

Status epilepticus in the elderly: differential diagnosis and treatment

Elizabeth Ann Mauricio
William David Freeman

Mayo Clinic, Jacksonville, FL, USA

Date of Preparation 28th January 2011
Conflict of interest: None declared.

Abstract: Seizures are not an uncommon occurrence in older adults, and the incidence of status epilepticus is much greater in the elderly than in younger populations. Status epilepticus is a neurologic emergency and requires prompt intervention to minimize morbidity and mortality. Treatment involves both supportive care as well as initiation of medications to stop all clinical and electrographic seizure activity. Benzodiazepines are used as first-line agents, followed by antiepileptic drugs when seizures persist. In refractory status epilepticus, urgent neurologic consultation is indicated for the titration of anesthetic agents to a level of appropriate background suppression on EEG. In light of our aging population, physician awareness and competence in the management of status epilepticus is imperative and should be recognized as a growing public health concern.

Keywords: status epilepticus, convulsive, generalized, nonconvulsive, refractory, elderly, treatment

Status epilepticus

Definition: Traditionally, status epilepticus is defined as continuous or intermitted seizure activity of at least 30 minutes in duration. However, continuous seizure activity or discrete seizures with incomplete recovery of consciousness lasting more than 5 minutes warrants treatment to prevent more prolonged or refractory status epilepticus.¹ When status epilepticus persists despite treatment with adequate doses of at least 2 antiepileptic medications, it is deemed refractory. Whereas convulsive status epilepticus refers to seizures characterized by motor activity, nonconvulsive status epilepticus may be more difficult to recognize clinically but should be suspected when there is prolonged alteration in consciousness in the absence of convulsions. Diagnosis requires a high index of suspicion as well as EEG confirmation.

Etiology: The incidence of epilepsy in individuals over the age of 65 years is estimated to be 134 per 100,000.² Status epilepticus is 2 to 5 times more common in the elderly than in young adults with an incidence of 86 per 100,000 annually in those over the age of 60.³ In fact, nearly one-third of older patients with new-onset epilepsy initially present in status epilepticus.⁴ Children often present in status epilepticus as a consequence of febrile illness, whereas the most common identifiable cause of seizures and status in the elderly include cerebrovascular disease, degenerative disease, neoplasm, infection, and trauma.⁵ Other potential causes include subtherapeutic levels of antiepileptic medications, electrolyte imbalance or other

Correspondence: William David Freeman
Mayo Clinic, 4500 San Pablo Road,
Jacksonville, FL 32224, USA
Tel +1 904-953-2000
Fax +1 904-953-0757
Email freeman.william1@mayo.edu

metabolic derangements, alcohol withdrawal, drug use or withdrawal, and toxins. The clinician must be cognizant of potential mimickers such as convulsive syncope, asterixis, myoclonus, and psychogenic nonepileptic attacks which may be mistaken for convulsive seizures. The differential diagnosis for nonconvulsive status epilepticus includes encephalopathic conditions and degenerative illnesses such as Creutzfeldt–Jakob disease which may present with a similar altered sensorium.

Economics: In the United States, an estimated 152,000 cases of status epilepticus occur each year, resulting in 42,000 deaths and inpatient costs of US\$4 billion annually.³ The morbidity associated with those who survive the event incurs significant additional expense that is difficult to precisely quantify.

Level of evidence: There are randomized controlled trials that provide a high level of evidence for appropriate first-line agents in the treatment of status epilepticus in adults. Drug treatment approaches in refractory status epilepticus are based on prospective observational studies, retrospective series, case reports, and expert opinions.

Search sources: PubMed, Cochrane Library, and websites of the World Health Organization, the International League against Epilepsy, and the American Academy of Neurology, 1983–2010.

Outcomes: Overall, the short-term mortality associated with status epilepticus is 22% and is independently related not only to seizure duration but also the etiology of the event and the age of the patient. In the elderly, status epilepticus is associated with a higher mortality rate than in younger patients. Mortality for those adults over 60 years of age is 38%, and nearly 50% for those over the age of 80.³ The short-term mortality risk for status epilepticus exceeding 60 minutes in duration is 10 times higher than status lasting less than 1 hour, which emphasizes the necessity for rapid

intervention. Refractory status epilepticus occurs in about 30% of status epilepticus cases and is associated with higher morbidity and mortality rates than nonrefractory cases. In elderly patients, refractory status epilepticus may lead to death in 76% of cases.⁶

Among the various etiologies of status epilepticus, anoxic brain injury is associated with the highest rate of mortality, whereas subtherapeutic antiepileptic drug levels have the lowest mortality rates.⁷ Recurrent episodes are not an uncommon phenomenon, on average 25% for most etiologies.

There is controversy as to whether prolonged seizures are associated with long-term cognitive effects and further studies are needed to assess neuropsychological outcomes after status epilepticus.⁸ One study examining 10 patients with episodes of nonconvulsive status epilepticus of various etiologies, lasting between 36 and 72 hours, demonstrated a decline in cognitive function and memory in all survivors. Only 2 of the 7 survivors had documented neuropsychometric testing before and after the events.⁹ A prospective study of adult epilepsy patients with and without episodes of status epilepticus demonstrated no change in IQ testing before and after the incidence of status compared with matched controls.¹⁰ Due to the presence of frequent pre-existing neurologic conditions, lack of baseline neuropsychometric testing, and varying etiologies, duration, and treatments of status epilepticus, this remains a difficult topic to study.

Consumer summary: Status epilepticus is a neurologic emergency that requires prompt intervention. Prolonged seizures are not an uncommon phenomenon in the elderly and they unfortunately carry a high risk of death and permanent neurologic injury. If the seizures persist despite the use of antiseizure medications, it may be necessary to use sedating medications to induce a coma and calm the brain activity. The ultimate prognosis not only depends on patient age and seizure duration, but also is determined largely by the underlying cause of the seizure.⁸

The evidence

There have been 6 randomized controlled trials on this topic to date. Initial management of status epilepticus in adults should be with a benzodiazepine and it is safe to begin therapy outside of the hospital. If available, intravenous lorazepam should be used in preference to diazepam

because of better efficacy and lower risk of seizure recurrence. Although intravenous valproic acid has demonstrated efficacy and safety in multiple studies, experience at this point is too limited to allow recommendation of its use as a first-line agent.

Table I Available evidence for the initial pharmacologic management of status epilepticus

Author	N	Interventions	Outcome measures	Results	Comments
Allredge et al ¹¹	205	IV diazepam (5 mg) vs IV lorazepam (2 mg) vs placebo	Termination of status, respiratory or circulatory complications	BZDs are safe and effective, lorazepam more effective than diazepam	Class I. Pre-hospital treatment of SE in adults
Leppik et al ¹²	81	IV lorazepam (4 mg) vs IV diazepam (10 mg) with repeat dosing if needed	Termination of status, adverse effects	89% success with lorazepam, 76% with diazepam, no significant difference in adverse effects	Class II.
Treiman et al ¹³	518	IV diazepam (0.15 mg/kg) + PHT (18 mg/kg) vs lorazepam (0.1 mg/kg) vs PHB (15 mg/kg) vs PHT (18 mg/kg)	Termination of status within 20 min of drug infusion and no return of seizure activity during next 40 min	Lorazepam superior to PHT in GCSE. No difference among drugs in NCSE.	Class I. No significant difference in lorazepam vs diazepam + PHT or lorazepam vs PHB, but lorazepam easier to use
Misra et al ¹⁴	68	IV VPA (30 mg/kg) vs IV PHT (18 mg/kg)	Clinical seizure cessation after infusion and seizure freedom at 24 h	VPA was more effective than PHT in controlling GCSE, both as the first (66% vs 42%) and second choice (79% vs 25%)	Class III. Excluded NCSE, included children and adolescents, underpowered
Gilad et al ¹⁵	74	IV VPA (30 mg/kg) vs IV PHT (18 mg/kg)	Clinical seizure cessation, drug tolerability	VPA effective in 87.8% and PHT effective in 88%. Side effects occurred in 12% of PHT group and none in VPA group.	Class III. Underpowered
Agarwal et al ¹⁶	100	After failure of control with diazepam, IV VPA (20 mg/kg) vs IV PHT (20 mg/kg)	Termination of status within 20 min of drug infusion and no return of seizure activity during next 12 h	VPA effective in 88%, PHT in 84%.	Class III. 30% of patients were < 18 years old

Abbreviations: N, number of participants; IV, intravenous; BDZ, benzodiazepine; SE, status epilepticus; NCSE, nonconvulsive status epilepticus; GCSE, generalized convulsive status epilepticus; PHT, phenytoin; PHB, Phenobarbital; VPA, valproic acid.

Conclusions based on literature review

- Initial treatment of status epilepticus should be with a benzodiazepine, preferably intravenous lorazepam.
- Seizures will persist in approximately one-third of cases and lorazepam should be followed by administration of intravenous fosphenytoin. Fosphenytoin can be infused more quickly and with less risk of side effects than phenytoin.
- Other antiepileptic medications such as levetiracetam, valproic acid, and lacosamide may prove to be safe and efficacious alternatives; however there are no randomized controlled trials to support their use as first- or second-line agents at this time.
- Refractory status epilepticus requires anesthetic levels of drugs, thus requiring intubation, mechanical ventilation, and often vasopressor support. Phenobarbital, pentobarbital, propofol, midazolam, and ketamine can all be used as continuous infusions and titrated to the desired level of seizure suppression or background slowing on EEG. There are no prospective randomized trials to demonstrate which drug is most effective, and retrospective series suggest that the choice of agent does not statistically affect mortality. Medical comorbidities of the patient often help to determine which medication is most appropriate.

The practice

Potential pitfalls

Potential pitfalls include failure to recognize and treat the underlying cause of the seizure, failure to recognize associated injuries or complications such as aspiration pneumonia, and failure to diagnose and treat nonconvulsive status epilepticus. If a patient presents with unexplained

altered mental status or if the level of consciousness and awareness fails to improve within 20 to 30 minutes after cessation of generalized seizure activity, one must rule out the presence of nonconvulsive status. Neurologic consultation is advised when status epilepticus is refractory to standard first- and second-line therapies, when EEG is

required to rule out nonconvulsive status, and when EEG is necessary in circumstances when neuromuscular blockade is initiated.

Management

Any seizure lasting more than 5 minutes warrants intervention because the longer a seizure propagates, the more difficult termination will become. The goal of treatment is to stop all clinical and electrographic seizure activity. If intubation is required for airway protection, prolonged neuromuscular blockade should be avoided so as not to confound the neurologic exam if possible. If neuromuscular blockade is used, EEG monitoring may be necessary to detect electrographic seizures.

Determining the etiology of the seizures will often guide further diagnostics and management. Acutely, a head CT is recommended to investigate for intracranial pathology once the seizures are under control. Further imaging such as brain MRI may be warranted if the CT is unrevealing. If infection is suspected as the etiology, empiric antibiotic and antiviral treatment should not be delayed and further diagnostics such

as lumbar puncture should be pursued once the seizures are aborted.⁸

Assessment

Important inquiries to make about the patient's history include prior seizures or diagnosis of epilepsy, antiepileptic medication compliance, systemic or intracranial malignancies, infections, metabolic disorders, toxic ingestions, alcohol use, and recent falls or head injuries. The history may provide clues as to the etiology of the seizure and guide further work-up and management.

Physical examination should first and foremost be dedicated to the assessment of airway, breathing, and circulation. A survey for evidence of trauma with special attention to the head or face should be performed. Assessment of level of consciousness and close observation of motor and eye movements can help determine whether the seizures are convulsive or nonconvulsive in nature, simple or complex, and focal or generalized.⁸

Treatment

Carried out in 5 time specific steps as described in Table 2.

Table 2 Treatment algorithm for status epilepticus in the elderly

Step 1 (0–5 minutes)

- Assess airway, apply oxygen and pulse oximetry
- Begin cardiac telemetry and hemodynamic monitoring
- Venipuncture to secure access with 2 large-gauge intravenous catheters
- Stat blood work: basic metabolic panel, liver function tests, calcium, magnesium, phosphate, complete blood count, toxicology screens, troponin, arterial blood gas, and antiepileptic drug levels if appropriate
- Check finger-stick glucose
- Begin normal saline drip

Step 2 (6–10 minutes)

- Administer 100 mg thiamine IV
- Administer 50 mL of 50% dextrose IV if hypoglycemic, but withhold if normoglycemic
- Administer 0.1 mg/kg IV lorazepam (< 2 mg/min)
 - If seizures persist, may repeat initial dose of lorazepam once
 - Beware of sedation, respiratory depression, and hypotension
- If no IV access, consider rectal diazepam 10–20 mg
 - If seizures persist, may repeat initial dose of diazepam once
 - Beware of sedation, respiratory depression, and hypotension

Step 3 (11 to 30 minutes)

- Administer 20 mg PE/kg IV fosphenytoin (< 150 mg PE/min) or IV 20 mg/kg phenytoin by slow push (< 50 mg/min)
 - Fosphenytoin
 - Beware of cardiac depression and arrhythmia, hypotension, parasthesias, and pruritis
 - Fosphenytoin is more expensive but can be infused at a faster rate, has a lower risk of peripheral infusion-site complications, and is compatible with glucose-containing IV fluids

(Continued)

Table 2 (Continued)

- o Phenytoin
 - Beware of cardiac depression and arrhythmia, hypotension, infusion site soft tissue, and vascular injury (“purple-glove syndrome”)
 - Incompatible with glucose-containing solutions
 - Monitor respiratory status, cardiac rhythm, and blood pressure and be prepared to adjust dosages and rates accordingly
 - If seizures persist, give additional IV fosphenytoin or phenytoin to a maximum total dose of 30 mg/kg
- Step 4 (31–50 minutes)
- If seizures persist, order urgent EEG and neurologic consultation and transfer patient to intensive care unit
 - Initiate intubation before using an anesthetic agent
 - Consider using one of the following:
 - o IV phenobarbital 20 mg/kg slow push (< 100 mg/min)
 - Then continuous infusion at 1 mg/kg/h to 4 mg/kg/h
 - Beware of respiratory and cardiac depression, prolonged sedation, allergy, and blood dyscrasias
 - Contraindicated in severe liver dysfunction
 - o IV pentobarbital 5 mg/kg (< 50 mg/min)
 - Then continuous infusion at 0.5 mg/kg/h to 5 mg/kg/h
 - Beware of respiratory depression, sedation, and hypotension
 - o IV midazolam 0.2 mg/kg (given over 20–30 seconds)
 - Dose may be repeated in 5 minutes if seizures persist
 - Then continuous infusion at 0.05 mg/kg/h to 2.0 mg/kg/h
 - Beware of respiratory depression, sedation, and hypotension
 - o IV propofol 1 mg/kg bolus
 - May give repeated boluses every 3–5 minutes to a maximum dose of 10 mg/kg
 - Beware of sedation, hypotension, bradycardia, allergic reaction, and “propofol infusion syndrome” at high doses (metabolic acidosis, cardiac failure with dysrhythmia, rhabdomyolysis, hyperkalemia, and lipemia)
 - Monitor acid base status
 - Continuous infusion involves a large lipid and caloric load
 - Non-sedating alternatives include:
 - o IV valproate bolus of 25 mg/kg to 30 mg/kg (< 3 mg/kg/min)
 - Not FDA approved for SE
 - May be useful in patients who are awake, patients with primary generalized epilepsy, or in situations where intubation is to be avoided
 - Beware of dizziness, hyperammonemia, hypotension, hepatotoxicity, thrombocytopenia, and pancreatitis
 - Contraindicated in severe liver dysfunction, thrombocytopenia, and active bleeding
 - Monitor liver profile, amylase, lipase, and complete blood cell count
 - o IV levetiracetam 20 mg/kg over 15 minutes
 - Not FDA approved for SE
 - May be useful in patients who are awake, patients with primary generalized epilepsy, patients with liver disease, or situations in which intubation is to be avoided
 - Beware of neuropsychiatric side effects
 - Dose must be lowered in those with impaired creatinine clearance
 - o IV lacosamide
 - Not FDA approved for SE
- Step 5
- If seizures persist, maintain continuous IV infusion of anesthetic agents and titrate dose to desired level of EEG suppression-burst as determined by the neurology consultant
 - Defer to neurology consultant for choice of maintenance antiepileptic drug and appropriate dosing

Adapted with permission from Waterhouse E. Status epilepticus. *Continuum Lifelong Learning Neurol.* 2010;16(3):199–227.⁸

Abbreviations: SE, status epilepticus; PE, phenytoin equivalents.

Further reading

- Waterhouse E. Status epilepticus. *Continuum Lifelong Learning Neurol.* 2010;16:199–227.
- Meierkord H, Boon P, Engelsen B, et al. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol* 2010;17:348–355.

References

- Lowenstein DH, Bleck T, MacDonald RL. It's time to revise the definition of status epilepticus. *Epilepsia.* 1999;40(1):120–124.
- Hauser WA. Epidemiology of epilepsy and seizures in the elderly. In: Rowan AJ, Ramsay ER, editors. *Epilepsy in the Elderly.* Boston: Butterworth Heinemann; 1997:7–18.
- DeLorenzo RJ, Hauser WA, Towne AR, et al. A prospective population based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology.* 1996;46:1029–1035.
- Cascino GD, Hesdorffer D, Logroscino G, Hauser WA. Morbidity of nonfebrile seizure status epilepticus in Rochester Minnesota, 1965–1984. *Epilepsia.* 1998;39:829–832.
- Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, MN: 1935–1984. *Epilepsia.* 1993;34:453–468.
- Logroscino G, Hesdorffer DC, Cascino GD, Annegers JF, Bagiella E, Hauser WA. Long-term mortality after a first episode of status epilepticus. *Neurology.* 2002;58:537–541.
- Lowenstein DH, Alldredge BK. Status epilepticus at an urban public hospital in the 1980s. *Neurology.* 1993;43:483–498.
- Waterhouse E. Status epilepticus. *Continuum Lifelong Learning Neurol.* 2010;16:199–227.
- Krumholz A, Sung GY, Fisher RS, et al. Complex partial status epilepticus accompanied by serious morbidity and mortality. *Neurology.* 1995;45:1499–1504.
- Adachi N, Kanemoto K, Muramatsu R, et al. Intellectual prognosis of status epilepticus in adult epilepsy patients: analysis with Wechsler Adult Intelligence Scale-revised. *Epilepsia.* 2005;46(9):1502–1509.
- Allredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med.* 2001;345(9):631–637.
- Leppik IE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA.* 1983;249:1452–1454.
- Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med.* 1998;339:792–798.
- Misra UK, Kalita J, Patel R. Sodium valproate vs phenytoin in status epilepticus: a pilot study. *Neurology.* 2006;67:340–2.
- Gilad R, Izkovitz N, Dabby R, et al. Treatment of status epilepticus and acute repetitive seizures with i.v. valproic acid vs phenytoin. *Acta Neurol Scand.* 2008;118:296–300.
- Agarwal P, Kumar N, Chandra R, Gupta G, Antony AR, Garg N. Randomized study of intravenous valproate and phenytoin in status epilepticus. *Seizure.* 2007;16:527–532.
- Meierkord H, Boon P, Engelsen B, et al. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol.* 2010;17:348–355.

Neuropsychiatric Disease and Treatment

Publish your work in this journal

Neuropsychiatric Disease and Treatment is an international, peer-reviewed journal of clinical therapeutics and pharmacology focusing on concise rapid reporting of clinical or pre-clinical studies on a range of neuropsychiatric and neurological disorders. This journal is indexed on PubMed Central, the 'PsycINFO' database and CAS, and is the official

Submit your manuscript here: <http://www.dovepress.com/neuropsychiatric-disease-and-treatment-journal>

Dovepress

journal of The International Neuropsychiatric Association (INA). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.