure management must occur simultaneously with the diagnostic assessment, which should include addressing life threatening causes (e.g. hypoglycaemia, malaria) and with attention given to the most likely aetiology in a particular region or setting. For ongoing seizures, initial treatment with benzodiazepines is indicated. There is evidence of efficacy for several agents and delivery modes. Longer-acting antiepileptic drugs (AEDs) should be on hand if acute seizures fail to respond to two doses of benzodiazepines. There is little direct evidence comparing the relative efficacy of different long-acting AEDs for acute seizure management in African children. Findings suggest that generalising data from Western settings, where different aetiologies and risk factors for seizures prevail, may be inappropriate.
*Discussion:* Though treatment options and diagnostics may be dictated by available medications and capacity, it is possible for virtually any healthcare setting to develop a relevant and feasible local guideline for seizure management. Clear specifications on when to refer to a higher level of care should be part of the care plan.

## African relevance

- Acute symptomatic seizures are a common paediatric medical emergency in the African setting.
- Poor epilepsy care contributes to the burden of seizures requiring emergency care.
- Status epilepticus is particularly challenging to manage in resource limited settings.
- More optimal management of acute seizures may decrease resulting brain injury.

## Introduction

Acute seizures are a common manifestation of neurological disease in children worldwide. Most seizures are brief, meaning less than five minutes in duration. Seizures longer than five minutes are considered prolonged. Status epilepticus, a life threatening condition, occurs when a prolonged seizure lasts more than 30 min or when two or more seizures occur sequentially without return to consciousness between seizures [1].

Acute seizures have several aetiologies. Metabolic challenges including hypoglycaemia are common. Infections may precipitate seizures, either as febrile convulsions or acute symptomatic seizures that

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occur as a result of the infectious process itself [2]. Children with epilepsy may have seizures due to poor outpatient management, refractory epilepsy, medication non-adherence, lack of access to medication and/or inter-current illness lowering the seizure threshold. In immune competent children, seizures arising from infections have generally better outcomes [3,4]. The risk of seizures in children with human immunodeficiency virus (HIV) is particularly elevated with many potential contributing factors, including the primary effects of HIV on the developing brain and/or antiretroviral drug side effects [5–7]. Various studies have observed a higher risk of acute seizures in children living in developing countries compared to those in developed ones [8–10]. Reasons for the elevated burden include parasites and other infections, head trauma and poor perinatal care [11–13].

Optimal care of seizures has been linked to better outcomes [14]. Sub-optimal care arises from delays in care seeking and the relative lack of both trained personnel and pharmaceutical resources. Seizures and epilepsy have physical, social and cultural aspects which influence treatment and outcome [15,16]. The African setting is unique in many respects with regard to acute seizures and seizure management—the cause(s) of the underlying seizures differ from other settings, with malaria being a prominent example [2,17,18]. Timelines for care-seeking may also be quite delayed in the African setting, relative to environments with well-developed emergency services. Since seizure duration prior to care impacts response to medications, data from settings with well-developed emergency services may not be relevant in resource-limited settings. And finally, resources for supportive care, such as invasive ventilation are important delineators of what is possible for aggressive seizure management. This review is aimed at providing guidance on the management of acute seizure while addressing the various factors at play in a resource limited setting.

In the present study, we sought:

1. to review guidelines for the management of acute seizures in children,
2. to review additional literature on the management of acute seizures in children relevant to resource limited settings to provide support and guidance for management and diagnostic assessment in this setting.
3. and to propose a staged approach for care depending on the resources and suggestions for when referral to a higher level of care is appropriate.

### Methods

To identify guidelines published in the last two decades, we conducted a PubMed and Google Scholar search on "seizure" and "guideline". Only guidelines or formal recommendations were reviewed. Studies detailing chronic management or care in adults only were discarded. See Table 1 for a summary of these guidelines.

All of the available guidelines except the World Health Organisation's (WHO) Paediatric Emergency Triage, Assessment and Treatment (ETAT) were developed for use in highly developed medical setting with ready availability of invasive ventilation and advanced diagnostic testing. The WHO ETAT recommendations were developed for use in resource-limited settings, but only addressed oxygen monitoring, oxygen use, and the choice and delivery mode of first and second line agents. Furthermore, in evidence-based guidelines, especially those grading of evidence quality, no data or limited quality data was often all that was available.

To identify the most relevant recent literature, we initially conducted a PubMed search on "seizures" AND "children" AND "Africa" from 2011 to present. This was complemented by a Google Scholar search on "guidelines for acute seizure management in children", with a focused review looking for guidelines relevant to resource limited settings and more recent guidelines. Where guidelines differed (for example, choice and route of benzodiazepine) a focused search for the

most recent literature was made. Unless otherwise cited, general recommendations for acute clinical management are congruent with recommendations from the WHO guidelines [19,20].

### Discussion

*Acute clinical care*

Acute seizures represent a medical emergency. Although most seizures are brief, the longer an acute seizure continues, the more difficult it is to terminate, and the greater the risk of developing convulsive status epilepticus with its associated neurological sequelae. Therefore, the approach to clinical management of a child who presents with a seizure lasting more than five minutes should be the same as that to a child in "established" status epilepticus [1,21]. Given the urgency of terminating seizures, the initial diagnostic assessment and medical treatment should occur simultaneously [20]. A brief history and rapid clinical examination should be conducted to ascertain the possible underlying aetiology (for example, head trauma, neuro-infection, poisoning, established epilepsy) and to confirm that the event of concern is indeed a seizure.

*General measures – stabilisation phase (0–5 min)*

The child presenting with an active convulsion should be stabilized. Airway, breathing and circulation (ABCs) should be assessed to ensure that the child has nothing in his/her mouth, is ventilating well and has a stable pulse. The child should be turned on his/her side to avoid aspiration in case of vomiting or excessive oral secretions [19]. Any object or clothing around the neck or face should be removed to facilitate respiration and prevent injuries. Respiratory rate, blood pressure, temperature and if possible, oxygen saturation, should be measured and recorded. Where available, oxygen should be administered by nasal cannula or mask even if the oxygen saturation is normal to optimize oxygenation since acute seizures place an extreme metabolic demand upon the brain and cardiovascular system. If blood oxygen saturation is low, suction may be needed to clear the airway of secretions and/or vomitus. Aside from the suction device, nothing should be inserted in the mouth to avoid the risk of oral injuries. Administration of oxygen whether by face mask or nasal cannula will have limited efficacy during ongoing tonic-clonic activity and/or apnoea, so focusing upon seizure cessation while suctioning with passive oxygen delivery is critical.

An intravenous (IV) line should be inserted to facilitate medication administration and blood should be drawn for diagnostic investigations. Hypoglycaemia requires immediate treatment both to stop seizures provoked by low glucose and to prevent hippocampal injury that might result in memory impairment, behavioural problems and/or possibly long term epilepsy. If IV access cannot be obtained, acute treatment with benzodiazepines through other routes is possible, but treatment for hypoglycaemia is best when given IV so efforts at IV access are warranted. Ideally, a rapid blood glucose level measured via bedside glucometer should be assessed prior to glucose administration, but if this is not readily available, treatment for possible hypoglycaemia should be undertaken presumptively. Hypoglycaemia is present if the measured blood glucose level is < 2.5 mmol per litre (mmol/l) (45 milligrams per decilitre [mg/dl]) in a well-nourished child, or < 3 mmol/l (55 mg/dl) in a malnourished child. Actual or presumed hypoglycaemia should be treated by giving 5 millilitre per kilogram (ml/kg) of 10% glucose solution rapidly by IV injection; another bolus of 5 ml/kg of 10% glucose solution can be repeated after 30 min if the glucose level remains low, or hypoglycaemia is suspected but glucose cannot be measured and the clinical condition remains poor. In healthcare facilities lacking the necessary equipment and expertise for intravenous administration of medications and fluids, nasogastric access for enteral treatments should be obtained. Unconscious children should be kept on maintenance IV fluids that include glucose or be

**Table 1**
Published guidelines for management of acute seizures in children.

| Citation | Specifics Addressed | Basis of Recommendations | Key recommendations |
| --- | --- | --- | --- |
| [36] in 2005 | Management of paediatric status epilepticus | Expert opinion. Not systematic review | First line treatment benzodiazepines (either diazepam or lorazepam)<br>Second line treatment phenytoin or fosphenytoin OR phenobarbital OR valproate (IV) WITH<br>ICU care including ventilation ± EEG monitoring ± invasive haemodynamic monitoring |
| [37] in 2006 | Seizures addressed in this guideline include partial seizures (simple complex and secondarily generalised), and generalised tonic and/or clonic seizures | Italian League against Epilepsy systematic evidence-based review | History and examination warranted though only observational studies support this<br>Investigations recommended–<br>CBC<br>Glucose<br>Urea<br>Electrolytes<br>Calcium<br>Creatinine<br>ALT, AST<br>Creatine kinase/prolactin<br>Urine analysis<br>Toxicological tests<br>With evidence in case-control and cohort studies<br>For infants, assessing for hyponatraemia has high level evidence from meta-analysis studies<br>Imaging with CT or MRI and EEG recommended based upon level 1 evidence with prospective cohort studies, clinical trials or meta-analysis |
| [38] in 2006 | Diagnostic assessment of child with status epilepticus | Evidence-based review by American Academy of Neurology and Child Neurology Society | Insufficient data to support blood cultures or lumbar puncture unless there is clinical suspicion of systemic or CNS infection and insufficient data to routinely recommend neuroimaging<br>Checking AED levels in child on an AED was considered "probably effective"<br>The following were determined to be "possibly effective"—toxicology studies, metabolic studies for inborn errors of metabolism, EEG for non-convulsive stats epilepticus |
| [39] in 2009 | Treatment of status | Finnish Neurologic Society | First line: buccal midazolam, rectal diazepam, or IV diazepam or lorazepam<br>Second line: phenobarbital<br>Third line: suppressive anaesthesia with continuous EEG |
| [40] in 2011 | Generalised convulsive status epilepticus in children | Canadian Paediatric Society providing care guidelines while acknowledging there is insufficient data to guide care. Pragmatic expert advice. | Check glucose then ABCs including positioning, suctioning, oxygen, and low threshold for ventilation<br>First line with IV is lorazepam, diazepam or midazolam. If no IV, then buccal lorazepam, buccal or intranasal lorazepam, or rectal diazepam<br>Second line IV fosphenytoin, phenytoin or phenobarbital. If IO then fosphenytoin, phenytoin or paraldehyde<br>Refractory status with IV midazolam or pentobarbital |
| [41] in 2011 | Generalised convulsive status epilepticus | Expert opinion noting there are no nationally recognised specific protocols in North America | Initially check glucose and ABCs. Intubation and ventilation. Ceftriaxone or vancomycin pending head CT and LP. Electrolytes and chemistries needed. EEG if non-convulsive status epilepticus of concern<br>Treatment with IV diazepam or lorazepam immediately. Then phenytoin or fosphenytoin. If further treatment needed, phenobarbital or valproate<br>For refractory status, continuous infusion with midazolam or propofol |
| [42] in 2013 | Treatment of convulsive status epilepticus | Italian League against Epilepsy systematic evidence-based review | First line preferred via IV lorazepam or diazepam. If no IV access, then IM or buccal midazolam or buccal lorazepam based upon RCT or meta-analysis of RCT<br>Second line phenytoin or phenobarbital or valproate based upon at least one RCT<br>For refractory status epilepticus, they recommend thiopental or propofol or midazolam based upon expert opinion |
| [43] in 2014 | | Multi-Disciplinary Group for the Management of Status Epilepticus in Children in India | Diagnostics to include total and ionized calcium in those < 2 years old, sodium in those < 6 months old, and CBC and LP if febrile. Second line diagnostics to include EEG and imaging<br>ABC with oxygen and CPAP or invasive ventilation if needed<br>First line treatment IV lorazepam, diazepam or midazolam. If no IV then IM/IN/buccal midazolam or rectal diazepam<br>Second line treatment phenytoin, fosphenytoin, phenobarbital or valproate. If this fails, pyridoxine in < 2 years old. Otherwise, levetiracetam<br>Refractory status midazolam or thiopental. |
| [44] in 2016 | Monitoring oxygen saturations, providing supplemental oxygen, evaluation and treatment of acute seizures | World Health Organization's Paediatric Emergency Triage, Assessment and Treatment Group | Re: monitoring oxygenation—strong recommendation with low quality of evidence for monitoring given low risk<br>Re: oxygen use—conditional recommendation with low quality of evidence for use of oxygen with judicious use and lower threshold for discontinuation where supplemental oxygen is a scare resource<br>Re diagnostic assessments with acute seizures—strong recommendation with low quality of evidence for checking glucose, sodium if there is dehydration or diarrhoea. Also for LP if febrile particularly for those < 18 months old, those with complex seizures, prior antibiotic use or not vaccinated for H. influenza and/or streptococcal meningitis. LP deferral if unstable. Image if new focal findings or comatose<br>First line treatment—With IV access has strong recommendation based on low quality evidence for treatment with benzodiazepine but condition recommendation on choice of agent with these being midazolam, lorazepam or diazepam, where IV access. Where there is no established IV access, there is strong recommendations based upon low evidence for |

*(continued on next page)*

**Table 1** (*continued*)

| Citation | Specifics Addressed | Basis of Recommendations | Key recommendations |
|---|---|---|---|
| | | | rectal diazepam, oral or intranasal midazolam, rectal or intranasal lorazepam, or intramuscular lorazepam or midazolam <br> Second line treatment is a conditional recommendation based upon low quality evidence for phenytoin or phenobarbital or valproate |
| [1] in 2016 | Compared anticonvulsant treatments for convulsive status epilepticus | Evidence-based guidelines from American Epilepsy Society | Of 38 studies RCTs, only 4 provided level 1 evidence ("established as effective") based upon blinded RCT. Two studies provided evidence "established as probably effective" from one or more unblinded or otherwise limited RCT. The remainder of the RCTs or observational studies provided evidence of "possible" effectiveness <br> Established as effective included IV lorazepam or IV diazepam for acute seizure management. There was insufficient evidence for superiority of lorazepam vs. diazepam <br> Established as possibly effective was rectal diazepam, IM midazolam, IV midazolam, buccal midazolam <br> For second line treatment, fosphenytoin is better tolerated than phenytoin. |
| [45] in 2017 | Management of status epilepticus | Expert panel developed consensus. No evidence ratings given | ABC with high concentration oxygen. Check glucose and establish IV <br> First line with IV is lorazepam. If lorazepam not available then diazepam. If no IV, then buccal midazolam <br> Second line phenobarbital or phenytoin <br> Refractory status with midazolam or thiopental |

ICU, intensive care unit; EEG, electroencephalogram; CBC, complete blood count; AST, aspartate transaminase; ALT, alkaline transaminase; CT, computed tomography; MRI, magnetic resonance imaging; CNS, central nervous system; AED, antiepileptic drugs; IV, intravenous; ABC; airway breathing circulation; IO, intraosseous; LP, lumbar puncture; RCT, randomised control trial; CPAP, continuous positive airway pressure; IN, intranasal.

given milk/sugar solution via nasogastric tube (NGT).

Besides hypoglycaemia, investigations undertaken at initial intake of a child with acute seizures will depend upon the available diagnostic resources and local disease epidemiology, which should direct the investigations based upon conditions likely to cause seizures. For example, in malaria endemic regions, a thick blood film to look for parasites or a malaria rapid diagnostic test is indicated. Other investigations to consider are included in Table 2. Note that treatment to halt seizures should proceed even as the diagnostic work up is being undertaken. Similar to stroke, time is brain when untreated seizures are allowed to persist beyond a few minutes.

Although acute treatment strategies are unlikely to be impacted, HIV status should be assessed in young children presenting with seizures whose status has not been recently assessed.

*First line anticonvulsant without and with IV line – initial therapy phase (5–20 min)*

If the child is still convulsing, benzodiazepines should be given, except in neonates (infants less than two weeks of age) who should receive phenobarbitone. Diazepam is the most widely available benzodiazepine. The dose for acute seizures is 0.25 milligram per kilogram (mg/kg) (0.05 ml/kg) IV. In the prehospital setting or in a health care facility that is not equipped to administer intravenous medications, 0.5 mg/kg (maximum dose of 10 mg) of liquid diazepam can be given rectally. Where it is not possible to obtain a reliable weight, dose estimates can be made based upon age. See Table 3. If a child is severely stunted or wasted, dosing should be based upon their age of appearance rather than their biological age. If the seizure has stopped spontaneously, treatment may be withheld while further clinical and diagnostic assessments are undertaken, assuming monitoring is ongoing to detect any further seizures. Intramuscular administration of diazepam is not recommended because of its erratic absorption. Higher doses of

**Table 2**
Diagnostic evaluations to consider in the child with acute seizures.

| Potential seizure aetiology | Investigation | Action to be Taken |
|---|---|---|
| Fever (i.e. febrile seizure) | Temperature | Unwrapping over-clothed children. Antipyretics –Paracetamol given via NGT or rectally |
| Acute infection including meningitis | Full blood count looking for elevated white blood cell count and/or bandaemia | Consider lumbar puncture to evaluate for CNS infection. |
| Metabolic abnormality | Electrolytes for hyponatraemia. Any other metabolic perturbations can lower the seizure threshold. | Address underlying metabolic problem (e.g. free water restrict for severe hyponatraemia) |
| Renal failure, hypertensive crises | Creatinine, BUN, BP with vitals | Medical management, evaluate for underlying cause of renal failure. May require dialysis if available. |
| Malaria (likely with P. vivax and P. falciparum) | Malaria rapid diagnostic test or thick blood film for parasite count | Treat malaria following national guidelines. |
| Toxin, poisoning | Lactate may help assess. Medication exposures that can cause seizure (efavirenz, high dose penicillin, isoniazid) | Address underlying poisoning. |
| Antiepileptic drug levels | Determine levels of medications taken by person with established epilepsy on outpatient therapy | If low or undetectable, treat with standard doses as outlined below. If AED levels are therapeutic or toxic, avoid further dosing of the same medication. |
| Trauma | Imaging with CT, MRI or ultrasound looking for acute blood. Ophthalmological assessment for retinal haemorrhages | May warrant surgical consult. Social services assessment needed. |

NGT, nasogastric tube; CNS, central nervous system; BUN, blood urea nitrogen; BP, blood pressure; AED, antiepileptic drugs; CT, computed tomography; MRI, magnetic resonance imaging.

**Table 3**
Rectal Diazepam dosing based upon weight or estimated weights by age [19].

| Age/Weight | Rectal Diazepam (10 mg/2 ml solution) Dose 0.1 ml/kg |
| --- | --- |
| 2 weeks to 2 months (< 4 kg) | 0.3 ml (1.5 mg) |
| 2– < 4 months (4– < 6 kg) | 0.5 ml (2.5 mg) |
| 4– < 12 months (6– < 10 kg) | 1.0 ml (5.5 mg) |
| 1– < 3 years (10– < 14 kg) | 1.25 ml (6.25 mg) |
| 3– < 5 years (14– < 19 kg) | 1.5 ml (7.5 mg) |

Mg, milligram; ml, millilitre; kg, kilogram.

benzodiazepines are often used in settings where early intubation and ventilator support are readily available, but in the absence of such support significant caution in exceeding the above doses is warranted.

Other agents appropriate for use in acute seizures include paraldehyde, lorazepam, and midazolam. Paraldehyde is delivered intramuscularly (IM) or rectally and may have fewer respiratory suppressive effects relative to diazepam, but is not widely available, and though an older agent, is prohibitively expensive in many settings. IM midazolam has shown a shorter interval of seizure termination when compared to IV diazepam in three paediatric randomized controlled trials (RCT's), but there was no significant difference in overall efficacy for termination of seizures [22–24]. Midazolam can be administered via IV, IM, intranasal or buccal routes with good effect for seizure cessation. Buccal midazolam was found as safe as and more effective than rectal diazepam for the treatment of prolonged seizures in an RCT conducted including 330 Ugandan children, although the benefits were limited to children without malaria suggesting that malaria-associated seizures may have a unique pathophysiology [25]. Similarly, intranasal lorazepam has been shown to be comparable to IM paraldehyde in Malawi[26]. It is critical to note that the use of midazolam is absolutely contraindicated in anyone on protease inhibitors, which substantially and unpredictably increase the half-life of this otherwise relatively short-acting sedative agent [27–29].

Intravenous lorazepam (0.1 mg/kg/dose; maximum dose of 4 mg) may be preferred over intravenous diazepam because of slightly superior benefit-risk profile demonstrated in adult populations only, but the data comparing the two is mixed. In one study conducted including children, IV lorazepam was found to be as efficacious as IV diazepam at stopping seizures lasting at least five minutes [1,22]. Chamberlain et al. [22] compared the efficacy of diazepam (0.2 mg/kg; maximum dose of 8 mg) versus lorazepam (0.1 mg/kg; maximum dose of 4 mg) in the treatment of paediatric status epilepticus in 273 children (aged three months to 18 years) and found no difference between IV diazepam versus IV lorazepam in stopping status epilepticus.

An RCT conducted by Malu et al. [30] in nine hospitals of the Democratic Republic of Congo and Rwanda found sublingual lorazepam at 0.1 mg/kg/dose to be less efficacious (p < 0.001) in stopping paediatric seizures lasting more than five minutes, than rectal diazepam at 0.5 mg/kg. Despite its apparent lower efficacy, the authors argue that buccal lorazepam could be a possible alternative where rectal diazepam is unavailable, impractical to use, or its administration would be delayed [31].

From a pragmatic perspective, to optimize care for children with acute seizures in any specific setting, the most important consideration should be to identify a benzodiazepine known to be effective for seizure management that can be reliably and sufficiently sourced as to remain in stock, readily available to staff on a consistent basis when needed. Then one must assure staff are properly trained to administer this agent emergently and in appropriate quantities. Changing the type of benzodiazepine available for acute seizure management often or unpredictably will increase the risk of potentially fatal medication errors, may deflate staff confidence in their capacity to manage this common problem, and will likely result in care delays as staff try to determine what is available and how to use it while a child with acute seizures is

awaiting treatment.

If the seizure persists for ten minutes after the first dose of a benzodiazepine (by any route), a second dose should be given. More than two doses of benzodiazepines preceding the use of phenobarbitone is associated with an increased risk of respiratory failure and subsequent death where ventilation is not available [20,32], so failure to respond to the second dose of benzodiazepine should prompt administration of a longer lasting antiepileptic drug (AED). As such, a long acting AED appropriate for administration to an unconscious child should be on hand even as the initial dose of benzodiazepine is given so there are no delays in treatment if a child fails to respond to two doses of benzodiazepine. When used in appropriate doses via an acceptable route, the risk of death from benzodiazepine-induced respiratory suppression is small. In fact, respiratory problems are more likely to occur as a result of untreated status epilepticus than appropriate delivered benzodiazepine therapy [1].

*Established convulsive status epilepticus (20–40 min)*

If a child fails to respond to the second dose of benzodiazepine, then status epilepticus has become established. This is a life threatening condition whatever the underlying cause and warrants referral to a tertiary care hospital for more intensive support and specialty care, whenever possible since management requires a health setting equipped for IV drug administration, close clinical monitoring and experienced medical staff. The child in status epilepticus requires continuous monitoring and if the capacity is available should be evaluated for intubation and ventilatory support. If at all possible, a long-acting AED should be given prior to transfer. In the unlikely event that IV access cannot be established on arrival to the referral hospital, an intraosseous (IO) line should be considered. Long acting AEDs recommended by the WHO's Mental Health Gap Action Program (mhGAP) guidelines [20] for use in established convulsive status epilepticus include phenobarbitone, phenytoin, and valproic acid. Other agents used where cost constraints are less problematic include fosphenytoin, levetiracetam, and lacosamide. See Table 4 for the dosing, route of administration, relative costs and particular risks and benefits of long acting AEDs for use in status epilepticus.

If parenteral formulations of long-acting AEDs are simply not available, then the use enteral formulations delivered via NGT is certainly warranted. Under circumstances where no parenteral formulations are available, the use of enteral phenobarbital, valproate or carbamazepine is also reasonable, although it is important to appreciate that carbamazepine can worsen seizures in primary generalised epilepsy. If available, oral levetiracetam syrup has excellent bioavailability and produces therapeutic serum levels within approximately one hour of delivery via NGT in unconscious children with malaria at a fraction of the price of IV formulations [33].

If seizures continue after a standard loading dose of a parenteral AEDs, loading with a second long-acting agent is indicated (see Table 4). There is little data to guide which combinations of long-acting AEDs is best for refractory status epilepticus, so selection based upon side effect profiles and or drug availability is reasonable. If phenobarbitone at 15 mg/kg was initially given and the child's respiratory status is stable, an additional 5 mg/kg for a total of 20 mg/kg can be given.

In addition to the treatments listed in Table 4, refractory status epilepticus can be treated with IV ketamine [34]. In ventilated patients, a loading dose of 1.5 mg/kg every three to five minutes until seizure on electroencephalogram (EEG) stops for a maximum of 4.5 mg/kg is used, to be followed by a maintenance infusion of 0.3–7.5 mg/kg/hour. In the absence of ventilation, 1.5 mg/kg IV load followed by 15microgram per kilogram per minute (mcg/kg/min) is used on the Paediatric Research Ward in Malawi with good effect for some. The short half-life of ketamine allows for brief bagging ventilation if needed. The challenge is appropriate mixing of the agent and careful nursing attention as the

**Table 4**
Long-acting AEDs for *Status Epilepticus*.

| Medication | Route/dose | Particular risk/benefits | Relative cost |
|---|---|---|---|
| *Recommended by WHO* | | | |
| Phenobarbitone | 15 mg/kg IV over 1 h then 5 mg/kg IV every 12 h Alternate route: IM divided into 2 injections and diluted with equal volume normal saline | Respiratory suppression, especially when used after > 2 doses of benzodiazepine | Very low |
| Phenytoin | 18 mg/kg IV given over 1 h, then 2.5 mg/kg/day every 12 h. Should be administered with normal saline, not dextrose | Causes severe skin subcutaneous injury if IV tissues—may result in loss if limb. Secure IV in larger vessel and close nursing care needed. Hypotension and cardiac arrhythmias during administration especially if given too rapidly | $$ |
| Valproic acid | 20 mg/kg IV over 30 min. Not for IM use. | Low risk of cardiorespiratory effects and effective for a broad range of seizure types. Can induce hepatotoxicity, pancreatitis and thrombocytopenia | $$$ |
| Fosphenytoin | 18 phenytoin equivalents [PEs] per kg IV over 15–25 min. Can follow with phenytoin for maintenance | Not associated with severe reaction of skin infiltration. Low risk of cardiovascular effects from rapid load | $$$$$$$ |
| *Other options with limited data to support first line use* | | | |
| Levetiracetam | 40 mg/kg IV then 30 mg/kg every 12 hourly If enteral formulation available, NGT load provides therapeutic levels within ~ 1 h [33] | Good safety profile | $$$$$$$$ Enteral much more affordable |
| Lacosamide | No definitive data | Slow IV delivery to avoid cardiac conduction issues | $$$$$$$ |

IV, intravenous; IM, intramuscular; NGT, nasogastric tube; mg, milligram; kg, kilogram.

**Table 5**
Staged approach for care based upon level of care facility.

| Setting | Acute management | Diagnostics | Resources required |
|---|---|---|---|
| Primary healthcare or rural centre | Evaluate children presenting after a brief seizure. Treat for ongoing seizures with standard benzodiazepine (max two doses). Refer for prolonged seizure or child who does not regain consciousness. Give single dose of long-acting AED prior to referral, if possible | Glucose check or treatment for hypoglycaemia. Blood film or RDT in malaria endemic regions Temperature assessment | Healthcare worker to place NGT. NGT for glucose or sugar/milk. Malaria treatment. Paracetamol. Benzodiazepine, IM, rectal or possibly iv Parenteral long-acting AED |
| Secondary level or District Hospital | Above plus single dose long acting AED Refer for seizures which are not aborted by single dose long acting AED or child who does not regain consciousness. | Above plus LP if indicated. Full blood count Electrolytes urea and creatinine, liver function test ketones in urine | Lab facilities. Healthcare staff able to perform LP. IV medications. Capacity for IV drug administration |
| Tertiary Care Setting RLS | Above plus treatment of status and/or evaluation of possible NCSE | Above plus EEG and neuroimaging (CT, MRI, ultrasound) Gas analysis – lactate and ammonia. Toxicology screening | Expertise in neurology and radiology. Imaging facilities. EEG. Multiple long-acting AEDS. Medications for refractory status |

AED, antiepileptic drugs; RDT, rapid diagnostic test; NGT, nasogastric tube; LP, lumbar puncture; IV, intravenous; NCSE, non-convulsive status epilepticus; CT, computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalogram.

medication must be continuous. Even a brief cessation in the continuous infusion can lead to recurrent seizures. Ideally, suppression of seizures with ketamine after refractory status epilepticus should be maintained for at least 24 h with at least one long-acting agent co-administered in therapeutic doses before discontinuation of ketamine, and if available, continuous EEG monitoring should be in place to assure the seizures are controlled, since conversion to non-convulsive status epilepticus is a concern. A single dose of a benzodiazepine in doses similar to those used for initial seizure management should be given just prior to discontinuing ketamine to avoid psychotic symptoms on wakening.

*Non-convulsive status epilepticus*

Extensive emerging data, including data from Malawi [17], indicate that among comatose children with malaria and/or children with seizures who fail to regain consciousness, ongoing seizure may be the underlying cause. Non-convulsive status epilepticus (NCSE), meaning electrical activity in the brain indicative of ongoing seizures but without any clinical correlate, may be a silent epidemic in Africa. There is little data. What is clear is that any child who presents with seizure and remains comatose or obtunded is at risk for this condition. Referral to a tertiary care facility for an urgent EEG to assess for NCSE is the

ideal management. If NCSE is discovered, aggressive treatment with ongoing EEG to guide care is needed. In the absence of EEG and/or definitive evidence of ongoing seizure, treatment with the safest agent in a therapeutic dose is reasonable though outcomes of untreated NCSE are likely poor. NCSE can also present with confusion and diminished responsiveness causing an "epileptic twilight" state [35].

*Developing local and national guidelines and care policies*

Clearly, primary and rural care settings will be unlikely to provide optimal care for children in status epilepticus. Nonetheless, it is critical that care be initiated at first point of care and proper referrals made. See Table 5 for suggestions in delineating care based upon the level of the care facility.

*Limitations and quality of evidence*

Evidence-based guidelines from the WHO and other authoritative bodies offer important support for the development of local and national guidelines for the management of acute seizures in children in resource limited settings. Nonetheless, much of the evidence-base is limited to adults and/or to children in Western settings and the

generalisability of the data to African children remains unclear. More locally relevant studies are needed. Best care will require determining what is feasible and sustainable within a particular facility and then assuring that staff are properly trained and resources for care are consistently available.

## Conflicts of interest

The authors declare no conflict of interest.

## Authors' contributions

GB and OC developed review approach. GB, MM and OC each wrote specific sections of the first draft. All authors revised and approved the revision.

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