Patient Management Problem—Preferred Responses

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Following are the preferred responses for the Patient Management Problem in this CONTINUUM issue. The case, questions, and answer options are repeated, and the preferred response appears in bold print, followed by an explanation and a reference with which you may seek more specific information. You are encouraged to review the responses and explanations carefully to evaluate your general understanding of the material. The comment and references included with each question are intended to encourage independent study.

Learning Objectives

Upon completion of this activity, the participant will be able to:

- Diagnose the epilepsy syndrome in a patient with new-onset epilepsy
- Select between appropriate antiepileptic drug therapy options for initial epilepsy management
- Employ IV antiepileptic drug therapy for acute seizures and status epilepticus
- Counsel women with epilepsy concerning teratogenic risk and bone health concerns
- Recognize evolution of refractory epilepsy
- Become familiar with the range of appropriate treatment options for refractory epilepsy

Case

A 21-year-old, right-handed woman presents to the clinic after a first witnessed generalized tonic-clonic seizure during sleep, reported by her husband after their marriage 3 months ago. Further history reveals that over the past year, she experienced two previous stereotyped spells, each occurring during the time of her menstrual period, in which she felt an odd rising feeling in her abdomen, then lost track of conversations, was reported to stare as if she were “in a trance,” and exhibited lip smacking. The spells were each approximately 45 seconds in duration and were followed by a feeling of exhaustion.
1. Which of the following seizure types has this patient most likely been experiencing before her recent generalized tonic-clonic seizure?

A. absence
B. clonic
C. complex partial
D. myoclonic
E. simple partial

The preferred response is C (complex partial). Terminology concerning classification of seizures and epilepsies is evolving, with a recent statement from the International League Against Epilepsy (ILAE) Commission on Classification and Terminology proposing the division of seizures into focal or generalized, depending on whether they are initially confined within one hemisphere (focal) or have more bisynchronous involvement from their onset from both hemispheres (generalized). This terminology also favors using a rather complex set of terms favoring a semiologic description of clinical seizure behavior. Complex partial seizures would be referred to as focal dyscognitive seizures in the revised classification.

However, the older 1981 ILAE terminology remains conceptually important in terms of inferring preservation or alteration of consciousness within focal/partial seizures, a clinically useful construct, so familiarity with the 1981 classification scheme remains important.

This patient had relatively brief episodes of altered consciousness with automatic behaviors, clinical events most suggestive of complex partial (focal) seizures. Complex partial seizures are typically under 1 minute in duration, involve consciousness disturbance or alteration, often feature oral-buccal or limb automatisms, and almost invariably have a postictal state of confusion, somnolence, or language disturbance. Simple partial seizures are “auras,” which usually involve either psychic or cognitive, autonomic, motor, or visual symptoms but do not involve altered consciousness. Absence seizures are brief (ie, 5 to 10 seconds) in duration, involve consciousness alteration with staring, and may have automatisms similar to complex partial seizures but do not involve a preceding aura or postictal state. Myoclonic seizures are characterized by a sudden unilateral or bilateral myoclonic jerk of the limbs or trunk (occurring either singly or in a cluster of a few nonrhythmic jerks) and, if massive, may involve falling. Clonic seizures are characterized by repetitive, rhythmic myoclonic jerks of the limbs.

The patient’s neurologic examination is unremarkable. A CT scan of the head from the emergency department visit is reviewed and appears normal. Magnetic resonance scan of the brain with conventional cut thickness on coronal imaging is unrevealing. The EEG in **PMP Figure 1** is obtained, shown in the longitudinal bipolar montage on a 10-second screen (sensitivity = 15 μv/mm, low-frequency filter = 1.0 Hz, high-frequency filter = 70 Hz). Odd-numbered electrode positions are on the left side of the head, even-numbered positions are on the right side, and electrode positions are denoted z on the central/midline. Electrode position abbreviations are as follows: FP = frontopolar, F = frontal, T = temporal, P = parietal, O = occipital.

2. Which of the following abnormal discharges is shown in the fourth second of the EEG tracing, denoted by the arrowhead at the top of the figure?
   A. generalized spike-wave
   B. left anterior temporal spike
   C. left temporal wicket wave
   D. right anterior temporal spike
   E. right temporal wicket wave

The preferred response is **D (right anterior temporal spike)**. The EEG example above shows a right anterior temporal spike discharge. Interictal epileptiform discharges (IEDs) should be distinguishable from and disruptive.
The characteristic morphology of a focal IED is a very sharp rise time, a complex waveform (often with several phases or baseline crossings), and an aftergoing slow-wave discharge that disturbs or disrupts the continuity of the background rhythm at least momentarily. Generalized IEDs are usually either typical or atypical generalized spike-wave complexes, or polyspike and/or polyspike-wave discharges. Wicket waves are by far the most commonly encountered benign variant, and a frequent source of over-reading and mistaken diagnosis of epilepsy on EEG. Wicket waves are single waveforms that occur in brief trains or clusters. In distinction to true epileptiform spikes, however, wicket waves have a more arciform appearance and earn their name therefore by looking like wickets. Wickets are most frequent in the temporal regions, occurring bilaterally or independently, and have a frequency of 6 Hz to 11 Hz and an amplitude ranging from 60 μV to 200 μV. Wickets are not accompanied by aftercoming slow waves, and are mainly seen in older adults during drowsiness and light sleep and become apparent when the alpha and other awake patterns drop out.


3. In view of the clinical history and EEG abnormality demonstrated, which of the following is the most likely provisional diagnosis?

A. extratemporal epilepsy
B. idiopathic generalized epilepsy
C. psychogenic nonepileptic behavioral spells
D. symptomatic generalized epilepsy
E. temporal lobe epilepsy

The preferred response is **E (temporal lobe epilepsy)**. Epilepsy syndrome diagnosis depends on an accurate diagnosis of the clinical seizure type, as well as the neurophysiologic characteristics from supportive EEG data, yielding an electrophysiological syndrome diagnosis, which is important to inform both the prognosis and the practical consideration of antiepileptic drug (AED) selection. This patient has complex partial (focal) seizures with an aura typical of mesial temporal lobe seizure onset, and clear-cut temporal IEDs supporting a temporal epileptogenic focus. Psychogenic nonepileptic behavioral spells are more likely to be nonstereotyped, prolonged clinical events. Extratemporal partial epilepsy could have similar types of complex partial seizure behavior to this patient but more likely would instead have either no aura or a visual or somatosensory aura, and other partial seizure types seen in frontal lobe epilepsy feature more prominent partial motor seizure activity such as posturing or hyperkinetic movements. Generalized epilepsies instead demonstrate generalized epileptiform EEG abnormalities. Idiopathic generalized epilepsy would feature absence, myoclonic, or generalized tonic-clonic seizures, while symptomatic generalized epilepsy most frequently has a mix...
of tonic, atonic/astatic, atypical absence, and generalized tonic-clonic seizures.


While the patient is receiving counseling concerning possible treatment options, she asks whether deferring treatment would be possible since she and her husband are planning to start a family. She asks how likely it is that she may experience further seizures without treatment.

4. Which of the following is the correct response concerning the approximate likelihood of seizure recurrence without treatment?
   A. 25%
   B. 45%
   C. 75%
   D. 95%
   E. 100%

The preferred response is C (75%). While the precise risk of seizure recurrence is often difficult to estimate, this patient has had at least 2 previous clinical seizures. The best longitudinal prospective study by Hauser and colleagues concerning the risk of seizure recurrence following repeated seizures suggests that the risk of further seizure recurrence following two previous seizures is over 70%. Specifically, from this crucial reference, the average risk of recurrence of a third seizure following a previous second seizure is 73%, and the risk of a subsequent fourth seizure following a third seizure event is 76%. Therefore, of the possible choices presented, the best answer for this patient is approximately 75%.


5. Which of the following AEDs would be the best choice for this patient’s epilepsy syndrome, with consideration toward her active efforts in trying to conceive and for minimizing impact on bone health?
   A. carbamazepine
   B. lamotrigine
   C. oxcarbazepine
   D. phenytoin
   E. valproic acid

After discussion of this information, the patient decides that she would like to initiate antiepileptic drug (AED) therapy. Family history also reveals several first-degree female relatives with osteoporosis (her grandmother, maternal aunt, mother, and older sister).
The preferred response is B (lamotrigine). This patient has a strong family history of osteoporosis, a recognized significant risk factor for development of osteopenia or osteoporosis in the patient herself. Patients with epilepsy are at elevated risk of fracture, with a twofold to sixfold increased risk above the general population. The older standard AEDs, particularly those with enzyme-inducing properties such as phenobarbital and phenytoin, as well as valproate, have been associated with reduced bone density. While evidence is conflicting for carbamazepine and oxcarbazepine, both are enzyme-inducing and some studies have shown that these drugs also have deleterious impact on bone health. Phenytoin, carbamazepine, and valproate each have demonstrated major teratogenic risks to the fetus during pregnancy and are US Food and Drug Administration (FDA) Pregnancy Category D, whereas lamotrigine and oxcarbazepine have unclear risks and are considered FDA Pregnancy Category C. While evidence from large prospective registries have been conflicting on teratogenic risk of these drugs, some evidence suggests that lamotrigine may be associated with risk of cleft palate. Of the choices presented, lamotrigine would be least likely to adversely affect bone density and raise teratogenic risk. Providing pregnancy counseling to women of childbearing potential is advised by the American Academy of Neurology (AAN) Epilepsy Quality Measures, and women of childbearing potential should also be advised to take folic acid daily to minimize teratogenic risk in event of pregnancy.


The patient continues to experience intermittent seizures following treatment with the first-line AED recommended (at therapeutic doses, and with adequate serum levels), as well as with adjunctive levetiracetam 1500 mg twice a day, and a subsequent trial of gabapentin 1200 mg 3 times a day. The latter two AEDs were pushed up to the brink of clinical toxicity, as on each occasion she reported the occurrence of mild but bothersome adverse effects of sedation and dizziness, limiting the ability to adjust either drug to a higher dosage.
6. Which of the following should be considered as the next most appropriate step in this patient’s care?

A. additional sequential trials of two to three newer AEDs
B. implantation of a vagus nerve stimulator
C. initiation of the modified Atkins diet
D. proceeding with temporal lobectomy
E. referral to a comprehensive epilepsy program

The preferred response is E (referral to a comprehensive epilepsy program). This patient continues to have recurrent seizures despite treatment with three previous trials of AEDs at typically efficacious and maximally FDA-labeled doses, despite the doses being pushed to the point of clinical toxicity from dose-related adverse effects of AED treatment. At this point, the patient has clearly failed to attain seizure control after three AED trials, including monotherapy and polytherapy. Most experts agree that at this point the patient may be considered to have refractory epilepsy, and important considerations are excluding “pseudoresistance” to treatment (due either to errant epilepsy syndrome diagnosis with inappropriate AED treatment or to an alternative nonepileptic spell diagnosis such as psychogenic nonepileptic behavioral spells or syncope). To verify the correct epilepsy syndrome diagnosis, ensure properly directed AED therapy, and enable consideration for nonpharmacologic treatment alternatives such as epilepsy surgery, neurostimulation, or dietary therapies, referral of the patient to a comprehensive epilepsy program capable of performing expert subspecialty history and physical examination, ictal video-EEG monitoring, definitive structural and/or functional neuroimaging, and presurgical evaluation is the best course of action.


Immediately before a definitive management step is taken, the patient’s husband calls during the night to report that the patient has had two generalized tonic-clonic seizures since this morning, and that she has remained obtunded after the second witnessed seizure for the past hour, and he cannot arouse her. This is distinctly unusual in that she usually arouses within 10 to 20 minutes after generalized seizures. She has a prescribed dose of rectal diazepam available, which the husband has been instructed in how to administer.
7. Which of the following is the most appropriate instruction to the patient’s husband?
A. administer a single test-dose of rectal diazepam
B. administer rectal diazepam repeatedly until she awakens
C. call emergency medical services immediately
D. give an extra dose of oral levetiracetam and call in the morning
E. wait 1 more hour, as postictal behavior is prolonged in some individuals

The preferred response is C (call emergency medical services immediately). At this point, it is apparent even by telephone that this patient is exhibiting a clear and alarming alteration from her usual characteristic postictal behavior. While atypically prolonged postictal behavior is still a possibility, the more likely probability of continuing nonconvulsive status epilepticus following her last generalized tonic-clonic seizure or evolving acute repetitive seizures without consciousness recovery following discrete seizure events needs to be promptly evaluated to prevent serious consequences.\(^1,2\) It is unlikely that orally delivered AEDs would promptly resolve this scenario. While rectal diazepam as an abortive therapy may be administered during prolonged generalized tonic-clonic seizures to arrest them, this treatment is not indicated for possible nonconvulsive seizures which in any event require prompt diagnostic EEG to confidently diagnose. Furthermore, diazepam could cause further airway or respiratory compromise in a deeply postictal patient. The possibility of a medical complication of status epilepticus, such as aspiration pneumonitis with sepsis or of acute unwitnessed head injury with brain hemorrhage (subdural or epidural hematoma) should also be promptly excluded. The only logical means of confident diagnosis and of ensuring cardiovascular stability as soon as possible is urgently summoning emergency medical services personnel for emergent assessment and hospital transfer.


8. The single most important initial management step in this patient is which of the following?
A. EEG
B. head CT
C. lorazepam 2 mg IV push
D. lumbar puncture
E. securing airway and respiration

After the above advice is provided to the patient’s husband, the patient remains obtunded and is transported immediately to the hospital. She arrives in the emergency department in an unresponsive state. On examination she is nonverbal, groans when stimulated, but is otherwise minimally responsive to pain and has repetitive rightward-beating nystagmoid eye movements.
The preferred response is **E (securing airway and respiration)**. Status epilepticus is one of the few truly emergent situations in neurologic practice. While terminating status epilepticus and promptly determining potential causes for acute seizures are key priorities upon presentation, the first priority is stabilizing the patients ABCs: airway, breathing, and circulation. **1-3** Neurologists cannot presume that emergency department personnel will have consistently attended to this immediate step and need to assume responsibility and direct this step of care as necessary, including request of intubation should the patient be clinically comatose and unable to protect his or her airway. Placement of a nasal trumpet and continuous pulse oximetry monitoring may help avoid premature intubation, with careful monitoring of respiratory rate, chest excursion, and oxygenation.


**9. Which of the following is the next most important management step in this patient?**
A. EEG
B. head CT
C. lorazepam 2 mg IV push
D. lumbar puncture
E. securing airway and respiration

The preferred response is **C (lorazepam 2 mg IV push)**. A key priority that is not listed among the possible choices above is ensuring an adequate glucose level by immediately obtaining a finger stick, which most status epilepticus algorithms would place ahead of initiating IV abortive therapies, since infusion of IV dextrose (along with thiamine 100 mg in event of malnutrition to avoid precipitating Wernicke encephalopathy) may remedy coma or acute symptomatic seizures resulting from hypoglycemia. Presuming this step has already been undertaken, with normal glucose levels assured (often done concurrently while preparing for lorazepam infusion), there is near universal agreement that benzodiazepines should be the first abortive treatment administered in status epilepticus, based on three major clinical trials and several expert-consensus treatment algorithms. **1-5** Options include IV lorazepam, 4 mg to 8 mg in increments of 2 mg/min, 10 mg IM midazolam, or 5 mg IV diazepam. **1-5** While additional diagnostic tests are important to consider, following emergency assessment for airway and circulation stabilization and exclusion of remediable hypoglycemia, the most crucial priority is abortive treatment to terminate status epilepticus before further medical or neurologic complications can evolve.

The patient’s nystagmoid eye movements cease following the above interventions. Noncontrast head CT is negative. An emergent EEG is obtained and demonstrates nonconvulsive status epilepticus. IV lorazepam is administered to a total dose of 8 mg.

10. Which of the following IV AEDs should be fully loaded as the next most important management step?
   A. fosphenytoin (20 mg/kg, at 100 mg/min to 150 mg/min infusion rate)
   B. lacosamide (400 mg, at 25 mg/min infusion rate)
   C. levetiracetam (3000 mg, at 500 mg/min infusion rate)
   D. phenobarbital (20 mg/kg, at 50 mg/min infusion rate)
   E. valproic acid IV load (40 mg/kg, at 100 mg/min infusion rate)

The preferred response is A (fosphenytoin [20 mg/kg, at 100 mg/min to 150 mg/min infusion rate]). EEG characteristics of nonconvulsive status epilepticus include either focal or generalized, persistent spike-wave or rhythmic waveforms that may or may not subtly evolve in frequency or topographic distribution. With the failure of IV lorazepam, the next most appropriate step in management is infusion of a full loading dose of IV fosphenytoin, 20 mg/kg, at 150 mg/min. Hemodynamic and cardiac telemetry monitoring is recommended during infusion to ensure significant hypotension or arrhythmias do not occur. Transfer to a neurologic intensive care unit capable of continuous EEG, hemodynamic, and clinical monitoring may be appropriate at this point, with continuing efforts to ensure that electrographic status epilepticus is terminated. The treatment endpoint is electrographic seizure suppression. If electrographic nonconvulsive status epilepticus continues, infusion of an IV anesthetic (eg, midazolam, propofol, ketamine, pentobarbital) is then the usual course, pushing the agent toward a burst-suppression EEG pattern and maintaining a burst-suppression EEG pattern for a period of 24 hours with subsequent attempts at weaning of the anesthetic agent. Propofol should be used with caution at the high doses required to control refractory status epilepticus because it may result in rapid and profound cardiovascular collapse, metabolic acidosis, and renal failure, known as the propofol infusion syndrome.

11. Which of the following findings is shown on this patient’s brain MRI?
A. cavernous malformation  
B. focal cortical dysplasia  
C. hippocampal sclerosis  
D. low-grade astrocytoma  
E. posterior cerebral-anterior temporal cortical branch arterial distribution infarction

The preferred response is C (hippocampal sclerosis). The brain MRI demonstrates clear-cut hippocampal sclerosis on the right side. Typical MRI findings of hippocampal sclerosis include hippocampal volume loss best appreciated on T1-weighted imaging (A), with hyperintensive signal within the hippocampus on FLAIR-weighted (B) and T2-weighted (C) images. Hippocampal sclerosis is the most common neuropathologic correlate of refractory mesial temporal lobe epilepsy, a surgically privileged epilepsy syndrome with an excellent outcome following anterior temporal lobectomy epilepsy surgery.
Focal cortical dysplasia is often manifested by abnormal T1 hypointensity and/or T2 hyperintensity without enhancement proximal to abnormal cortical dysplastic tissue, or may show abnormalities of gyration on T1-weighted imaging sequences. Cavernous malformations are small vascular malformations that typically demonstrate T1-weighted hypointensity and T2 hyperintensity, accompanied by homogeneous gadolinium contrast enhancement. An ischemic infarction would instead be expected to conform to a vascular distribution, with increased T2-weighted signal intensity.


12. Presuming the patient is willing to assume the risks of the procedure, which of the following surgical options is most likely to effect seizure freedom?

A. anterior temporal lobectomy
B. focal neocortical resection (topectomy)
C. hemispherectomy
D. temporal responsive neural stimulator implantation
E. vagus nerve stimulator implantation

The preferred response is A (anterior temporal lobectomy). While it is worthwhile to attempt additional trials of AEDs or consider placement of the vagus nerve stimulator device in some patients with refractory epilepsy who are not optimal surgical candidates, these measures are not robustly effective for most patients, offering no more than a 5% to 10% likelihood of achieving seizure freedom when epilepsy is refractory. The Neuropace responsive neural stimulator system is a novel neurostimulation device that has recently completed pivotal clinical trials and has been filed for possible FDA approval for treatment of refractory epilepsy; while the device demonstrated a statistically significant reduction in seizure frequency above sham treatment, seizure freedom was not common and seen in only 7.1% of patients during active responsive neural stimulator therapy. Vagus nerve stimulation (VNS) is an appropriate consideration for patients with refractory partial epilepsy who are not suitable resection surgery candidates. VNS may produce between 35% and 45% median seizure frequency reduction over time, but only about 5% to 15% of patients receiving VNS achieve seizure freedom. Hemispherectomy is typically reserved for cases of catastrophically refractory multilobar cortical dysplasia or Sturge-Weber syndrome, and would not be indicated in a patient with well-localized temporal pathology and seizure focus. Focal neocortical resection is offered for patients with lesional or nonlesional temporal neocortical or extratemporal refractory epilepsies.
and is not offered for mesial temporal lobe epilepsy. Evidence from a single Class 1 randomized controlled trial has demonstrated that anterior temporal lobectomy for refractory mesial temporal lobe epilepsy is clearly superior when compared to continued AED therapy in carefully selected candidates.\(^1\) In some candidates and at some epilepsy centers, alternative procedures such as selective amygdalohippocampectomy may be considered, and ongoing investigations of noninvasive techniques such as radiosurgery or minimally invasive techniques such as laser surgeries offer promise of reduced morbidity and comparable seizure-free patient outcomes.

Early referral to a comprehensive epilepsy center to determine optimal candidates for surgical resection or best alternative nonpharmacologic therapies should be considered the standard of care for refractory mesial temporal lobe epilepsy cases, a practice supported by the AAN Epilepsy Quality Measures.\(^1\) While the timing for referral remains somewhat unclear and the single pivotal clinical trial meant to address this question was unfortunately halted prematurely because of slow patient accrual,\(^4\) general expert consensus exists that soon after refractory epilepsy is identified (after failure of two to three appropriately selected and dosed AED trials), referral for surgical evaluation should be strongly considered.