OPTIMAL PREHOSPITAL MANAGEMENT OF SEIZURE EMERGENCIES

OVERVIEW

In this program, the faculty will review and provide updates on the guidelines for managing seizure emergencies and address how participants can reduce the barriers to prehospital treatment through the use of Seizure Action Plans. They also will discuss recent clinical trials that may improve caregiver acceptance of rescue medications for status epilepticus. In addition, the faculty will address the similarities and differences in managing seizure emergencies for pediatric and adult patients.

TARGET AUDIENCE

This activity is intended for adult and pediatric neurologists, primary care and osteopathic physicians, pediatricians, neurology nurses, school nurses, advance practice providers, and all other healthcare providers who interact with patients who have epilepsy.

LEARNING OBJECTIVES

- Identify strategies that will improve the prehospital management of seizure emergencies by caregivers
- Use current evidence and clinical trial data to select an appropriate treatment to arrest a cluster of repetitive seizures
- Engage patients and caregivers to develop an effective Seizure Action Plan

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Editor's Note: This is a transcript of the virtual satellite symposium presented at the AES conference on December 6, 2020.

INTRODUCTION

I am Greg Cascino, and it is my honor and privilege to participate in a satellite symposium of the annual meeting of the American Epilepsy Society entitled *Optimal Prehospital Management of Seizure Emergencies*. I'd like to recognize our sponsoring institution, the Annenberg Center for Health Sciences, and also indicate that this important, educational activity was supported by an educational grant from Neurelis.

This is an extremely important topic, seizure emergencies, even in these unprecedented times of having used Zoom presentations to conduct the annual meeting. During this presentation, there will be a short interactive poll. Please click on your answers when they show on your screen. Use the Q&A button anytime during the meeting to submit questions, and we will have the opportunity at the conclusion of this program to discuss the questions and answers.

I would like for you to meet our excellent faculty who's participating in this program, Dr. Juliann Paolicchi and Ms. Lucretia Long. They will discuss several important aspects of seizure emergencies, including childhood epilepsy, as well as in the office practice.

We will have a series of videos White Board Animations that will be presented, depicting the caregiver and the patient perspective and some of the barriers they face that impact seizure emergencies and how they can be handled. At the end of the video, there will be 3 questions. We would for like you to answer these so we can see your thoughts on prehospital care and how it can be improved.

White Board Animation

Narrator: Successfully treating seizure emergencies depends on what happens before the patient has a seizure and what caregivers do when a patient has a seizure. Let's look at some of the barriers that get in the way of the optimal management of seizure emergencies. Jesse's been diagnosed with epilepsy because he's had several unprovoked seizures. Let's watch to see how this scenario unravels.

Doctor: If a seizure doesn't stop on its own, or you keep having one seizure after another, you will need treatment to stop them. The prescription is for those seizures. Here's how to use it. Any questions?

Caregiver: I think we understand what to do.

Coach: What's happening?

Caregiver: I think we have medication for this. Did we bring it? Should I wait to give him his medication?

Coach: This doesn't look right. Do you want me to call for an ambulance?

Paramedic: How long has this seizure lasted?

Caregiver: 10 minutes.

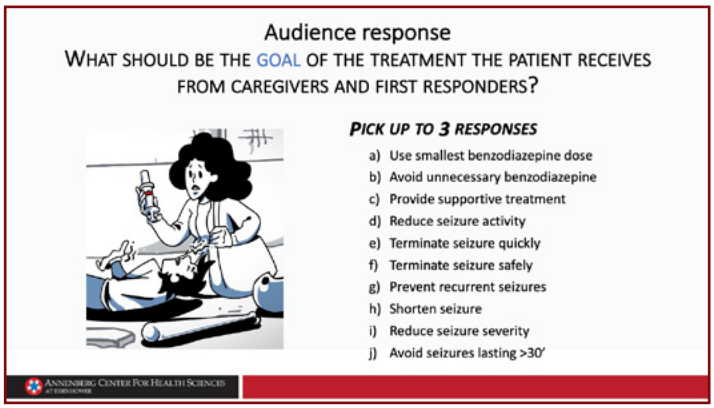
Paramedic: Should we use his rescue medication or try an IV?

Caregiver: Is it working?

Narrator: This case has illustrated many of the barriers to optimal prehospital management of the patient who is status epilepticus. Think about when this patient had a seizure at the softball game. What should be the goal of the treatment he received from caregivers and first responders?

Greg Casino, MD

Please pick up to 3 responses. What should be the goal of the treatment the patient receives from caregivers and the first responders?

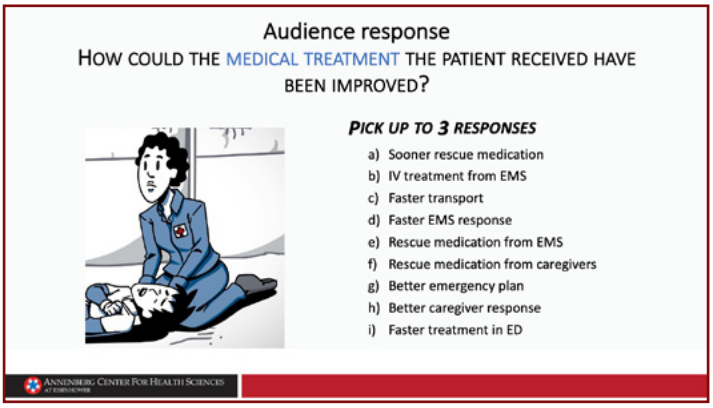


White Board Animation

Now, just think about how the scene unfolded when the patient was having a seizure at the softball game. How could the medical treatment he received have been improved?

Greg Casino, MD

So how could the medical treatment the patient received have been improved? Again, please select 3 choices. This is invaluable to have the thoughts and comments of the participants before the formal lectures.



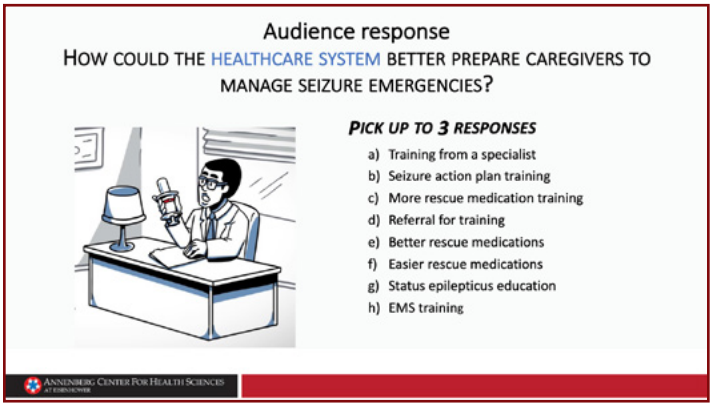
White Board Animation

And finally, think just about the patient's last appointment. How could the healthcare system have better prepared the caregiver for this seizure emergency?

Greg Casino, MD

Please select up to 3 choices.

The program overview will include a number of topics related to seizure emergencies. We'll focus on both adult and pediatric issues, including the advances in prehospital management of patients who develop acute seizure activity and have seizure emergencies. Importantly, we'll focus on caregivers and healthcare providers and discuss optimal management of seizure emergencies that should be provided. Key points summary will be included in each of the talks, and at the conclusion we'll have a faculty Q&A panel. My remarks were restricted to the care and management of adult patients with seizure emergencies.



STATUS EPILEPTICUS DISEASE BURDEN

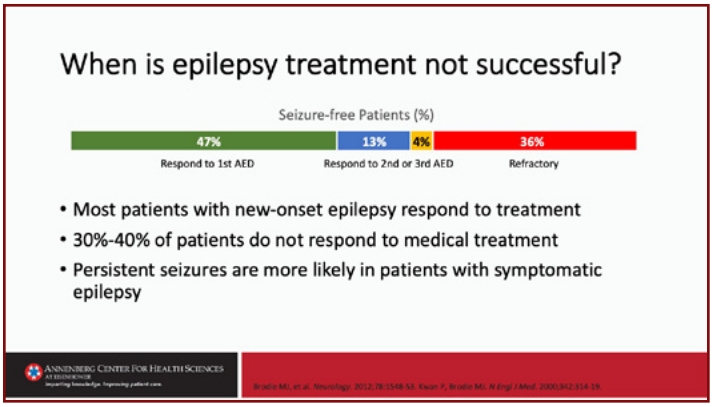
Greg Casino, MD

We know that epilepsy is a very common neurologic disorder. The Institute of Medicine report in 2012 outlined that 1 in 26 Americans will develop a seizure disorder during their lifetime. Nearly 10% of Americans will have 1 or more seizures. We know that epilepsy appears to be twice the prevalence of autism spectrum disorders, multiple sclerosis, and Parkinson's disease combined. If we use the new definition of epilepsy by the International League Against Epilepsy, which may include individuals with a single seizure who have biomarkers indicating increased seizure recurrence, then certainly the incidence is well over 200,000 individuals per year in the United States, making epilepsy one of those common chronic neurologic disorders.

The goal of treating the patient with a seizure disorder is really 3-fold. First to render the patient seizure-free, no seizures. Second to avoid any adverse effect associated with the treatment, no side effects. And third is to allow the patient to become a participating and productive member of our society, meaning no lifestyle limitations. The goals are no seizures, no side effects, no lifestyle limitations. This is the goal whether the patient has a single seizure, a seizure disorder, a seizure emergency, or status epilepticus.

The burden of epilepsy goes well beyond seizure activity, and we know that patients may have significant morbidity that adversely affects their quality of life. This may include comorbid conditions such as a mood disorder with depression, anxiety, [affecting] perhaps a quarter to a half of patients with seizures. Issues regarding metabolic bone disease and balance difficulties that can predispose to fractures, significant neurocognitive disorders that may embarrass the individual's quality of life, and of course, mortality, and mortality may relate to physical trauma, but not uncommonly the important causes of death in patients who have seizure disorders are status epilepticus or seizure emergencies and sudden unexplained death in epilepsy. Perhaps 25,000 to 50,000 Americans die each year of seizure-related complications, some of which are the seizure emergencies that we'll be discussing.

We know that the most effective antiseizure medication is the first drug; use it very wisely. Appropriately used, perhaps half of the patients will be rendered seizure-free on initial therapy, but unfortunately, despite receiving multiple antiseizure medications, there are individuals who have drug-resistant or treatment-resistant epilepsy. This may be a third of patients who have seizure disorders, and we know the likelihood of being rendered seizure-free after multiple antiseizure medications are utilized is very small. Perhaps 36% of patients have a refractory or pharmacoresistant seizure disorder that adversely affects the quality of life of the individuals. Their seizures may be physically, medically, and socially disabling.



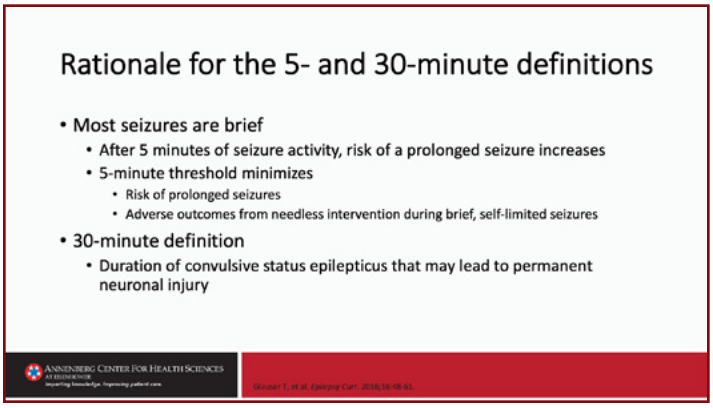
The risk factors associated with the development of drug-resistant epilepsy include those who have underlying pathologic substrates or symptomatic seizure disorders. But suffice it to say a significant percent of the patients who have a seizure disorder will have drug-resistant epilepsy and may be predisposed to developing seizure emergencies.

Let us define seizure emergencies, and these are the traditional definitions that you'll find very commonly used, especially prior to 2016, when the American Epilepsy Society evidence-based guidelines were produced. Brief seizures, less than 5 minutes. We know from studies that have been done in epilepsy monitoring units that most individuals who have generalized tonic-clonic seizures, the seizure duration will be less than 1-2 minutes in duration. Excellent studies have shown that the vast majority of patients' seizures will terminate spontaneously in less than 5 minutes. A generalized tonic-clonic seizure that goes beyond 2-3 minutes should be a cause of significant concern and warrant appropriate investigation and treatment.

The traditional definition of status epilepticus has been 30 minutes, and we learned on Friday at the Judith Hoyer lecture where that number came from. Much of it was related to morbidity, including animal models of status epilepticus, where pathologic changes were identified in animals that had

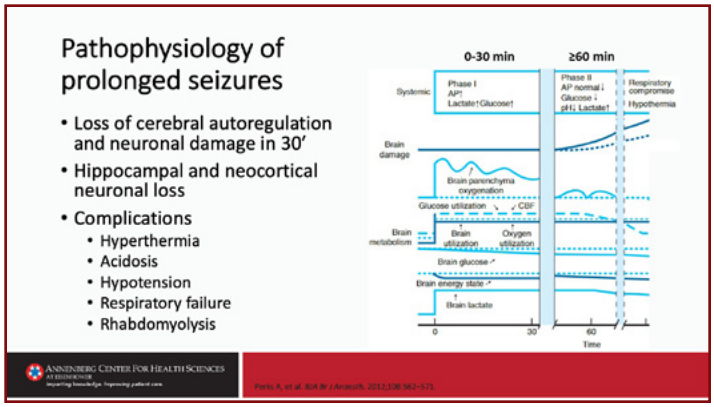
seized longer than 30 minutes in duration. The traditional definition has been status epilepticus is 30 minutes or longer because, at 30 minutes, they may develop significant morbidity with continuous seizure activity and may be predisposed to having neuronal damage. The operational definition of status epilepticus utilized by the American Epilepsy Society, and other organizations, has suggested that we should be discussing treatment at 5 minutes or earlier in patients, especially certain seizure types like generalized tonic-clonic.

A prolonged seizure is that interval between 5 minutes and 30 minutes. Patients can have acute repetitive seizures, and this can be a cause of concern, including cluster seizures, where their mental status is preserved between seizures, but they have an increase in seizure tendency. They have an increased risk of prolonged seizures. These may be physically and socially disabling and are a common concern for patients who have pharmacoresistant seizures.



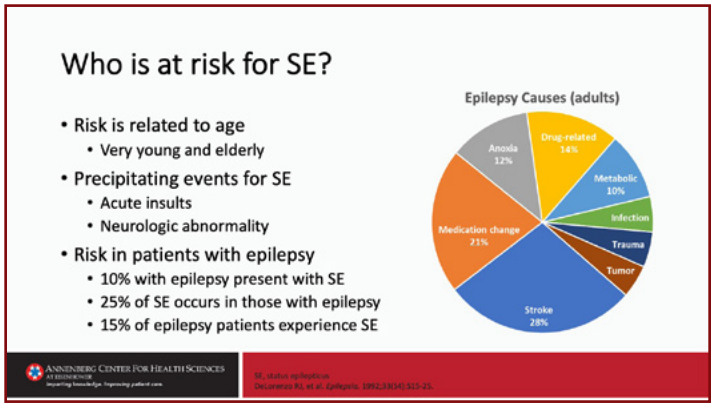
These are the definitions that are oftentimes used in discussing the management of seizure emergencies, but the operational definition is now 5 minutes or beyond, especially for generalized tonic-clonic seizures, and the rationale for the 5 and 30 minute definitions, number one, and it really depends on the unique seizure type. We know that the generalized tonic-clonic seizures tend to be brief, like 1-2 minutes, whereas patients who have focal seizures that may be more prolonged at 5 minutes. There is a significant risk that a prolonged seizure will continue. This is a very appropriate threshold to consider the risk of prolonged seizures and intervention. And certainly even shorter than 5 minutes, as I mentioned, at 2 or 3 minutes, patients should be considered for appropriate intervention. At 30 minutes, they're at significant risk for permanent neuronal injury and adverse effects, including hemodynamic changes that occur. We certainly do not want patients to be observed for 29 minutes prior to instituting appropriate therapy.

Now the pathophysiology of prolonged seizures is quite interesting, and this came, really, from 2 sources, 1 from animal models and the work of Brian Meldrum using baboons, where patients were observed in these animal models of the baboons with prolonged seizure activity and then were sacrificed, looking for pathologic changes. And the second has been patients who have had refractory forms of status epilepticus, and well before 30 minutes, but at 30 minutes and beyond there, significant dynamic change that occur that cause loss of cerebral autoregulation and significant risks for neuronal damage. And very susceptible areas include the hippocampal

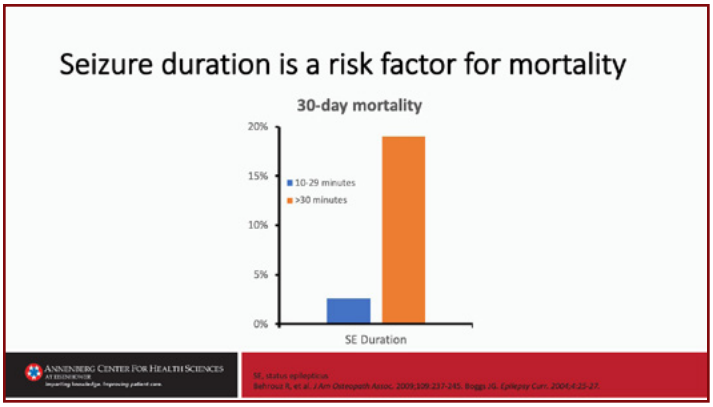


formations and the medial temporal lobe probably from excitotoxicity. This may cause a variety of changes, including being very proconvulsant, including neuronal loss. The change in the first 30 minutes tend to be beneficial: hypertension, increased cerebral blood flow. Decompensation then occurs at 30 minutes, and there's additional physiological alterations with hyperthermia, acidosis, hypotension, respiratory failure, rhabdomyolysis. If you look at the brain specifically beyond 30 minutes, there may be hypoglycemia, reduced cerebral blood flow. So, these dynamic changes are very important. They predict significant adverse effects, including morbidity, mortality, and continued seizure activity. Prior to 30 minutes, you'd like the investigations of the treatment to be instituted and effectively to terminate seizure activity.

There is no good classification for status epilepticus, and the terminology changes. It is different than seizure types, where we discussed focal-impaired awareness seizures or focal seizures evolving into bilateral convulsive tonic-clonic. And this is probably as reasonable as any classification that has been used: convulsive vs nonconvulsive, convulsive being repeated, generalized, tonic-clonic seizures, or myoclonic, where there's abnormal motor activity. Nonconvulsive, which could be subtle forms of status epilepticus, spike-wave-stupor. There's a variety of different names that are utilized where there is an alteration in consciousness with a correspondent EEG pattern. And then patients may have repeated focal seizures, and these can be focal aware seizures or focal impaired-awareness seizures, depending on the clinical state.



Who is at risk for status epilepticus, and as is true of the patients who have seizure disorders, the risks are the very young and the very old, and we know that the risk is anywhere from zero to 99 years of age. Patients who are at risk for



status epilepticus may have acute neurologic or medical insults that are proconvulsant. They may have pre-existing neurologic abnormalities. If you look at patients who have status epilepticus, 10% of patients with epilepsy will present with status epilepticus and 25% of status epilepticus occurs in those with epilepsy. A significant number of patients who have seizure emergencies may not have an underlying seizure disorder that has been diagnosed, and we can anticipate that 15% of patients with epilepsy during their lifetime will experience status epilepticus.

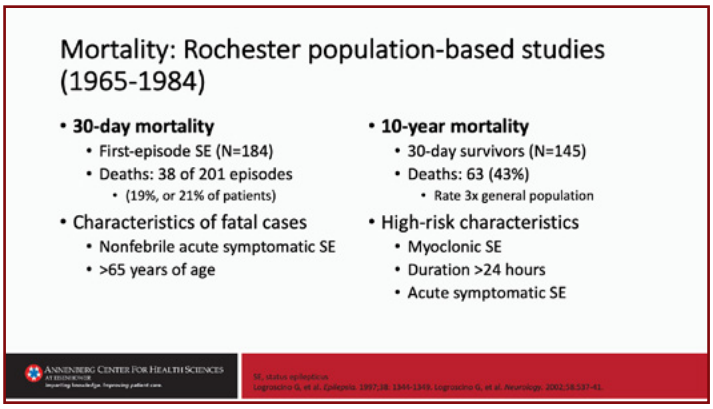
This is from Dr. DeLorenzo's work, and excellent series, of patients who've had status epilepticus. You can see here are the symptomatic etiologies in adult patients. Important to look at the patient population. You can see that medication change, that would be antiseizure medication, is appropriate, but there's other corresponding neurologic disorders, including stroke.

The mortality following status epilepticus is a significant concern. This is a potentially fatal medical condition, and we need to emphasize that both in terms of evaluation and treatment, especially when there are concerns on the part of physicians regarding treating patients because of worries about adverse effects. Perhaps 55,000 deaths per year. The overall incidence of status epilepticus is somewhere between 100 and 150,000. We know that at least 25% of patients with status epilepticus have nonconvulsive seizure types. Undoubtedly, this is an underestimate because many of these patients may be called metabolic encephalopathy or confusional states. If they did not have EEG recordings, they would not be diagnosed.

The risk may be related to a number of factors, including what type of seizure they have. Is it generalized tonic-clonic seizure? Is it focal aware seizure? And the underlying etiology. Patient age is important. Again, a bimodal mortality distribution. Overall, if you look at the risk of death, mortality in status epilepticus in adults, the older, the higher the mortality. 50% of our patients over 80 years of age; 38 over 60 years of age; 26 overall.

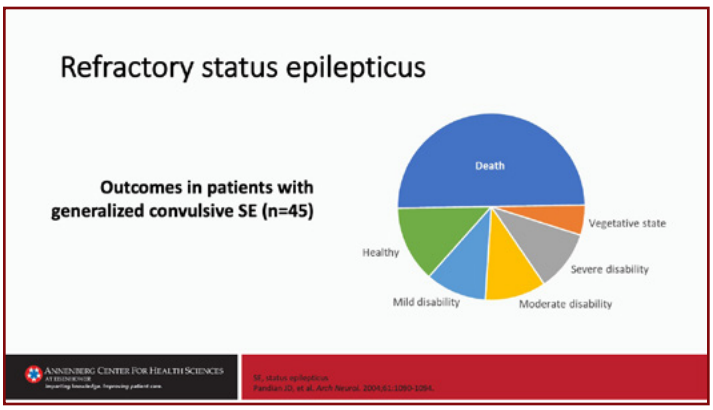
And, finally seizure duration is an important factor, and it does appear the longer the seizure activity occurs in patients with status epilepticus, the more difficult it is to control the seizure activity to avoid seizure recurrence and reduce neurologic morbidity.

This slide points out specifically the importance of seizure duration. This is a 30-day mortality, so 1 month, and you can see in 10 to 29 minutes what the mortality would be as compared to over 30 minutes. And again, the operational definition as set aside by the appropriate organizations, including the American Epilepsy Society, is that intervention should begin at 5 minutes, and patients should be appropriately managed well before a 30-minute mark, and an important reason is to reduce the risk for mortality.



This is from the Rochester Epidemiology Project. We looked at 30-day mortality and 10-year mortality. 30-day this patient presents with status epilepticus. These were a consecutive population-based study, 184 patients. We found that the mortality was 21% of the patients died. That number probably has not changed in the time period from when this study was conducted, which was 1965 to 1984. Characteristics of fatal cases were older patients over 65 and patients who had acute symptomatic seizure activity that was not febrile seizure in childhood. What was interesting is how do these patients do at 10 years? Notice almost half the patients are dead, 43%, 3 times the general population. So, these were the 30-day survivors who were followed out.

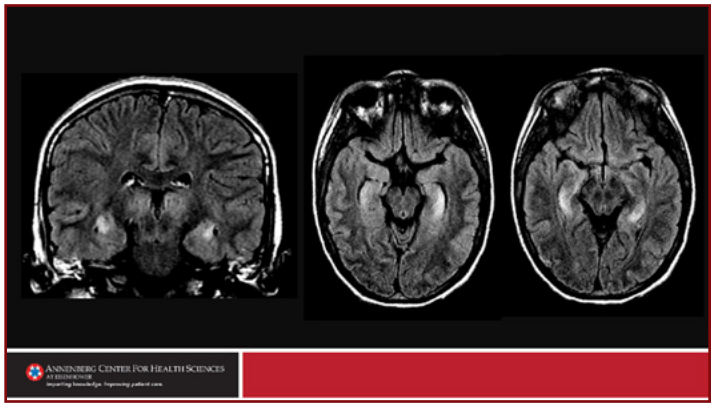
High-risk characteristics may be that they had prolonged duration of seizure activity initially. They had acute symptomatic status epilepticus, and they may have had myoclonic status epilepticus, and perhaps that was associated with anoxic myoclonus. So not only does status have a high mortality initially, but if you look at the long-term consequences, there's a significant risk at 10 years. What about refractory status epilepticus? This was a study that I participated in. It was done specifically looking at patients who had long-term EEG monitoring in the neurocritical care unit, and a component of the patient population had generalized convulsive status epilepticus. By definition, for this study, they failed benzodiazepines and phenytoin patients were under continuous EEG monitoring, and basically, if you look at that



pie, about 50% of the patients died. The percentage who are healthy and well is very small. A significant number had major morbidity. Again, pointing out in a very select population, neurocritical care, continuous EEG monitoring, and drug resistant status epilepticus, very high mortality.

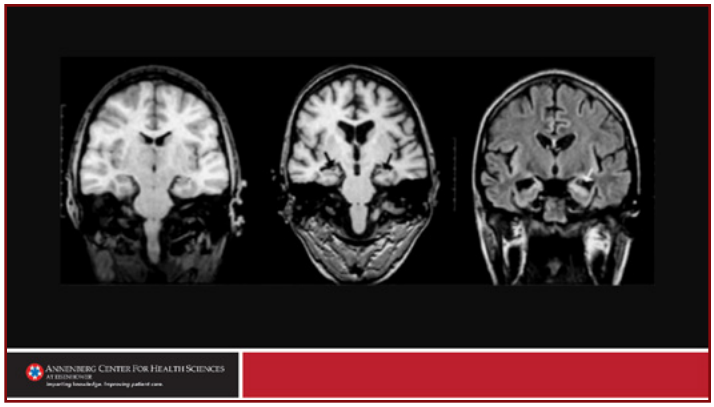
In the Rochester population-based studies, if you combine mortality with other risks of morbidity, including did they have recurrence of status epilepticus and did they subsequently develop epilepsy, you can see the 30-day mortality, the 10-year mortality, which we discussed. Up to 19% had a recurrence of status epilepticus, and 26% who did not have a seizure disorder developed epilepsy. So there are important morbidity and mortalities looked at even in population-based studies, and this is very important because one of the things we'd like to do with the initial treatment is to minimize both morbidity and mortality associated with seizure emergencies.

Now we can look at MRI findings in acute seizure emergencies without doing autopsies and having pathologic information from animal models, and that of course is by using high resolution MRI head seizure protocols. There are 2 big changes that we see in status epilepticus. The first is the peri-ictal MRI abnormalities. These often may be cortical with enhancement or increased sensitivity for T2 and FLAIR signal. They may have a corresponding ipsilateral hippocampal enlargement. Patients may have transient FLAIR or T2 changes, and that's the acute change. The more chronic change we may see may be evidence for atrophy with hippocampal atrophy and signal change and diffuse cortical atrophy. So initially they may have a focally increased T2 signal. They may have a reduced ADC, reflecting both cytotoxic and vasogenic edema, and these patients can develop secondary hippocampal sclerosis, which is not always ipsilateral to the area of seizure onset.

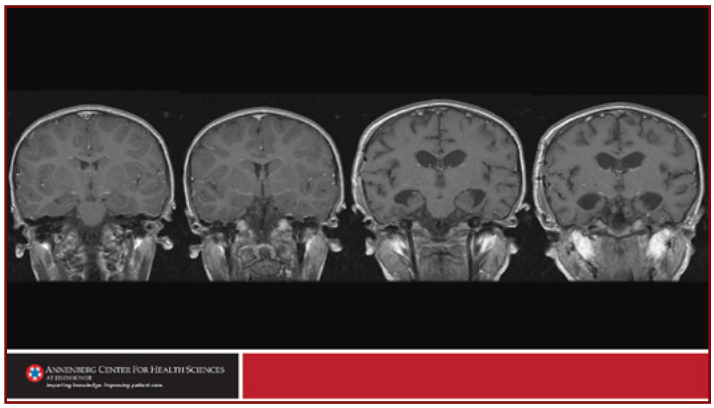


This is a patient who had a status epilepticus prolonged refractory to treatment. Patient was on third line and fourth line agents to try to control seizure activity. Had constant video EEG monitoring. What you can see here on the FLAIR studies in multiple planes of imaging is an increased signal in the region of the hippocampus. The hippocampus was enlarged and swollen. There was no pathologic enhancement. This patient went on to develop significant bilateral hippocampal atrophy and did have neurocognitive changes.

This is 1 patient that points out the dynamic change that may occur, using MRI in patients who have status epilepticus. The scan on the left was the premorbid scan when the patient was diagnosed with status epilepticus. It was a normal MRI.



Within several months—and this patient did have a prolonged episode of status epilepticus that required third line treatment agents—the patient developed bilateral hippocampal atrophy and diffuse cortical atrophy. And you see on the third scan on the right, several months after the initial presentation, the patient has severe bilateral mesial temporal sclerosis. There's a signal change in FLAIR. There was corresponding atrophy. Patient had bitemporal spikes, had a drug-resistant focal seizure disorder and significant cognitive impairment. You can very nicely see on a series of MRI in 1 patient sequentially, the pathologic change that may occur as a consequence of status epilepticus.

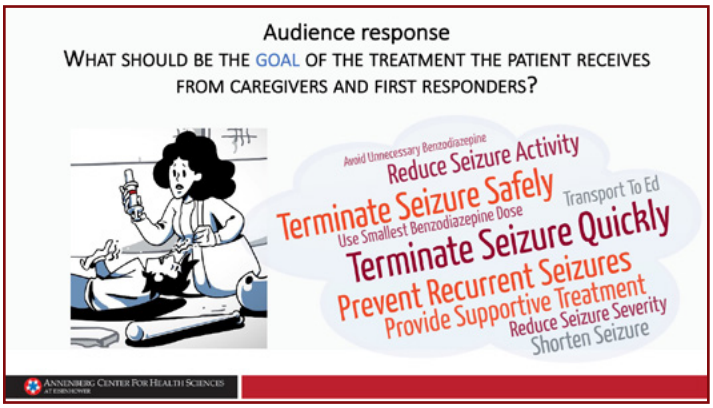


This is from a young child who presented with nonconvulsive status epilepticus, drug-resistant. Multiple treatment options were considered. The patient was refractory. The 2 scans on the left are at presentation. The 2 scans on the right are approximately 1-2 years following the presentation of status epilepticus, and you can unfortunately see the consequences. There is diffuse cortical atrophy that is most striking in the region of the hippocampal formations. There is hydrocephalus ex vacuole because of the amount of cortical loss as well. The child did have appropriate neurologic problems. So again, you can see on MRI the change that may occur relevant to seizure activity.

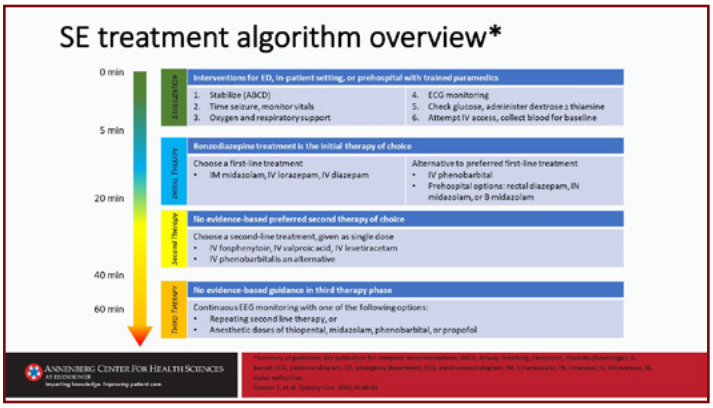
GUIDELINES FOR MANAGING STATUS EPILEPTICUS

This is the audience response on what should be the goal of the treatment the patient receives from caregivers and first responders. And in the larger letters are the changes that are most important to emphasize in this material.

The American Epilepsy Society does have evidence-based guidelines. You all are familiar with this. The goal of therapy is rapid termination of both clinical and electrical seizure activity, and timing is an appropriate parameter to be concerned about because it reduces the risk of mortality and morbidity.



What are the pitfalls in achieving appropriate treatment? Basic critical care and emergency principles apply and are widely accepted, but pharmacologic management varies. Patients may not receive adequate treatment because there is concern about a therapy aimed at reducing rather than terminating seizures. Inefficient therapies are used such as sedatives or paralytics, and insufficient doses of medication are used. Prehospital care is oftentimes neglected, and acute rescue medication is underutilized or not utilized at all, and these are important concerns before the patient arrives in the emergency department.



This is the treatment algorithm that you're all very familiar with. This has been supported by multiple organizations. Time 0-5 is appropriate for the patient to receive the appropriate medical care that they require, the ABCs, the oxygen respiratory support. We need to monitor the patient with EKG monitoring, trying to attempt intravenous access. The important issues to maintain the patient's life at this point with a serious medical concern. The second treatment is a benzodiazepine. First line therapy may be intramuscular midazolam, intravenous lorazepam, intravenous diazepam. There are alternatives that can be used.

The third line therapy, if the patient continues to have seizure activity, it would be to use a second line treatment. Fosphenytoin, valproic acid, levetiracetam would be the most commonly considered. And then finally, if the patient requires third line therapy, they should undergo continuous EEG monitoring, and as we'll discuss, maybe considered for an anesthetic dose of medication. On this list is thiopental, midazolam, phenobarbital, or propofol. This is the algorithm that we should all be very familiar with and constantly educate our colleagues on in terms of the management of these patients, especially that 0-5 minutes and the 5-20 minutes. That's the critical time for many of these patients.

There have been excellent studies that have been performed that have given us some information, and these are evidence-based medicine studies, randomized controlled trials on what is the preferred therapy. The 1998 VA study that we're all familiar with, approximately 384 patients had overt generalized convulsive status epilepticus. There were 4 treatment arms: lorazepam, diazepam followed by phenytoin, phenobarbital, or phenytoin alone. The study did demonstrate the superiority of IV lorazepam over IV phenytoin. The others were equally efficacious. The 2001 Alldredge trial was important because there was some concern, is a lower benzodiazepine such as lorazepam or diazepam preferred to placebo prehospital? It was clearly demonstrated that the benzodiazepines were more effective than placebo. And there was evidence that lorazepam may be preferred to diazepam therapy. The RAMPART study, you're all familiar with, which is a critical study of 893 patients, a rapid anticonvulsive medication prior to arrival for therapy. The study was looking at IM midazolam and IV lorazepam, and they use an autoinjector to give the midazolam. And they demonstrated that midazolam was more effective because patients may not have vascular access, but benzodiazepines and this would both be used, and this was a noninferiority study. So, IM midazolam would be an alternative therapy.

The adverse effects of the medications and the treatments need to be considered. Physicians are well aware that the fact that the treatment-emergent adverse effects may be respiratory and cardiac, depending on the medications. Importantly, respiratory depression was lower in patients receiving benzodiazepines than placebo. And that's very important. And the Alldredge study showed that, and that's because status epilepticus can cause respiratory depression and hemodynamic consequences. There's no substantial difference between benzodiazepines and the phenobarbital in the instance of cardiorespiratory adverse effects.

Initial phase for adult patients in terms of management, if you did not have an intravenous access, intramuscular midazolam would be preferred. There is no significant difference between intravenous lorazepam and diazepam. Benzodiazepines would be preferred over phenobarbital because of the slower admission rate for the barbiturate. And obviously, there's new approvals as well.

The second line therapy phase highlights are also important, and these are roughly equivalent. When you get to the first line therapy and you move to the second line, then the VA study in 1998 showed that these drugs here were all equal equivalent treatments for the management of status.

Finally, the Established Status Epilepticus Treatment Trial, which was very important, completed recently, published in *New England Journal of Medicine* in 2019, 384 patients

divided into 3 groups, randomized control trial. Good news and bad news. The good news is we now have data to show which drugs may be effective. Bad news is they were all equally effective, which was less than 50%. Levetiracetam, fosphenytoin and valproate. One could argue that any of these drugs would be a preferred drug in an individual patient. There was a similar incidence with all treatments in terms of effectiveness, hypotension, and need for endotracheal intubation was higher in fosphenytoin but not significant. Deaths were higher in levetiracetam, but not significant. This would be an appropriate treatment options to consider, but we still have over half the patients here not being effectively treated.

The TRENDS trial looked specifically at lacosamide vs fosphenytoin. And this is in patients with nonconvulsive status epilepticus. There was a total of 74 patients. They were divided up between the 2 groups. And they found that the 2 drugs were very similar in terms of the efficacy. Again, it was a noninferiority type of study, and lacosamide would be a preferred agent in selected patients as well.

That brings us to the end, which is the third phase. And now we have really no evidence-based medicine to guide us. We know patients at this point have a much higher risk of morbidity and mortality, and maybe continued status epilepticus or recurrence of seizure activity. Certainly by the time the patient reaches this point in 40 minutes, you should have the patient be in an appropriate neurocritical care unit or receiving appropriate ICU care.

Treatment options here may include anesthetic doses of thiopenal, midazolam, pentobarbital or propofol. These patients at this point would be intubated. We would require emergency and ICU care and should be under continuous EEG monitoring. So, as we pause in the adults, before we move on to the children, the care and management of the adult patient with seizure emergencies, we not only need to look at terminating seizure activity but trying to restore the quality of life of the individual so that these patients can go on and continue to be participating members of our society. And now it is my pleasure to introduce my colleague, Dr. Juliann Paolicchi, who will discuss the pediatric aspects regarding the management of seizure emergencies.

PEDIATRIC PERSPECTIVE ON CARE FOR SEIZURE EMERGENCIES

Juliann M. Paolicchi, MD

Some things are very important for us to review, and Dr. Shinnar did a marvelous job, of course, at the Hoyer Lecture, reviewing some of the studies that go into status epilepticus. The nice thing about the video meeting is if you missed that talk, I would strongly recommend, of course, going back to review it. In it, he felt that the pathophysiological underpinnings of the treatment of status epilepticus are really basically the same in children and adults. And I'm going to be reviewing some of the same studies that Dr. Cascino showed us in terms of the outcomes for children. And as you'll see, they are very similar. So why do we have to have a separate talk in children?

Couple of reasons. Of course, the first is, as Dr. Shinnar mentioned, time equals brain. And Dr. Cascino's talk points out how important it is for intervention early in order to protect as much brain as we can from the toxicity related to the excitotoxicity of status epilepticus. But in the case of children, this is developing brain. In general, the brain is not as well localized in terms of function. It can have far more outreaching effects. And the child, as comparted to the adult, has a long time of life in which to live with some of the effects of the status epilepticus. In addition, we saw that one of the main outcome variables of status epilepticus is etiology. And we know that the etiologies of pediatric epilepsy in general are far more varied than the adults in the adult epilepsy group. Of course, MTS is very common, cortical dysplasias, secondary vascular. And as we learned, very importantly, in the annual meeting course today, also looking for genetic causes. But in pediatric epilepsy, we see a wide range of presentations showing with status epilepticus. Febrile seizures with febrile status epilepticus is very common, cortical dysplasias, infection-related hypoxia, genetic congenital malformations, intrauterine and postnatal insults, anoxic injuries, vascular malformations. All of these can be presenting as status epilepticus in the young children.

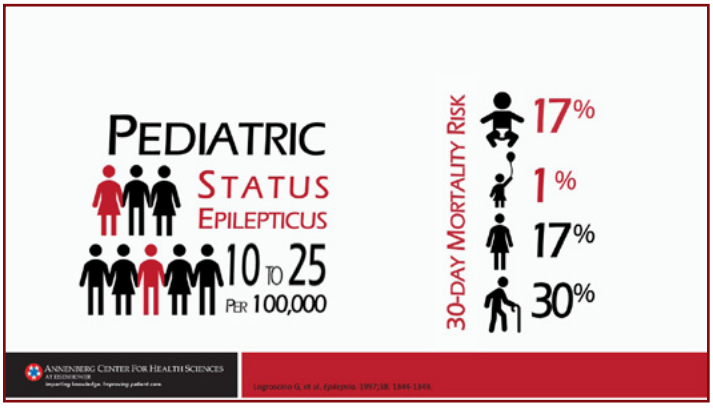
In addition, several seizure syndromes underlying the epileptic encephalopathies are known for their high predilection to status epilepticus. This would include Dravet syndrome, where we see status epilepticus in approximately 90% of our patients. Angelman's often presents with a myoclonic status epilepticus, Rasmussen's, Sturge-Weber and Lennox-Gastaut patients can present, about 50% to 75% of patients, with a nonconvulsive status epilepticus. So we have a high group of patients with ideologies very prone to status epilepticus presentations.

Other things to keep in mind in the treatment of children as compared to adults is that we have to dose for body weight, sometimes greater. And the dose for emergency treatment of diazepam in very young children is actually higher than children later on in life. And in addition, in terms of IV preparations, we can't simply give a standard dose of adult benzodiazepines to a very young child. There are specific medications that we need to have further precautions about. Propofol has been approved by the FDA for the treatment and use in children, however long-term and high-dose use of propofol can be toxic to mitochondria and cause significant adverse effects in children.

In addition, there is not as much direct clinical research in pediatric patients, which is why it's so important to discuss the research that we're going to review. Bioequivalent is not always equivalent, although often used for the approval of medications. And as I mentioned briefly, as in the case with diazepam, there can be very rapid ... sorry, metabolism in very young children requiring sometimes increased doses per weight.

The outcome of status epilepticus in pediatric patients is not a singular issue. It is a global issue. And I think the MRI cases that Dr. Cascino presented in a child really provide a very strong point for that. The 1-year recurrence after the first episode of convulsive status epilepticus is estimated to be 16%. The

percentage of recurrence within 4 years is 20%. It is actually quite high within that population. Fatalities within the UK and US, and we're going to be talking about breaking that down per age, is between 3% and 5%. But in other parts of the world—it's been studied in sub-Saharan Africa—it may be as high as 15%. Subsequent epilepsy, a quarter of patients. And that's again, a very significant proportion of children who are subsequently developing epilepsy. In addition, studies have shown that neurological, cognitive and behavioral impairments outside of the epilepsy can be detectable within 6 weeks of convulsive status epilepsy. And by 9 years follow-up, approximately a third of patients will have some neurological consequence to prolonged status epilepticus.

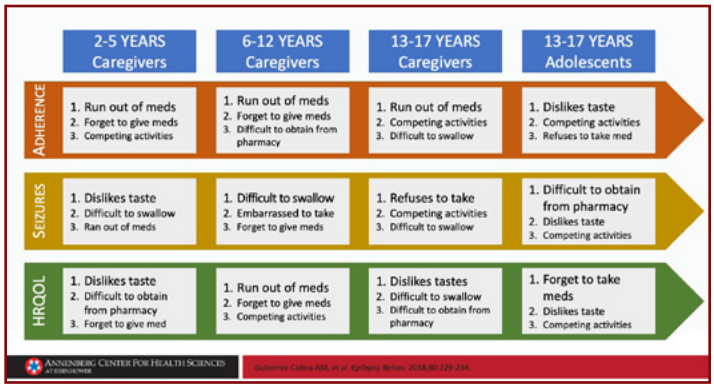


This just goes to emphasize that pediatric status epilepticus is not uncommon. 10-25 per 100,000 patients can present in status epilepticus. There is variability towards the incidence because of the definitions in various studies as to the inclusion of status epilepticus, and whether studies included only convulsive status epilepticus or the other forms, partial, recurrent, myoclonic, or nonconvulsive status epilepticus. About 10% of children with epilepsy will present for the very first time with convulsive status epilepticus.

And risk factors are age of presentation, in this case, early age of presentation. And as Dr. Cascino pointed out, there's a bimodal curve in terms of the incidence risk in the population. Symptomatic etiologies have a higher risk, as well as a history of prior status epilepticus. Again, increased risk, especially if the etiology is 1 of the syndromes I named in the epileptic encephalopathies that predispose a patient to status epilepticus.

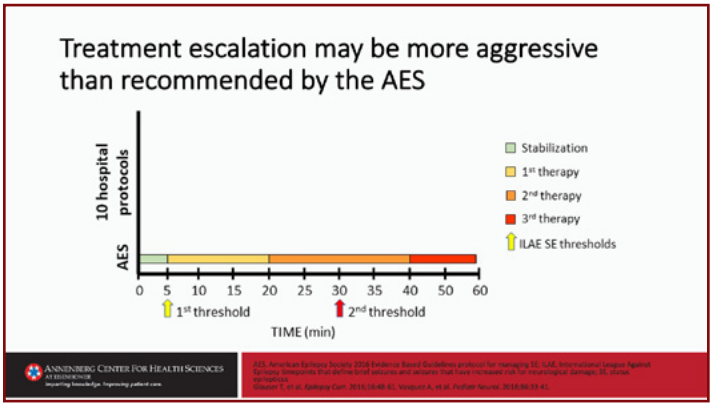
In terms of mortality, again, this is a significant feature. Although it's very low in children, towards young adults and adolescents it can increase to 17%. It is 17% in very young children. This also comes out of the Rochester cohort showing, again, a relationship with age-symptomatic status epilepticus, and recent work by Abend et al has shown a very high percentage of mortality associated with electrographic status epilepticus. About 25% of pediatric patients found to have continued electrical epileptic status epilepticus eventually went on to die, with an odds ratio of 2.42.

Part of this talk is to really mention what could we do to reduce some of that risk? The first is just for us to know, and certainly, we all do in our clinical practice, that about 15% of patients presenting with epilepsy will have some form of status epilepticus. And 1 of the most common, and

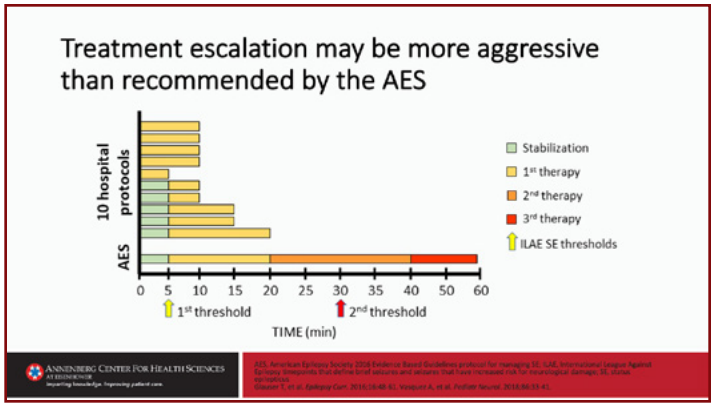


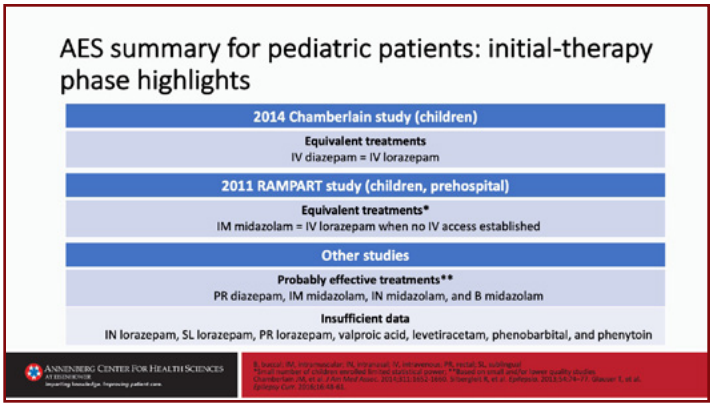
probably easily modifiable risks, is low or absent antiseizure medication doses or levels. The approach is also age-based. And the very interesting study by Gutierrez-Colina showed that there can be different reasons for adherence problems based on age. Most young children are taking formulations that are liquid. And so that taste, forgetting, swallowing, maybe higher in that age group, where later on, as a patient is approaching adolescence, more logistical issues, going to the pharmacy, having the medication, being too busy, may be those issues. A follow-up graph in the same paper showed the differences between adherence that led to seizures, that led to quality of life, and just the fact that it affected adherence overall. In terms of looking at the large yellow arrow, we can see that what could be leading to seizures really has a lot to do with formulation availability in young children, difficulty in swallowing, difficult taste. Later on, it has more, as we mentioned, of these logistical factors of getting to the pharmacy, being too busy and just not wanting to accept the need for continued antiseizure medication.

This is also, as Dr. Cascino mentioned, the timeline as recommended by the AES guideline for the treatment of status epilepticus. This is shown a timeframe on the x-axis. However, the pSERG group, the Status Epilepticus Research Group, evaluated the protocols at 10 hospitals utilized within the pSERG group, and they saw even a variation of the protocols used at the hospitals.



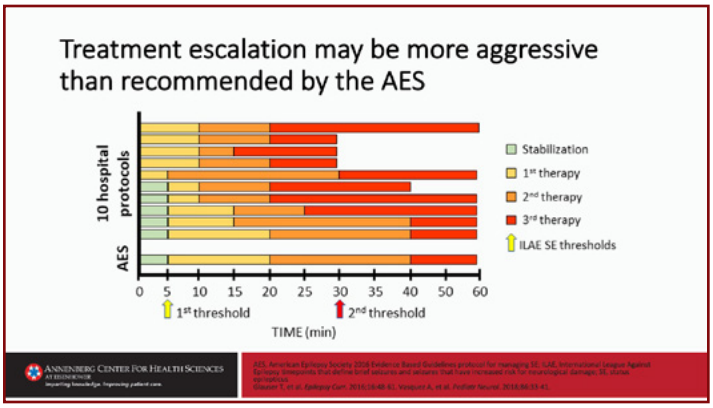
We can see in this edition, the protocols used at these hospitals and their variation. About 5 out of 10 hospitals for pediatrics recommended initial administration of benzodiazepine. And this factor comes out from just a clinical observation that many patients have been seizing prior to arriving. One may not know how long that time interval may be, and there was a transportation factor in bringing the child to the emergency





room. So, presenting in a seizure, 5 out of 10 went ahead and utilized first therapy.

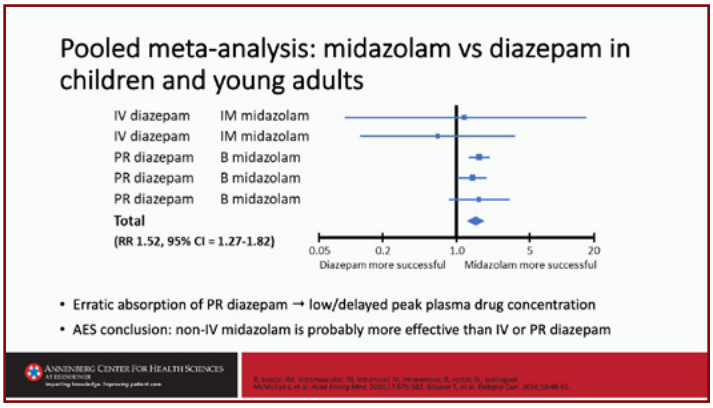
We can see building on that, that within 5-10 minutes, there was moving forward with the second therapy, so that 9 out of 10 hospitals in the pSERG group had a protocol for earlier administration of the second therapy, and 8 out of 10 for an earlier administration of the third-line therapy. But it seems to be a recognition of moving forward, treating this as soon as possible that's being utilized, at least in the protocols. But again, we're going to have to follow up on how well that's done in real life.



These are a review of some of the very same studies that Dr. Cascino reviewed in relationship to children, because children were added to many of these cohorts. In the first study, the Chamberlain study, this was a Class I study using 273 children in a double blind, randomized control trial. The use of IV diazepam was compared to the use of IV lorazepam, and there was not seen to be a difference. They were found to be equivalent. I do need to point out that the overall dose of the diazepam was 0.2 mg per kg. And again, in younger children, we have a tendency to use higher doses due to more rapid metabolism of the drug.

The next study was the RAMPART study, also mentioned. This was also a Class I study. It involved 120 children in the cohort. And IM midazolam vs IV lorazepam were compared. They are found to be effective, especially if there's no IV access available. However, true equivalency could not be stated because there were not statistically enough pediatric patients to make that determination. Other studies in other assortment of Class I through III studies have shown Class B evidence, probably effective treatments for other forms of emergency use of benzodiazepines, including PR diazepam, IM midazolam, intranasal midazolam, and buccal midazolam. However, there's insufficient data previously to discuss intranasal lorazepam, sublingual, per rectum lorazepam, and as well as utilizing the other medications, the antiseizure medications, in terms of first-line therapy.

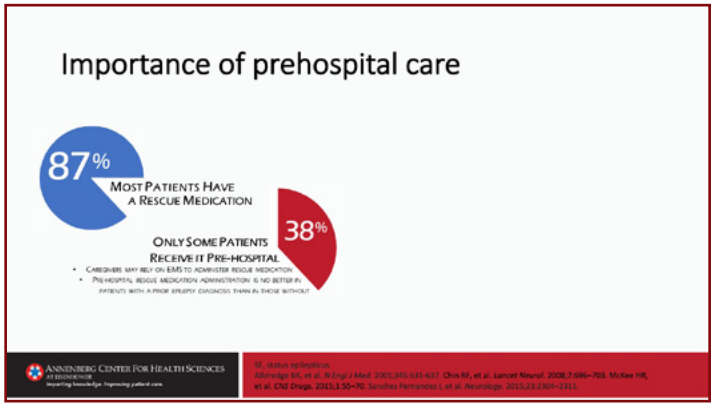
This study was a pooled analysis using a meta-analysis technique for 6 studies involving 774 children, so a large cohort. IV forms of diazepam and per rectum forms of diazepines vs non-IV forms of midazolam. The first 2 cases IM, and in the next 3 cases buccal. And equivalency, as you can see, was around the 1.0, although there was some variability, overall, non-IV midazolam was felt to be slightly more effective than either IV or per rectal diazepam. Especially in the case of per rectal diazepam, which has been our stalwart, especially in pediatric epilepsy for the home treatment of breakthrough seizures, clusters and status epilepticus, there seemed to be more variability due to a delayed peak plasma drug concentration, as well as administration of the medication.



In terms of other studies that we have looking at the second therapy in terms of the Chamberlain study, again, 273 children in a double-blind, randomized control trial, I've found that there was similar efficacy between IV valproic acid and IV phenobarbital used as a second-line therapy, but there were fewer adverse effects in the IV valproic acid group. The EcLiPSE trial and the ConSEPT trial are similar in that they are large open-label randomized control trials.

The first, EcLiPSE, involves 400 and patients out of the UK, and ConSEPT involves 223 patients out of Australia. In this case, the utilization of levetiracetam vs phenytoin was utilized to see if there was any differences in efficacy, and that could not be seen. They were either noninferior or equivalent in these 2 trials. And Dr. Cascino mentioned the ESETT trial. This did include 225 patients who were in the pediatric population.

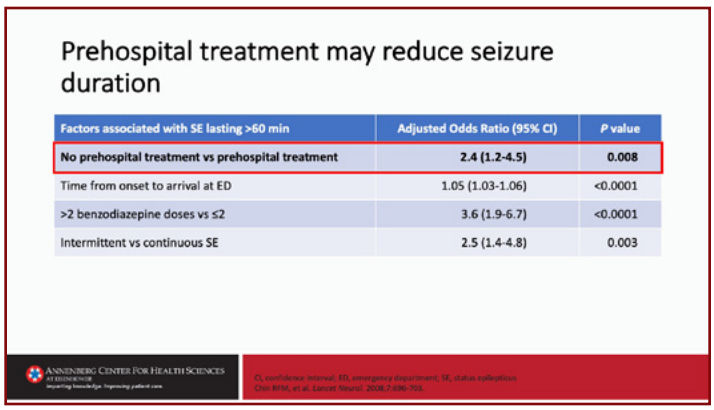
Again, it was a double-blind randomized controlled trial of levetiracetam, fosphenytoin and valproic acid with the primary outcome looking at no seizures in 10 minutes, no utilization of further antiseizure medications, and a return to consciousness. And as he mentioned, the data was very similar. Levetiracetam was 52%, valproic acid was 52%, and fosphenytoin was 49%.



87% of patients, it was found in the Alldredge study of 2001, have a rescue medication. 38% received it. And obviously, this just shows this wide treatment gap—gap in education, gap in utilization—that we have between what patients may have been prescribed and what they're actually utilizing. When prehospital care is neglected, when there is a delay, we see not only a treatment delay, but an increased need for third-phase treatments. We see an increased duration of convulsive status epilepticus, as well as the potential for more severe outcomes.

This was a prospective trial of the outcome of children in North London and the NLSTEPS group, looking at not what guidelines were followed, but in prospective—but in the end—how did they come out? Looking at, if you will, the real-life outcomes of status epilepticus. Again, they looked at an outcome measure that the factors associated with status epilepticus lasting for greater than 60 minutes. And if there was no prehospital treatment, there was a 2.4 increase in the adjusted odds ratio with a significant *P*-value. Time from onset to the arrival at ED was 1.

This is again from the NLSTEPS group, with Chin as the primary author, that showed that utilizing 2 benzodiazepine doses, first of all, had only a 20% efficacy. It was very low in terms of how often that worked. But it had a 3.6 increase in the odds ratio of a patient having continued status epilepticus, as well



as a 3.2 odds ratio in having respiratory depression. This is a frequent problem in pediatric epilepsy, where we see patients getting numerous rounds of benzodiazepines prior to moving on to second-line therapy. We know from the Alldredge trial of 1995, the prehospital treatment is important. The duration of status epilepticus is decreased, with prehospital treatment, almost in half. The rate of status epilepticus recurrence is dramatically different, with 58% with prehospital treatment and 85% without prehospital treatment.

When we look at the association of time-to-treatment with short-term outcomes for pediatric patients with refractory convulsive status epilepticus, this is the outcome information from the pSERG group. So, looking at essentially, how well did we do? We saw that within 10 minutes, 33% of patients had first-line benzodiazepine treatment, but 66% had delayed treatment. In addition, looking at a multivariate analysis of this group, there was a risk of death, need for continuous infusion, increased convulsive seizure duration and risk of hypotension, all were factors. We are seeing that although people have instituted policies for the treatment of status epilepticus that may have been even more aggressive than that described by the AES, in terms of our ability to follow through with those protocols, we still have a way to go. Conclusions, among pediatric patients with refractory convulsive status epilepticus, timely first-line benzodiazepine treatment is independently associated with a higher frequency of death, use of continuous infusions, longer convulsion duration and frequent hypotension. And the results of the study raised the question as to whether poor outcomes could in part be prevented by earlier administration of treatment.

Towards an acute pediatric status epilepticus intervention team, the authors, again, in the pSERG trial raise the question, should we have seizure codes? And I think that really goes back to what Dr. Shinnar was making the point about, which is that time equals brain, and we not yet reached the degree of urgency as our stroke colleagues have, and really emphasizing that early treatment can prevent the damage to neuronal tissue. Rapid initiation and escalation of status treatment has been associated with shortened seizure duration, more favorable outcomes, and really, better administration of how these protocols are carried out could certainly benefit our patients.

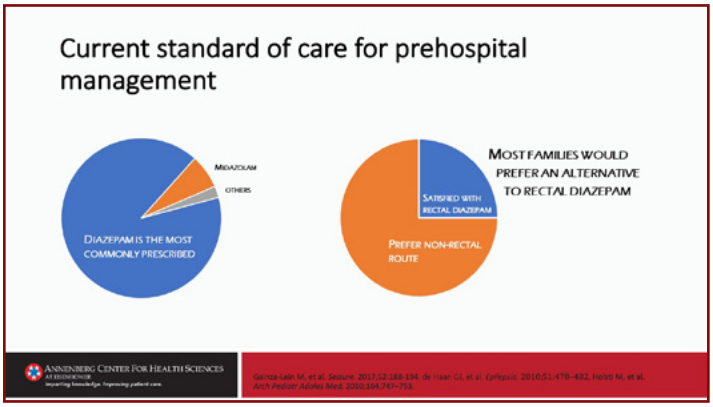
This just goes through the rest of those words, pSERG and other studies have shown the time to antiseizure medication for pediatric status epilepticus remains delayed in both the pre- and hospital settings, as we showed in the last group of slides. And barriers to the timely prevention likely include the following: suboptimal preventative care, inaccurate seizure detection, infrequent or restricted use of home rescue medications, delayed summoning or arrival of emergency personnel. So the latter is probably a special point during COVID when there's been a huge utilization of our EMS services. And, of course, use of inappropriately dosed medication, which has been found in multiple studies to be a problem. This is especially an issue within the pediatric population, when the appropriate dose changes as the child grows, but there may not have been a change in the dose of the medication.

The overall improved preventive care seizure detection and rescue medication may advance this prehospital management.

RESCUE MEDICATION OPTIONS

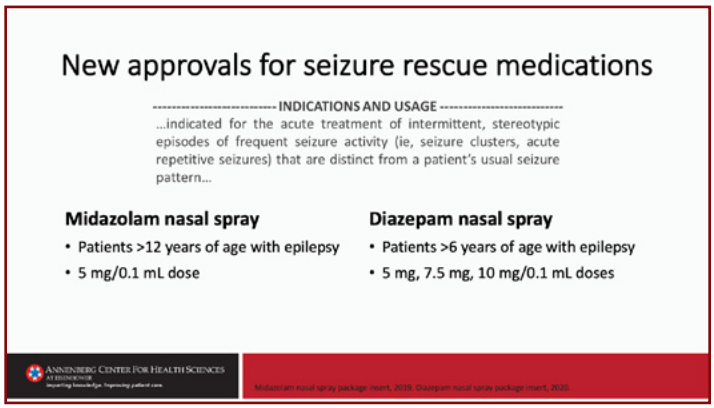
Juliann M. Paolicchi, MD

The current standard of care for prehospital management has been, as we mentioned before, the use of diazepam predominantly through rectal means of administration. However, when we ask families what you would prefer, the majority say, "I would prefer a nonrectal route." Well, there are some patients who are very satisfied with rectal diazepam. Our group was actually conducting a very similar study, looking at the criteria and acceptability of utilizing in-home emergency therapies prior to the onset of COVID. And we hope we can continue this research and look into this very important question, once things are more stable. In addition, off-label medications are used for the treatment of status epilepticus, and these can include nonrectal benzodiazepine formulations, such as buccal midazolam, compounded midazolam. Something we would use in patients who either had a side effect to diazepam or it was ineffective, utilized through an oral route, and clonazepam orally disintegrating tablets. The patient can have the ease of curing with them for utilization. And of course, for patients who have a VNS therapy, they can utilize their VNS magnets.



Characteristics of an ideal prehospital treatment would be, immediate duration of action of course, very quick efficacy, rapid cessation of seizures, easy to use, and I think this is now our very important point that we need to discuss with our patients. It is safe, does not cause discomfort and has low interest intrapatient variability. And of course, a long shelf life since patients may carry this or a caregiver may carry the preparation for some time. It may be in the school nurse's office for some time prior to its utilization, and it needs to be stable in that timeframe. Intranasal vs other administration routes—intranasal shows high perfusion, rapid absorption through the mucous membranes of the nose. It is easy, it is accessible, minimal training, low risk. Rapid distribution into the CNS since it does not have to go through oral absorption and small volume vs rectal preparation.

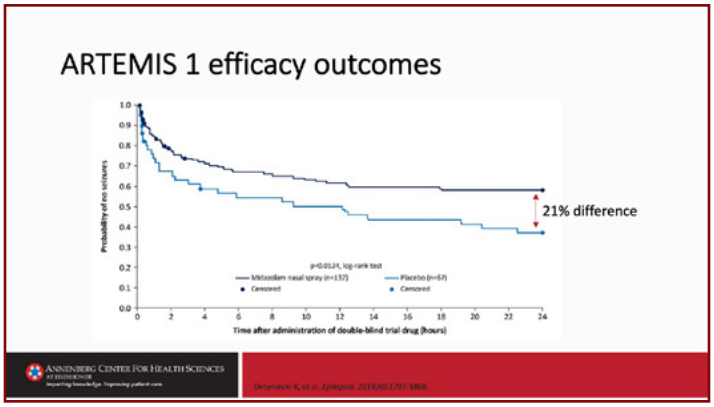
Recently, there's been 2 new approvals for rescue seizure medications, which allows us the flexibility and choice of prescribing these preparations for our patients. They are both indicated for the acute treatment of intermittent stereotype episodes of seizure activity. Whether that be clusters, acute repetitive seizures. The first to come available was midazolam nasal spray. This is approved for patients greater than 12 years of age with epilepsy and has 1 dose equivalent. Diazepam nasal spray is approved for patients greater than 6 years of age with epilepsy and comes in multiple doses.

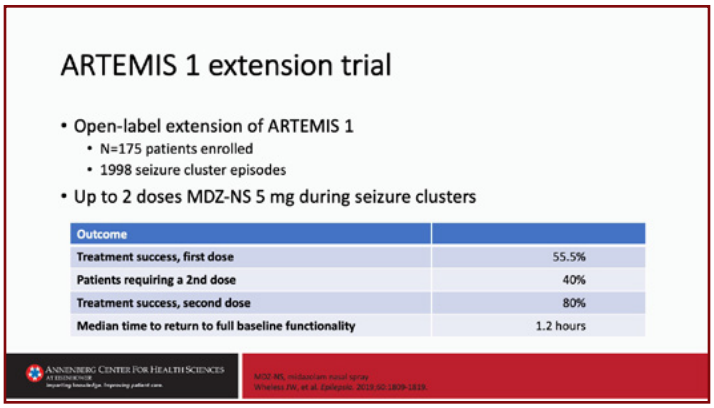


The approval of the intranasal midazolam came from the work of the ARTEMIS phase 3 trial. And this trial was, again, a double-blind randomized controlled trial with patients greater than 12 years of age involved, and 292 patients. The primary outcome was seizure termination within 10 minutes and no recurrence after 10 minutes to 6 hours. Secondary outcomes were the percentage of patients with recurrence in that timeframe and the time to the next seizure being greater than 10 minutes. Patients were given a test dose in the clinic setting and then sent home with either placebo or active agent. They were instructed to utilize their preparation within 5 minutes, and if the seizure continued, they would utilize the medication itself, the midazolam nasal. The results show that the primary endpoint, both seizure termination within 10 minutes and no seizure recurrence, occurred in 53% of patients with the midazolam vs 34% in placebo. Similarly, seizure recurrence was higher in placebo and lower, 38%, in the group who had the intranasal midazolam.

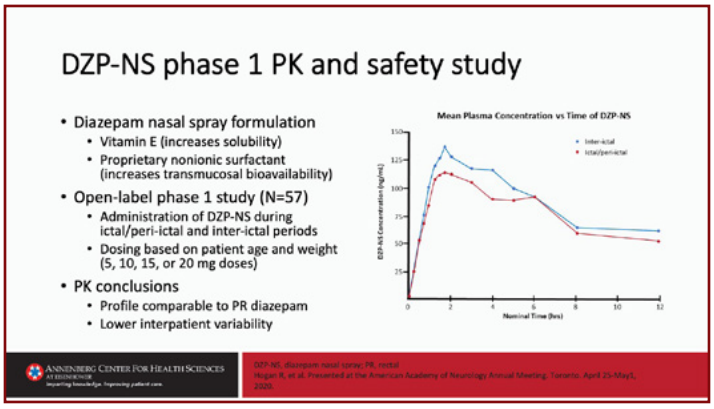
This is a time graph showing a similar result, which is on the x-axis, the time of after administration after the double-blind trial, in terms of hours. And on the Y, a probability of seizures overall. And we can see that there was a much greater recurrence after administration of the dose with the placebo, which is the blue line as compared to the midazolam group which was the black line. This was actually a 21% difference. Overall safety outcomes showed that they were consistent with known benzodiazepine or adverse effects such as sedation. There was mild nasal discomfort, but no discontinuations related to treatment emergent adverse events and there was a very low rate of respiratory depression.

In the extension phase of the trial, in which patients had similar instructions to use the intranasal midazolam and if seizures persisted use a second dose, it was found that treatment success in the first dose was 55%. Patients requiring our second dose was 40%, but overall treatment success was 80%. And this led to the recommendation that patients have 2 doses and, if the seizures persist, to utilize the second dose. The median time to return to full baseline functionality was seen





at 1.2 hours. In terms of diazepam nasal spray, remember there was already approval for the use of diazepam as a rectal preparation for the treatment of repetitive seizures or clusters of seizures. Therefore, it was necessary to have a bioavailability trial between rectal and intranasal diazepam in healthy adults showing congruent results between ictal and peri-ictal as well as interictal PK studies in adults and no notable differences between the PK in healthy adults and adult patients with epilepsy.



The diazepam nasal spray formulation contains vitamin E which increases insolubility as well as a nonionic surfactant for transmucosal bioavailability. And an open-label phase of the PK study. The administration of this diazepam nasal spray was done in both ictal and peri-ictal periods as well, as interictal was found to have no significant difference. That's shown on the graph on the right with the interictal being the blue and the ictal/peri-ictal being the red. Dosing was based on patient age and weight. And the PK conclusions were that the profile was very comparable to PR diazepam, and there was a low interpatient variability.

In terms of treatment-emergent adverse events, there was nothing that resulted in discontinuation, most were consistent with events expected with nasal administration. There were no clinically significant abnormalities and vital signs changes in laboratory tests or ACGs.

In terms of interim analysis, the safety and tolerability has been stratified based on the frequency of use, whether it's moderate, 1-2 doses per month, or frequent use greater than 2 doses per month. And no consistent trends have been seen. There is no consistent trend observed with the higher use frequency. Nasal irritation for both groups was seen to be mild and transient. And that smell test showed that if there were olfactory changes, they were minimal and transient and they were not necessarily related to usage frequency. That does not appear to be an increase anesthesia to smell based on utilization of more doses.

FACULTY DISCUSSION
ADDRESSING TREATMENT GAPS

Juliann M. Paolicchi, MD

At this point I would like to transition and have my other 2 esteemed faculty members join me for a discussion regarding this new data and how it may affect our treatment of status epilepticus as well as acute prehospital treatment of status epilepticus. My first question goes out to Dr. Casino, and I would just like to ask what factors in the adult population do you feel can be used to improve the treatment gap of status epilepticus in hospitals, both pre- and at the hospital treatment?

Greg Casino, MD

Both are significant gaps at present, as you know, both in terms of deciding when to use second-line therapy and which drug to use. And then, of course, when they go on to third-line therapy and select the medication that's appropriate. A major factor that seems to be an issue right now is understanding the mechanism or etiology of status epilepticus. And obviously not all patients who have acute repetitive seizures or seizure emergency have the same disorder. At present we presume that they do, and we treat them all the same way with benzodiazepine therapy, prehospital. And there's no question these acute rescue medications are being underutilized probably even more so in adults than in children. And many individuals are not even aware of the fact that these medications exist and that they should be given prescriptions. Education of the part of the caregiver of the patient or the patient themselves is critical right now.

An important gap, I think, has been the education process. Very little is done to inform patients about the possibility that an acute rescue medication may be lifesaving, may keep them from the emergency department, may prevent episodes of status epilepticus, and may prevent a tragedy. The biggest gap I see right now is an educational process, and we still need to understand better the "why." Why some patients go into these seizure emergencies and what factors we can try to control with biomarkers, be it MRI or other factors on EEG that are important to know about. The education process of

the patient and the primary care provider are really very important right now.

Juliann M. Paolicchi, MD

And Ms. Long, if I could ask you a very similar question, what types of education communication do you feel we can employ in order to improve this barrier between prescription of emergency medications and their acceptance or utilization?

Lucretia Long, C-ANP, FAES

I think that we have a lot of opportunity to implement educational interventions for patients, even in the midst of the pandemic. And with telehealth we have the opportunity to talk about SAPs and also the opportunity to provide patients with resources that they may have but they may not be aware of. I think the important thing is to focus on those resources that are available for patients and to be intentional in terms of providing them with information that can help them as we look at customizing seizure action plans.

Juliann M. Paolicchi, MD

Another question for both of you is, we all have to, of course, we're familiar with quality measures, quality measures in the hospital, through our EMR, etc. Do you feel that there would be a role for a quality measure in EMU, perhaps a longitudinal study that we could also do looking at quality measures and discharging patients with seizures or epilepsy in terms of this education and utilization of rescue medications?

Greg Casino, MD

Julianne, that's an outstanding question and comment both because the answer of course is yes. And all of us are very busy and we focus on treatment—we don't focus on prevention. In my mind, discussing issues like acute rescue medication and having SAPs is a critical part of preventing the tragedy. And I suspect we probably give a lot of lip service to what we focus more on managing epilepsy than trying to control some of these factors. So, the answer would be yes, and I would strongly support that.

Lucretia Long, C-ANP, FAES

I am going to echo Dr. Casino's comments. In fact, I think we can learn from our pulmonary experts and I think for every patient who is discharged from an epilepsy monitoring unit, it should be mandatory for them to have a SAP. And certainly in patients who have asthma, those patients, before they're discharged, have an action plan. I think we can again use some of the things that our colleagues in other specialties have implemented and utilize them for our patients and family members suffering from epilepsy, as well.

FOCUS ON CAREGIVERS AND HEALTHCARE PROVIDERS: IMPROVING PREHOSPITAL CARE

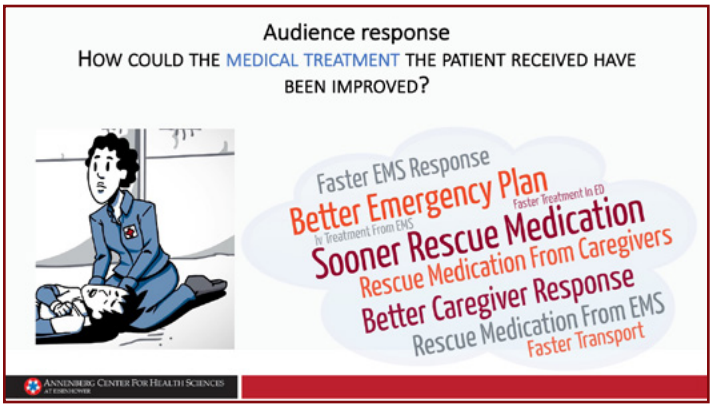
Juliann M. Paolicchi, MD

That is a great segue into the next discussion and it is my great pleasure to introduce everyone to Ms. Lucretia Long who is a fellow OSU faculty member and on the epilepsy team. Lucretia is a staunch advocate for her patients. And she combines that advocacy with a curiosity and exploration through research and has done wonderful research on SUDEP as well as this idea of improving prehospital care.

Lucretia Long, C-ANP, FAES

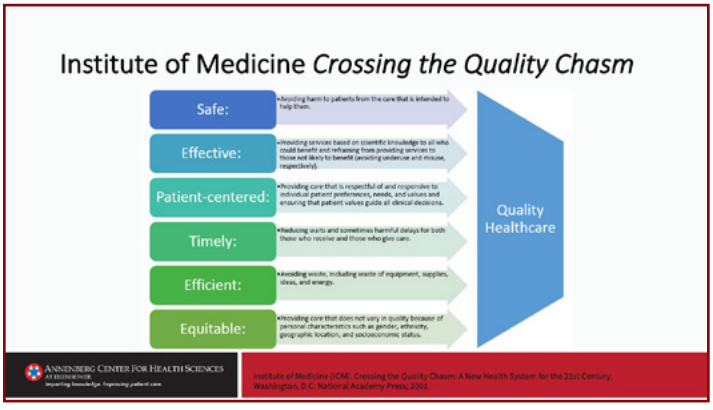
I am going to talk about how we might improve prehospital care as it relates to caregivers, as well as healthcare providers.

Before I dive into the discussion, why don't you review your responses to the 2 audience response questions that Dr. Casino posed earlier? The first one, of course, was how could the medical treatment the patient in the previous video received have been improved? And certainly as Dr. Casino mentioned, the larger answers are the ones that you all highlighted and it looks like most of you felt that sooner rescue medication, rightfully so, could have improved the medical treatment. Also, a better emergency plan. We're going to talk a lot about SAPs throughout tonight's discussion and also a better caregiver response. We will be highlighting a lot of these comments that you all made, again, as it relates to how we might improve medical treatment for patients and families who are dealing with repetitive seizures in prolonged seizures.



Second audience response question, how could the healthcare system better prepare caregivers to manage seizure emergencies? Why it's important to have a SAP. Easier rescue medications. And we'll talk a little bit about some of the research that's been done in the past, looking at this and assessing what patients prefer in terms of a rectal administration of medications vs some of the other alternatives. And then obviously the idea of rescue medication training, which both Dr. Casino and Dr. Paolicchi alluded to earlier.

This slide really sort of summarizes and highlights the 6 domains of quality healthcare emphasized by the Institute



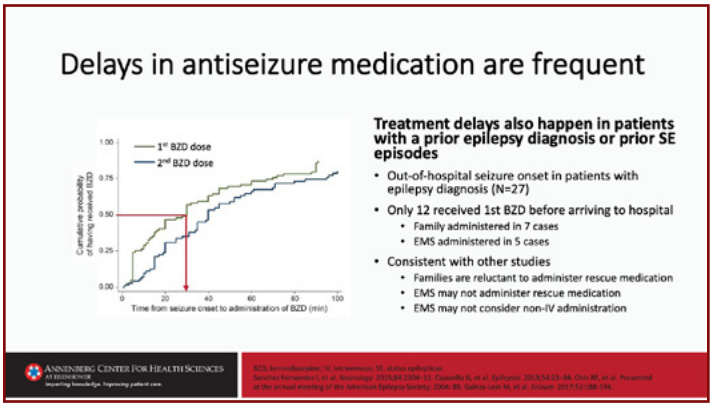
of Medicine. When we look at medication intervention, we want to make sure that the medication is safe and that we're not initiating harm. Obviously, the medication needs to be effective but safety is equally important. And I will be highlighting the idea of providing customized SAPs. And certainly individualizing care and having a patient-centered focus, I think is crucial. I honestly believe that every patient with a history of seizure and a history of epilepsy should have a SAP. And I sometimes when I make that statement, I get some interesting looks, but certainly I think that your patient, for example, with Dravet syndrome or your patient with LGS, those action plans are clearly going to be different than your female patient with a history of some simple partial seizures around her menstrual cycle. But certainly, I think every patient with a history of seizures and a history of epilepsy should have a customized SAP.

We have highlighted the importance of timely intervention. I think it is important, as we look at increased morbidity and mortality, that these action plans, and these interventions, be implemented sooner rather than later. And certainly Dr. Casino and Dr. Paolicchi did an excellent job talking about the importance of efficient and timely intervention related to SAPs. We also want to ensure that the quality healthcare that's provided is actually available for everyone. And this is regardless of demographics and also regardless of the socioeconomic background.

Dr. Casino highlighted this evidence-based guideline where Tracy Glauser and associates documented the treatment for convulsive status epilepticus in both adults and children. We believe that these guidelines have received widespread acceptance and are routinely implemented.

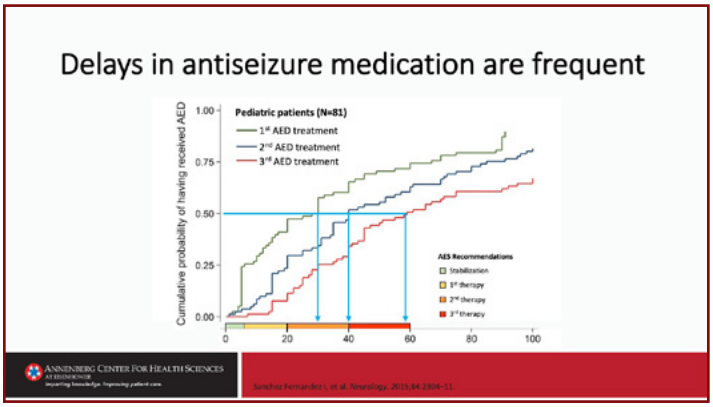
But despite the fact that these guidelines have been implemented, we still know that patients are receiving inadequate treatment. And we think that some of this is probably related to inefficient therapies, as well as the administration of insufficient anticonvulsant doses. And we'll talk a little bit about some of the studies that have been done, looking at insufficient doses as this relates to intervening prehospital in terms of SAPs and related medication.

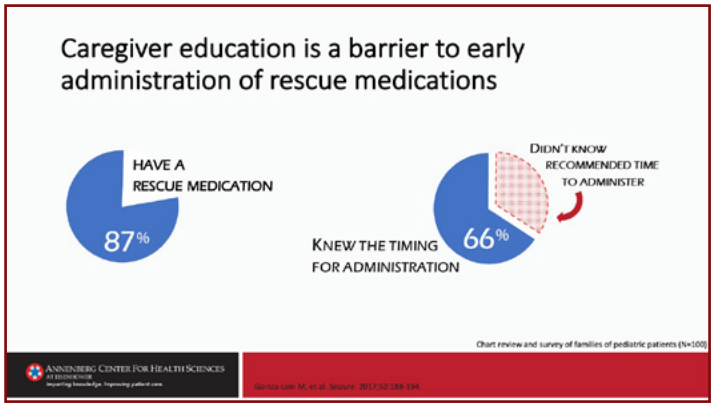
This study actually looked at the time from convulsive status and the onset of antiseizure medication administration in pediatric patients. I believe the patients in this study were age 1 month up to 21 years. There were 81 patients and the median age in this study was 3.6 years. And the findings were really interesting in that the median time of antiepileptic drug administration was 28 minutes for the first dose of benzodiazepines; 40 minutes for the second dose of benzodiazepines; and 59 minutes for the third dose. As we think about timeliness of intervention, these numbers are pretty interesting and really sort of speak to the idea that we have some work to do as it relates to counseling patients about earlier intervention and related outcomes.



And in this study, they actually looked at the number of patients who had a history of epilepsy. A diagnosis of epilepsy and patients who had seizure onset before coming into the hospital. And there were 27 patients who met that criteria and only 12 of those patients actually received benzodiazepines before arriving to the hospital. And, as I documented on the slide, in 7 of those cases the family members administered the benzodiazepines, and in 5 of the cases the EMS administered those medications. So we think—and this is consistent with other studies that basically emphasize the idea—that families are reluctant to administer these medications prehospital. And we sort of chatted about that in the discussion with Dr. Paolicchi earlier. There was a suggestion that the EMS may not be considering medicines that are not administered intravenously. Now, certainly we could argue that when this study was published, the medicines that are now available were not FDA approved, but certainly we want to look at the opportunity to educate our EMS colleagues about the importance of using other alternative medicines to minimize related complications.

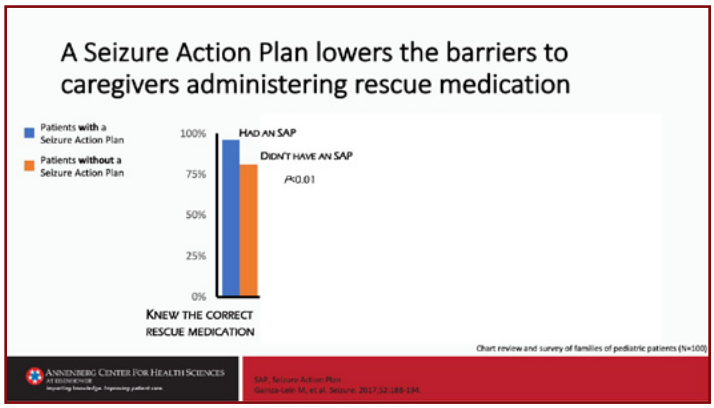
This study actually analyzed the use of prehospital seizure rescue medication, and caregiver knowledge and comfort, and correlated that with prescription patterns. This, again, within a pediatric group, and I believe there were 100 surveys that were completed out of the 114. And what we saw, and Dr. Paolicchi sort of touched on this earlier, is that





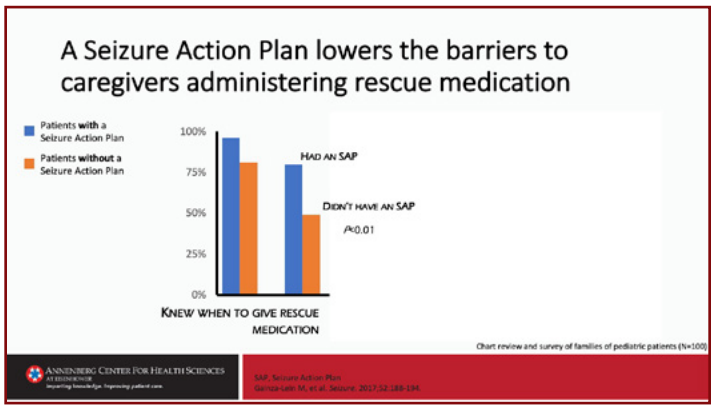
87% of patients in the study had a rescue medication, but interestingly only 66% of people in the study actually knew the timing for medication administration. This is important as we look at early intervention. Again, we know with certainty that the earlier we intervene, the better the treatment outcomes.

This study looked at the idea that a SAP can lower the barriers to caregiver administration of rescue medication. And what you see with the blue bar is the outcome in patients who had a SAP compared to the orange bar that summarizes patients who did not have a SAP and certainly you can see a really clear correlation in terms of patients who had a SAP and being aware of the correct name of that medication compared to those who did not have a SAP.

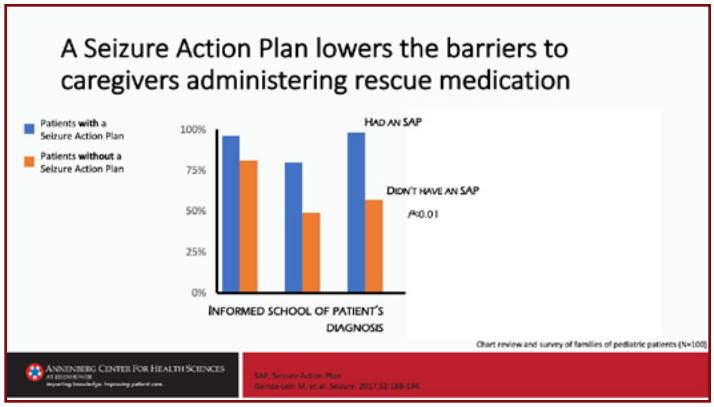


We also looked at the correlation between knowing when to administer the rescue medication, which is obviously crucial. Those who had a SAP were more likely to be aware of when to administer that medication compared to those who didn't have a SAP. And you can see the percent of about 75% being aware with the SAP compared to less than 50% of those who were not aware of when to administer the medication.

Additionally, there was clearly a correlation between patients who had a SAP and the school nurses or school staff being aware of the patient's diagnosis. And certainly you see a huge gap in terms of barriers for those patients. Of those who've had an action plan, almost 100% informed the school and school nurse of the patient's diagnosis compared to about 50% or so of those patients who did not have a SAP.

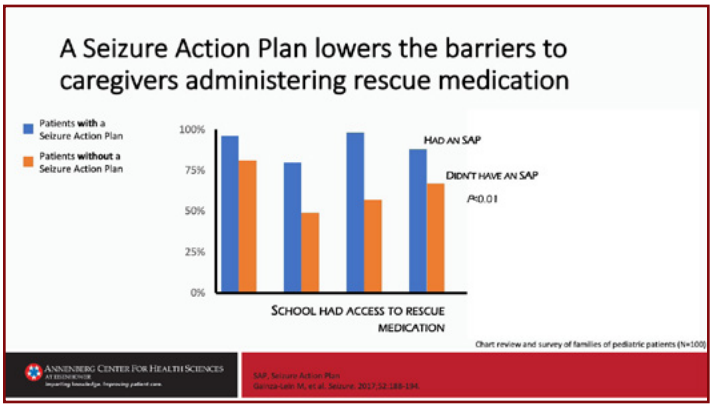


And these numbers were relatively a little low, maybe in both groups, but this looked at the percent of patients who had an action plan and the school having access to that medication is certainly a much higher percent of patients who had a SAP.

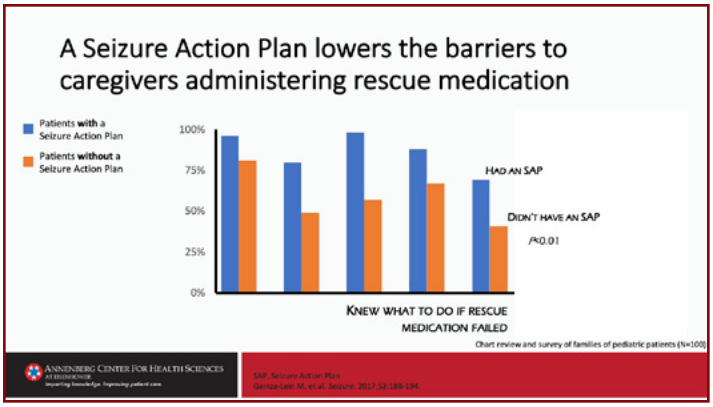


Their schools have access to related medication compared against those with the orange bar who did not have a SAP. And finally, there was a correlation with reduce barriers for SAP and knowing what to do, if that rescue intervention did not work. Again, in those who had a SAP compared to those who did not.

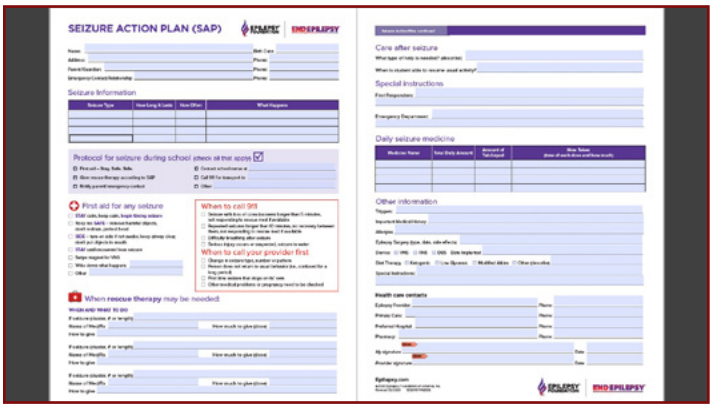
We know that the SAPs work, but it appears that they are not very widely utilized. This study actually summarized the idea that parents who recalled having a SAP was only about 45%. A large number of parents who did not have access to a SAP, and I suspect those of you in the pediatric world have done a much better job than we have in the adult world in terms of providing patients with tangible SAPs. And I suspect some of this is because what you do in terms of your students going to school it is mandatory for you guys to have a tangible SAP. And so certainly I think a part of the reason that the pediatric colleagues have probably done a better job than we have in the adult world is because it's mandatory for some of your clients to have a SAP in order for them to go to school or to participate in some of those daycare facilities.



I think you all have certainly done a better job than we have, but certainly in this study there was a huge percent of people who did not, and parents who did not use the SAP. There is an opportunity for us in terms of counseling intervention. So, we know as we look at SAPs, that it is really important that the action plan includes information obviously about the patient's semiology and epilepsy syndromes. The SAP needs to document how to respond during the seizure, and whether that's a rescue medication administration. With SAPs, we want to focus on the semiology, also the specific type of medication that's being administered, and again, when that seizure plan or seizure event constitutes an emergency.



This is actually probably one of the most used SAPs and many of you are familiar with this. It is available through the Epilepsy Foundation and it really provides a nice comprehensive summary of customizing care, again, as it relates to a SAP. You can see it's a 2-page item.



It includes patients' demographics, and also gives you an opportunity to document the patient's typical seizure pattern. And this action plan provides you with an opportunity to document 3 different seizure types, provides information in terms of how long the seizure lasts as well as the frequency, and the typical semiology. Additionally, it allows you to create, again, a customized action plan related to rescue therapy. Again, with 3 different seizure types. It gives you the opportunity to talk about seizure clusters, seizure duration, and when that intervention is necessary. And actually how much of this seizure rescue medication to administer. It also, on the right-hand side, gives you some opportunities again to customize when your patient needs to call 911, compared to when it's necessary to call the provider first.

We have to be a little careful in that we're not being too rigid with some of these recommendations. Certainly when you look at a change in seizure type, some would argue that perhaps you may need to call 911, if the seizure type is different than a patient's baseline. And also a first time seizure that stops on its own, there could be some debate as to whether or not that requires a 911 intervention, vs contacting the provider. But clearly this SAP, again, gives you the opportunity to customize care for patients and families dealing with recurrent seizures.

This has not been published. This is a part of expert opinion consensus that we've had the opportunity to submit for publication. This was the PI on this study Pat Penovich. There's also a couple of other colleagues, Tracy Glauser and Anup Patel. And what we try to do is really capture really important resources and adjustments to implement SAPs, and we're calling this the ASAP, which I love that, because it actually provides an opportunity to emphasize the urgency for intervention as it relates to SAPs.

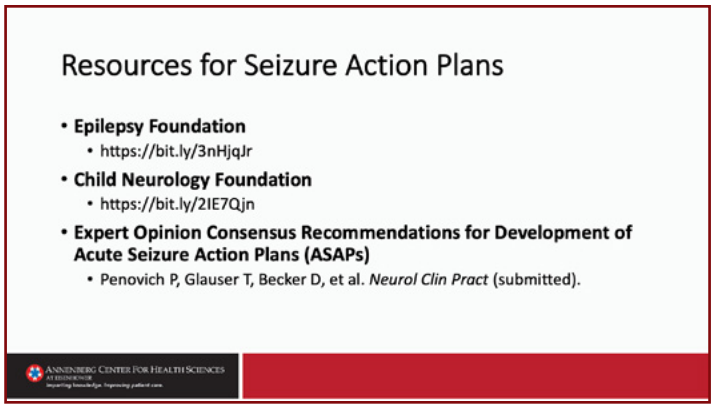
We like this SAP, because it is a very user-friendly action plan. Again, for some of you who are familiar with the Asthma Action Plan, this looks very similar to that, in that we have a green light, a yellow light and a red light. And again, we like it because it's 1 page. It also provides for those patients with language barriers or patients who have some difficulty reading. It gives them the opportunity to look at a quick visual to determine when intervention is needed.

This is an easy-to-use, single-page format, unlike some of the other SAPs that are available. This one is pretty quick in terms of intervention and documentation, certainly in the presence of our administrators, wanting us to see more patients in less time, we wanted to provide you all with something that is relevant in terms of allowing you to be more efficient with the limited time that you have. And we're hopeful that you will agree that this is something that is a little more user-friendly and less time consuming than some of the other SAPs.

Obviously the ASAP includes patient information, caregiver contact information, as well as physician contact information. Additionally, it allows you to document seizure triggers and seizure semiology. In the green section, it gives you standardized care and customized care for responding to a typical seizure and some step-by-step instructions. Some visual elements provide some instructions. And again, as you think about language barriers and the urgency of needing to intervene, I think this allows for a nice visual, as opposed to patients having to read specifics with some of the other SAPs. We like the idea of this being visual in terms of early intervention and related instruction.

The yellow area provides information on rescue treatment, again, allowing for a more customized approach when to administer rescue medication, with step-by-step instructions. The red area is where we provide some additional assistance in terms of recognizing seizure emergencies and customizing action plans related to that seizure emergency.

The ASAP plan also provides an opportunity for record keeping and reminders to update and maintain a SAP. And we will talk a little bit more about this again in a couple of the



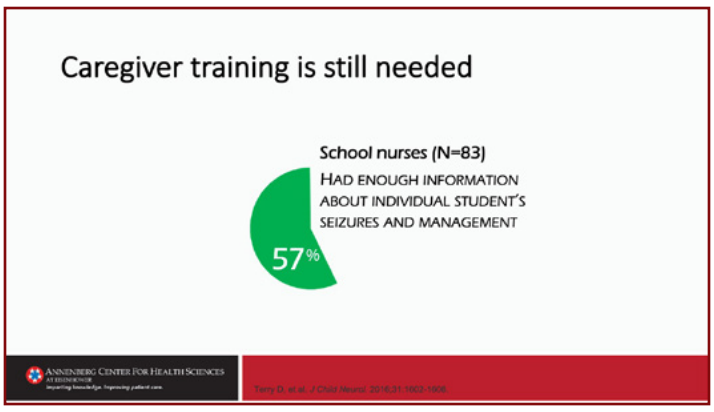
other slides. This is a list, the resources associated with SAPs. If we were face-to-face, I would recommend collaborating, and for those of you who may be aware of other resources related to SAPs to share that with your colleagues. The Epilepsy Foundation provides a resource, and we chatted about that earlier for child neurology, and then we're hopeful that our expert opinion consensus recommendation for the ASAP plan will be available via *Neurology Clinical Practice*. We have submitted that and are hopeful that we can not only again, provide you with some expert information in summary of current research, but also provide you with something tangible in terms of a user-friendly resource that you can use in your clinical environment.

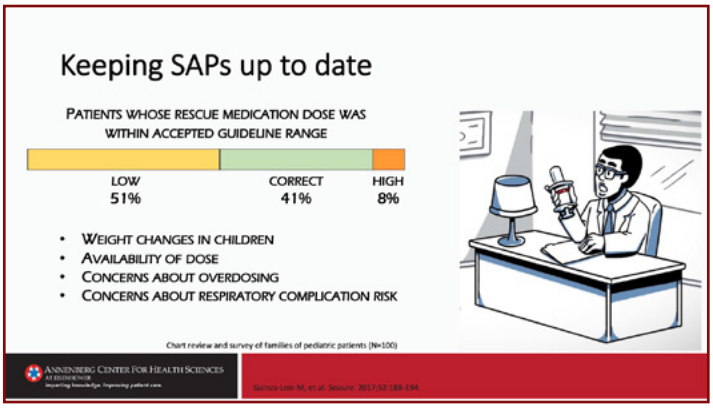
We have talked a lot about the idea that caregiver training can in fact, be improved. This study looked at perceptions of training for parents. And interestingly, what we see here is that there was a correlation between parents being trained and the age of patients who are younger, there appears to be a higher correlation of parental training, again, as it relates to medication administration. The parents prefer training by a neurologist, but also they were okay with training by medical staff, and the difference was small but significant. In addition, the parents wanted more hands-on training. We talked a lot earlier about the idea of updating those SAPs and providing refresher interventions and also providing educational materials for other caregivers, which I think is equally important.

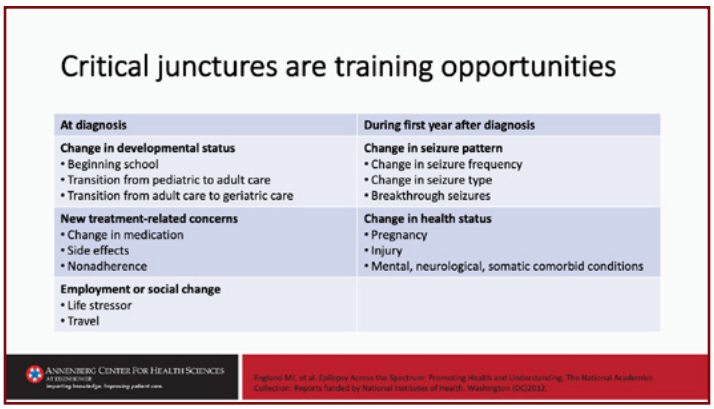
This study was published by my colleague, Debbie Terry, and many of you may be familiar with her. She recently retired, actually, and collaborated with a Anup Patel who is our nationwide children's colleague. But she looked at school nurses and their perception of whether or not they received information and barriers concerning treatment related to patients with seizures. Again, 83 nurses were surveyed and the study basically suggested that only 57% of those school nurses had enough information about individual student's seizures and management.

Interestingly, she also noticed in this study that about 84% of the school nurses were trained to administer rectal diazepam compared to just 63% of those school nurses who were trained to administer intranasal midazolam. Now keep in mind, this study was published before the 2 medications that we have now were FDA approved. And so certainly one could argue that perhaps providers were not prescribing the intranasal midazolam because it wasn't approved, but like many of you, we certainly were prescribing the intranasal midazolam before the recent approval. This could be one of the limitations of the study.

We referenced this study earlier. The study that actually analyzed the use of prehospital rescue medication and caregiver knowledge. And what we see pretty consistently or clearly is that only 41% of people surveyed received the correct dose of their rescue medication. And this is interesting and that we know that in terms of being effective, we need to ensure that patients are receiving the right dose. Again, in this study only 41% received the correct dose based on current guidelines, and over 50% of these patients had less than what was recommended. Now, clearly there could be some challenges in terms of weight changes particularly as it relates to our pediatric group, and the availability of dose could be one of the concerns. Also, we talked a little bit about this earlier in terms of the concerns about adverse effects and respiratory complications, so maybe there is a perception of a need to recommend lower doses until we evaluate whether or not the patient will respond on a lower dose, vs what is currently recommended.







This summarizes some of the critical times for training opportunities and Dr. Cascino and Dr. Paolicchi sort of alluded to this, the importance of training as it relates to the SAPs and really keeping these SAPs current…certainly. And for those of you who work in pediatric areas, you know that the beginning of the school year certainly is a high time for implementing and adjusting the SAPs. I was on a call a week ago talking about SAPs, and actually one of my colleagues mentioned that one of the things she was sort of happy about as we look at some of these kids who are learning from home or not going into the school, was that she didn't have to fill out all the paperwork related to the SAPs.

The beginning of the school year, in general, is important in terms of adjusting the SAPs. Any type of change in health status, employment and social changes in situations can also provide you with an opportunity to adjust that SAP for those plans that include a list of medications. Whenever you change medication, you need to update that SAP as well.

The next thing we'll look at now is a video that demonstrates how having a SAP can really improve a patient outcome associated with seizure emergencies. Again, as we look at prehospital intervention.

White Board Animation

Narrator: Successfully treating seizure emergencies depends on what happens before the patient has a seizure and what caregivers do when the patient has a seizure. In this case study, let's look at how a SAP can help improve the outcomes in patients who have a seizure emergency. Grady has been diagnosed with epilepsy, which is discussed with his family caregivers and healthcare providers. Let's see how those around him respond when he has a seizure.

Teacher: He's having a seizure, please get the school nurse and let her know what's happening.

School Nurse: I have a SAP and rescue medication. How long has he been seizing? This isn't normal, it's lasting too long.

Teacher: What do we do?

School Nurse: We need to give him this medication and call for an ambulance. His seizure started about 20 minutes ago and we gave him his rescue medication. (silence)

Narrator: A seizure becomes a medical emergency when it lasts longer than 5 minutes. Another seizure starts before complete recovery, or when the seizure doesn't fit the normal pattern or frequency. Prolonged seizures can have serious outcomes. So when emergencies occur, the goal of treatment should be to end seizure activity as soon as possible. All patients should have a SAP that tells caregivers what to expect. Cord symptoms and treatments, has instructions for when and how to give rescue medications and helps caregivers recognize when to call 911. Doctors, nurses and caregivers can help you develop a SAP. This should be discussed with family members, school faculty, coworkers, and even other physicians. Remember to review it regularly with your neurologist and update it. Caregivers should also refresh their training on how to use rescue medications when the SAP is updated. You can find SAP templates online. This case shows how having an up-to-date SAP, is important for optimizing the management of seizure emergencies.

Lucretia Long, C-ANP, FAES

This video will be available for training opportunities for patients, and you can look at the information in terms of where you can download that, but really important as we look at again, maximizing opportunities for educational interventions related to SAPs.

PROGRAM SUMMARY AND FACULTY Q&A

Lucretia Long, C-ANP, FAES

I would like to invite my other faculty members to join in and summarize for those in the audience: If you had to provide a take-home message of 1 or 2 sentences related to your discussion, what would those items be? And so certainly for me, I would like you all to appreciate the importance of all patients having a SAP.

Greg Casino, MD

My first comment for adults and probably for children as well is time is neurons. And in living in a rural part of the United States, like I do right now, if your action plan is if they have a seizure, and it looks like it is going to be a seizure emergency, or it is going to be a seizure situation that requires appropriate medical care, and you have to wait for the ambulance to go to the emergency room, and you have to look at the time element of when the seizure began, so when they're initially receiving appropriate benzodiazepine therapy. There are a significant number of patients who will have tragic outcomes.

Prolonged seizure activity, status epilepticus, hemodynamic changes, and then of course, concerns as we see on MRI with a number of neurologic problems that may be very incapacitating, even catastrophic. And then the subsequent development of seizure disorders or intractable epilepsy. So, time is neurons, and I think everyone should be receiving appropriate care even before they call 911, and they go into an ambulance. And if the emergency department is the only

place they'll receive appropriate medical care, then I think we'll have some very unsavory comments about the treatment of these patients, because they'll have very unsatisfactory outcomes. So, that would be my goal as to plan ahead. Time is neurons. Try to avoid neurologic morbidity.

Juliann M. Paolicchi, MD

One thing that really motivates me is what you mentioned. I did have a very young patient and they didn't have their diazepam available. They went to the local fire station. They didn't have an emergency treatment. They finally got the patient to the hospital and that young child was never the same. We are all motivated by those stories where we really unfortunately learn tragically the time equals neurons.

I think that all the talks together sort of emphasize that we know what to do based on evidence-based protocols. And in addition, we know the importance of prehospital training, where we are falling short, we have opportunity. And those 2 major opportunities are number 1, in the implementation like as a group of epileptologists working together to better educate our acute treatment areas and where we can be beneficial and moving forward on status epilepticus protocols. And the second I think affords us, with these newer preparations, the ability to really have a conversation with our patients, not just about what antiseizure medicine works for them, but what is their life like, what rescue medicine would work best for them? What are their difficulties? We've now been trained to have these discussions about quality of life and the antiseizure medications and comorbidities, but we now need to do the same thing with the choices that we have for antiseizure medications and acute rescue therapies prior to the hospital. Thank you.

Greg Casino, MD

Julie and I have been trying to answer some of the questions that have come in. We've gotten most of them… but I've received one, and I'd like to get Juliann's comment about this one. In resource limited countries, where they don't have a number of these newer products, what treatment options should a caregiver at home use … or how would you treat a child in a resource limited or resource developing country that may not have the medications available as in the United States? Do you have an answer?

Juliann M. Paolicchi, MD

I do actually, because as we all know, pediatric neurologists are crafty at making up different preparations that may not have been available to our patients. So, prior to having significant access to diazepam rectal, or having it approved or having the patient be happy to do so, many of us utilized locally compounding formulations of liquid diazepam and liquid forms of lorazepam, and midazolam in easily administered form.

So, obviously limited resources make it more challenging, but certainly the IV preparations of the benzodiazepines can be administered in small insulin-like syringes either nasally or buccally. Now, please understand this is non-FDA, non-evidence-based. This is years of experience-based, and as Greg mentioned, having to treat rural patients who need access to appropriate medications.

Greg Casino, MD

Do we have emergency medication orders for patients in the epilepsy monitoring unit? I think I can speak for my institution and probably many others. The answer is absolutely "Yes!" We have a rescue plan. We're bringing people in the adult or pediatric EMU or reducing medications. They may have tonic-clonic seizures. They may have seizure emergencies. So, they all have a rescue plan individual to that particular patient's need.

That brings us to the end of what I hope has been a very enjoyable and informative period of time. I'd like to thank the 2 excellent speakers. We've covered a large area of material. There is a form that you'll be getting on chat for your CE and CME credit. We would like your feedback as well. Obviously this is a very unprecedented time to have a course for the Annual Meeting of the American Epilepsy Society. I'd like to thank everyone involved. Those who helped us develop the slides, the videos, the education program, and most importantly, the participants who have been with us this evening. We wish you all the very best. Stay safe and please stay well. Thank you.

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