



ACEP 2004 Clinical Policy Highlights: Seizure Management in the ED

Andy Jagoda, MD, FACEP

**Professor of Emergency Medicine
Mount Sinai School of Medicine
New York, NY**

Key Learning Points

- The ACEP seizure policy was first published in 1993 and has been revised two times; the most recent revision will be published in the June 2004 issue of the *Annals*. The recent revision uses a “critical questions” format.
- Preparation for the seizure policy revision included review of 7 existing practice guidelines written by other societies on acute seizure management.
- ACEP developed 6 clinical questions that were relevant to ED practice and had not been systematically addressed in the literature.
 1. What lab tests are indicated in the otherwise healthy adult patient with a new onset seizure who has returned to a baseline normal neuro status? Level B recommendations: Determine a serum glucose and sodium on patients with a first time seizure with no co-morbidities who have returned to their baseline / Obtain a pregnancy test in women of child bearing age / Perform a LP after a head CT either in the ED or after admission on patients who are immunocompromised.
 2. Which new onset seizure patients who have returned to a normal baseline require neuroimaging in the ED? Level B recommendations: When feasible, perform a head CT of the brain in the ED on patients with a first time seizure / Deferred outpatient neuroimaging may be utilized when reliable follow-up is available.

3. Which new onset seizure patients who have returned to normal baseline need to be admitted to the hospital and / or started on an AED? Level C recommendations: Patients with a normal neurologic examination can be discharged from the ED with outpatient follow-up / Patients with a normal neurologic examination and no co-morbidities and no known structural brain disease do not need to be started on an anti-epileptic drug in the ED.
4. What are effective phenytoin dosing strategies for preventing sz recurrence in patients who present to the ED with a subtherapeutic serum phenytoin level? Level C recommendations: Administer an intravenous or oral loading dose of phenytoin or intravenous or intramuscular fosphenytoin, and restart daily oral maintenance dosing.
5. What agent(s) should be administered to a patient in status who continues to seize despite a loading dose of a benzodiazepine and a phenytoin?
 - Administer one of the following agents intravenously: “high-dose phenytoin,” phenobarbital, valproic acid, midazolam infusion, pentobarbital infusion, or propofol infusion.
6. When should an EEG be performed in the ED? Consider an emergent EEG in patients suspected of being in nonconvulsive status epilepticus or in subtle convulsive status epilepticus, patients who have received a long-acting paralytic, or patients who are in a drug-induced coma.

Background

Over the past fifteen years there has been a proliferation of clinical policies (also referred to as practice guidelines or practice parameters). There are over three thousand policies in existence, written by a variety of organizations, fulfilling a number of different goals and agendas. To facilitate guideline utilization, a National Guideline Clearinghouse has been established which can be accessed on the internet at <http://www.guideline.gov>. Readers of a clinical policy are left with the task of trying to determine the value of the document and how to appropriately utilize its recommendations. This presentation is intended to provide background on clinical policy development and applications.

There are currently 15 ACEP Clinical Policies. The first clinical policy was published in 1990 and dealt with the diagnostic approach to chest pain. Including chest pain, twelve topics were prioritized by the Board of Directors when the Clinical Policies Committee was formed. Topics were chosen based either on their frequency or their potential liability and included “The initial approach to patients presenting with a chief complaint of seizure, who are not in status epilepticus”. This clinical policy on seizures was first published in 1993 and revised in 1997. In June 2004, a second revision of the policy will be published that takes a “critical questions” approach using evidence based methodology.

The critical questions for the 2004 Seizure Clinical Policy revision were developed after a review of existing published guidelines by other societies on acute seizure management. The subcommittee identified seven applicable guidelines:

- Treatment of convulsive status epilepticus. Epilepsy Foundation of America. JAMA 1993; 270:854-859.
- The neurodiagnostic evaluation of the child with first simple febrile seizure. AAP. Pediatrics 1996; 97:769-775.
- The role of phenytoin in the management of alcohol withdrawal syndrome. Am Soc Addiction Med 1994 / 1998
- Evaluating the first nonfebrile seizure in children. AAN. Neurology 2000; 55:616-623.
- Role of antiseizure prophylaxis following head injury. BTF / AANS. J Neurotrauma 2000; 17:549-553.
- Treatment of the child with a first unprovoked seizure. AAN. Neurology 2003; 60:166-175
- Antiepileptic drug prophylaxis in severe traumatic brain injury. Neurology 2003; 60:10-16

Six questions were formulated by the subcommittee, reviewed by the full Clinical Policies Committee, and approved by the Board.

Methodology

The methodologies used to develop clinical policies can be divided into two general categories: Those that are consensus driven, and those that are evidence based. Evaluating policies involves understanding the rationale for why a policy was developed and how the final recommendations were derived. Under the most ideal of circumstances, a policy is developed to help readers comprehend and apply the large amount of literature available on a given subject and to provide sound recommendations based on the best available information. Unfortunately, at times clinical policies are developed to promote special interest agendas or to give a forum for an opinion or point of view that is not necessarily supported by scientific evidence. Consequently, it is important to fully understand the developmental process used in order to comprehend how to apply (or not apply) the policy's recommendations.

Consensus clinical policies: Consensus policies may be formulated either by an informal or a formal process. In informal consensus policy development, there is usually a group of experts who assemble, discuss the issues at hand, and draw their conclusions based on those discussions. This process may or may not involve some degree of literature review. This approach to clinical policy development has been described as “global subjective judgment” and is influenced by the bias that enters the decision making process. ACEP's first chest pain policy is an example of this type of policy. Though informal consensus can be reached by authoritative sources, it should be viewed with skepticism.

In formal consensus policy development, there is again a group of experts assembled but in this case there is an actual process in which the appropriate literature is reviewed and discussed. However, the final recommendations are ultimately determined by the panel's opinion or interpretation of the evidence. This process is limited by its lack of defined analytic procedures or clear criteria on factors used in creating recommendations. Therefore, formal consensus documents must also be viewed with caution since the experts' opinions and biases may have overridden the scientific evidence. An example of a formal consensus document is ACEP's 1997 “Clinical policy for the initial approach to patients presenting with a chief complaint of seizure who are not in status epilepticus”.

Evidence based clinical policies: Evidence based clinical policies are emerging as the preferred method for policy development. In this method, appropriate literature is reviewed by a panel experienced in reading the literature, and each piece of evidence is graded according to set criteria. Recommendations are then made based on the strength of evidence that is available. Tables 1, 2, and 3 provide the criteria used by the ACEP Clinical Policies Committee in grading strength of evidence and generating recommendations. Examples of evidence based clinical policies are ACEP's Clinical Policy published after 1998.

The absence of directed research may make the creation of a “standard” problematic. In these cases, expert opinion is often the only evidence available; an example of this is the use of oxygen in patients with suspected myocardial infarction. This is the circumstance that confronted ACEP's Clinical Policies Committee in its complaint based policies. In some cases, resource availability may limit the implementation of a recommendation made in a clinical policy. However, in such cases, if there is strong strength of evidence to support the action, and the studies findings are externally valid, then the clinical

policy's benefit to the health care system would be in effecting change in the system. An example might be forcing the immediate availability of a CT scanner in a hospital that has agreed with EMS to receive suspected stroke patients. Finally, there are situations where there is clear evidence to support an action but the issue at hand may not have value or relevance to society; in these cases the action will be driven by the societal value placed on an outcome. An example of this situation would be the intubation of the hypoxic patient who is end-stage with a terminal process.

Once a clinical policy is developed, its recommendations can be constructed into an implementation tool such as a "clinical pathway" or an "annotated algorithm" which take into account the resources available. However, it is critical that these flow charts allow for practice variability as determined by the strength of evidence discovered in the development process.

Questions and Recommendations

What laboratory tests are indicated in the otherwise healthy adult patient with a new onset seizure who has returned to a baseline normal neurological status?

Level A recommendations. None specified.

Level B recommendations.

1. Determine a serum glucose and sodium on patients with a first time seizure with no co-morbidities who have returned to their baseline.
2. Obtain a pregnancy test if a woman is of child-bearing age.
3. Perform a lumbar puncture, after a head CT, either in the ED or after admission, on patients who are immunocompromised.

Level C recommendations. None specified.

Implications: There is surprisingly limited literature available on this topic. Most studies are retrospective and those that are prospective have design flaws. As a result there are no “Level A” recommendations. There is no literature to support laboratory testing beyond a glucose and serum sodium (set of electrolytes) in the otherwise healthy adult patient who has returned to a normal baseline; the key here is “otherwise healthy adult patient” since patients with significant co-morbidities put them at risk for electrolyte abnormalities and / or infections. The implication of this recommendation is that it minimizes unnecessary laboratory testing without increasing risk of missing significant diagnoses.

There is no literature supporting a lumbar puncture as part of the ED evaluation of the defined patient subset (i.e. otherwise healthy who has returned to a normal baseline); emphasis was placed on the need for lumbar puncture in patient who are immunocompromised either in the ED or after admission. The implication of “or after admission” is that, despite being immunocompromised, if they have returned to a normal baseline with a normal exam, there is no urgency in performing the test in the ED.

Patient Management Recommendations: Which new onset seizure patients who have returned to a normal baseline require a head CT in the ED?

Level A recommendations. None specified.

Level B recommendations.

1. When feasible, perform a neuroimaging of the brain in the ED on patients with a first time seizure.
2. Deferred outpatient neuroimaging may be utilized when reliable follow-up is available.

Level C recommendations. None specified.

Implications: In 1996 a multi-disciplinary group which included ACEP published a practice guideline on neuroimaging after a first time seizure. The group used 30 day morbidity or mortality as an outcome measure and found very little literature to support the need for emergent imaging in patients who had returned to a normal baseline. The policy supported outpatient imaging of these patients after discharge from the ED. In writing the revision of the ACEP seizure policy, the subcommittee chose “change in disposition” as an outcome measure recognizing that many of our patients do not have access to timely outpatient care. Most of the studies reviewed were retrospective and “abnormal CT” was identified in up to 40% of patients with a first time seizure. Consequently, neuroimaging (generally a noncontrast head CT) is recommended when feasible; however, recognizing that there is no outcome data to suggest harm if there is a delay in obtaining the study, the seizure policy revision allows for an outpatient study if reliable follow-up is available. The corollary to this is that if a neuroimaging study is not available and if the patient does not have follow-up, the patient should be admitted to the hospital for a diagnostic evaluation.

Which new onset seizure patients who have returned to normal baseline need to be admitted to the hospital and/or started on an antiepileptic drug?

Level A recommendations: None specified.

Level B recommendations: None specified.

Level C recommendations:

1. Patients with a normal neurologic examination can be discharged from the ED with outpatient follow-up.
2. Patients with a normal neurologic examination, no comorbidities, and no known structural brain disease do not need to be started on an antiepileptic drug in the ED.

Implications: Almost no literature was found on the outcomes of patients seen in the ED with a first time seizure who had returned to a normal baseline. Prognosis in patients with a first time seizure is based on the seizure’s etiology. Young age and a normal neurologic exam make the risk of a recurrent seizure less, while older age and an abnormal neurologic exam make risk of recurrence higher. The need for admission and or treatment depends on stratifying the risk of recurrence, which is best done by incorporating the results of a neuroimaging study and EEG when available. The best available evidence supports an outpatient evaluation in those patients with a first time seizure who have returned to a normal baseline. Since all of the anti-epileptic drugs have potential risks, it is reasonable to withhold pharmacologic treatment in patients with no co-morbidities pending completion of a diagnostic evaluation.

What are effective phenytoin or fosphenytoin dosing strategies for preventing seizure recurrence in patients who present to the ED after having had a seizure with a subtherapeutic serum phenytoin level?

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Administer an intravenous or oral loading dose of phenytoin or intravenous or intramuscular fosphenytoin, and restart daily oral maintenance dosing.

Implications: There are no studies in the literature specifically looking at short term seizure recurrence in patients on phenytoin who come to the ED after having had a seizure and found to have a subtherapeutic phenytoin level. These patients when seen in a private MD's office are generally treated with oral phenytoin, yet in the ED concern of seizure recurrence generally drives intravenous loading. Intravenous phenytoin loading requires an IV and monitoring; risks included ataxia, confusion, hypotension, and phlebitis. Intravenous phenytoin has a pH of 12 and infiltration of an infusion results in necrosis and potential loss of limb. Fosphenytoin offers the advantage of no propylene glycol vehicle which may cause hypotension, water solubility, with a more neutral pH. It causes no tissue irritation/necrosis and indeed it can be safely administered IM with therapeutic levels within 30 – 60 minutes. Oral phenytoin achieves therapeutic serum levels within 4 – 6 hours of administration. Oral, IM, and IV loading are all acceptable and the route chosen must be tailored to the individual patient. IM fosphenytoin offers the advantage of dependable therapeutic levels within one hour with no need for monitoring or risk of phlebitis. Oral loading offers the advantage of no monitoring, inexpensive, but requires observation in the ED for 6 hours which can be problematic in busy departments.

What agent(s) should be administered to a patient in status epilepticus who continues to seize after having received a benzodiazepine and a phenytoin?

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Administer one of the following agents intravenously; “high dose phenytoin”, phenobarbital, valproic acid, midazolam infusion, pentobarbital infusion, and / or propofol infusion

Implications: Despite many recommendations in text books and from consensus panels, there are no comparative trials supporting the use of any one third line agent over another in status epilepticus. It is known that the longer a seizure persists, the harder it is to control; it is also known that seizures that do not stop with a benzodiazepine have only a small chance of being controlled with a phenytoin and these patients generally have a serious underlying etiology of their seizure. Recommendations for a second half loading dose of phenytoin or fosphenytoin are based on case series, as are recommendations for barbiturates, propofol, and benzodiazepine drips. There are no outcome studies that can

be used to reliably compare the benefit of one agent over another. The advantage of barbiturate and propofol infusions is that they both will demonstrate neuronal burst suppression. However, these agents have potential side effects which require that the clinician be familiar with their use and to be practicing in an environment that allows for their safe administration.

When should EEG testing be performed in the ED?

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Consider an emergent EEG in patients suspected of being in nonconvulsive status epilepticus or in subtle convulsive status epilepticus; patients who have received a long acting paralytic, or who are in a drug-induced coma.

Implications: Several studies have demonstrated that approximately 10% of patients treated for status epilepticus who appear to have stopped seizing continue to be in status at a neuronal level (nonconvulsive status) when an EEG is done. There is some evidence that untreated nonconvulsive status epilepticus is associated with poorer outcomes however the evidence is weak and insufficient to drive high level recommendations for emergent EEGs.

Impact

The seizure clinical policy addresses a number of issues relevant to clinical care. Though all of the recommendations are at a “B” or “C” level, they nonetheless are recommendations based on the best available evidence; as such, they provide a strategy in management that can assist clinical decision making. The recommendation for blood testing should minimize unnecessary tests such as phosphate and magnesium levels that have not been shown useful, add to expense, and may add to delays in making a disposition. The recommendation for neuroimaging supports outpatient management in select cases which again can improve ED efficiency. The recommendations regarding admission and initiation of an antiepileptic medication may improve hospital bed utilization and avoid unnecessary use of medications with their potential side effects. Issues related to managing subtherapeutic phenytoin levels are encountered on a daily basis in most EDs and the recommendation in this policy should provide support for oral or IM loading which should help decompress some EDs which are overcrowded and have limited numbers of monitored beds. The recommendations on second and third line interventions for status epilepticus call attention to the paucity of helpful literature on this emergent condition but provides guidance on the alternatives that the emergency physician can choose from and tailor to the setting. Finally the recommendation on emergent EEG monitoring calls attention to the existence of persisting nonconvulsive status in patients who were treated for convulsive status and the importance of considering this diagnosis in patients with prolonged postictal states.

Conclusion

Critical questions with evidence based answers help with clinical decision making. The evidence based approach requires a careful analysis of the methodology used in a study's design and recommendations are generated based on the strength of the evidence. The seizure policy demonstrates that there are few good studies in the literature and much of what we do is based on "experience" or "opinion". It becomes clear from reading the literature that few studies have defined outcome measures and patients studied are often too heterogeneous to allow for clear conclusions. The benefit of an evidence based approach to developing clinical policies is that it not only helps to counter misinformation from "experts", but it also identifies areas in need of future research. There needs to be a good prospective study on laboratory testing in patients with a first time seizure who have no co-morbidities; there needs to be a prospective study on the outcome of patients with a new onset seizure and a normal exam who have a neuroimaging study in the ED versus as an outpatient. There needs to be a well designed prospective study on seizure recurrence in patients treated in the ED. Studies are also needed to investigate the outcome of patients loaded with phenytoin orally versus IM or IV. Better studies need to be done to help guide the choice of second and third line AEDs for patients in status. Finally, prospective studies on the diagnosis and outcomes of patients in nonconvulsive status need to be performed. Emergency medicine is on the forefront of managing acute seizures and status epilepticus and there exists many opportunities to perform important research that can improve patient care.

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Andy Jagoda, MD, FACEP
March 19, 2004

Andy.Jagoda@msnyuhealth.org
www.FERNE.org

2004_acep_emc_jagoda_szclinpol_final.doc