AN EVIDENCE-BASED GUIDELINE FOR PEDiatric PREHOSPITAL SEizure MANAGEMENT USING GRADE METHODOLOGY

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Objective. The objective of this guideline is to recommend evidence-based practices for timely prehospital pediatric seizure cessation while avoiding respiratory depression and seizure recurrence. Methods. A multidisciplinary panel was chosen based on expertise in pediatric emergency medicine, prehospital medicine, and/or evidence-based guideline development. The panel followed the National Prehospital EBG Model using the GRADE methodology to formulate questions, retrieve evidence, appraise the evidence, and formulate recommendations. The panel members initially searched the literature in 2009 and updated their searches in 2012. The panel finalized a draft of a patient care algorithm in 2012 that was presented to stakeholder organizations to gather feedback for necessary revisions. Results. Five strong and ten weak recommendations emerged from the process; all but one was supported by low or very low quality evidence. The panel sought to ensure that the recommendations promoted timely seizure cessation while avoiding respiratory depression and seizure recurrence. The panel recommended that all patients in an active seizure have capillary blood glucose checked and be treated with intravenous (IV) dextrose or intramuscular (IM) glucagon if <60 mg/dL (3 mmol/L). The panel also recommended that non-IV routes (buccal, IM, or intranasal) of benzodiazepines (0.2 mg/kg) be used as first-line therapy for status epilepticus, rather than the rectal route. Conclusions. Using GRADE methodology, we have developed a pediatric seizure guideline that emphasizes the role of capillary blood glucometry and the use of buccal, IM, or intranasal benzodiazepines over IV or rectal routes. Further research is needed to compare the effectiveness and safety of these medication routes. Key words: clinical practice guideline; evidence-based medicine; prehospital care; seizure; status epilepticus

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BACKGROUND

Pediatric seizures are a high-incidence condition in the prehospital setting, and the potential morbidity and mortality of poorly managed seizures and their sequela can be substantial if not rapidly treated. Pediatric prehospital seizure management is characterized by variability in care related to providers’ infrequent exposure to children, difficulty maintaining skills, and limited knowledge of pediatrics. Prehospital providers may have more difficulty in rapidly obtaining intravenous (IV) access in children relative to adults and the stress of managing critically ill children poses an added challenge. While high quality studies are available to guide the management of adult patients with seizures in the prehospital setting, more research is needed to guide the practice of pediatric seizure management in the prehospital setting.

The Institute of Medicine (IOM) and the National Emergency Medical Services (EMS) Research Agenda emphasize the importance of evidence-based guidelines (EBG) to provide systematic aids for making complex medical decisions throughout the...
health-care continuum, with the potential to enhance health-care quality and outcomes. However, a review of ten sample statewide protocols for seizure management by the investigator group found substantial overall variation in practice, in terms of both medication selection and mode of administration. Given the high incidence, potential morbidity, and wide practice variation associated with pediatric prehospital seizures, there is a need for an evidence-based guideline to inform management.

Using the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) methodology, the National Highway Traffic Safety Administration (NHTSA) and the Emergency Medical Services for Children (EMSC) Program at the Health Resources Services Administration (HRSA) pilot tested the National Prehospital EBG Model for the development of a pediatric seizure guideline.

**OBJECTIVE**

The objective of this guideline is to recommend evidence-based practices for timely prehospital pediatric seizure cessation while avoiding respiratory depression and seizure recurrence.

**SCOPE**

This guideline applies to children for whom EMS personnel witness, either upon scene arrival or during prehospital transport, what they believe to be a seizure, defined as an episode of unresponsiveness with or without fever that is associated with one or more of the following: eye deviation, focal or generalized tonic or clonic movements, or loss of bowel or bladder control. The panel created the guideline with the assumption that this description of a patient’s seizure meets the time and/or frequency requirement for the definition of status epilepticus. It excludes patients whose seizure is presumed to be due to trauma.

**INTERPRETATION**

This guideline was developed using GRADE methodology and contains both strong and weak recommendations. According to the GRADE paradigm, the implication of a strong recommendation is that it should be adopted in policies and protocols in most settings covered by the scope of the guideline. When the evidence base is suboptimal the GRADE process does not restrict the formulation of recommendations, rather it provides a transparent and standardized method for identifying limitations to the reader. In the case of weak recommendations based on very low or low quality evidence, the reader is alerted to the lack of evidence, can follow along with the decision-making rationale, and can understand the values and preferences that contributed to the strength of each recommendation. This in turn could help policy makers appropriately adapt weak recommendations to their system, based on differing regional values and preferences.

None of the recommendations were made in the total absence of evidence.

**METHODS**

Further details on the methods used to generate this EBG may be found in a separate publication. This project was the first of two major initiatives to test the National Prehospital EBG Model approved by the Federal Interagency Committee on EMS (FICEMS) and the National EMS Advisory Council (NEMSAC) for the development, implementation, and evaluation of prehospital EBGs. A core working group from the NHTSA Office of EMS, EMSC Federal Project Office, EMSC National Resource Center, and the EBG National Steering Committee used a consensus-based process to select EBG panel members who were in the original IOM study group, members of NEMSAC, or EMSC grantees. Panel members were also chosen based on expertise in one or more of the following areas: pediatric emergency medicine (PEM), prehospital medicine, and/or evidence-based guideline development; the panel consisted of physicians, prehospital providers, and EMS researchers.

The panel used a face-to-face, modified Delphi technique to achieve consensus on all decisions. In March 2009, the EBG panel chose seizures as the clinical condition of focus due to its high incidence with risk of morbidity and/or mortality, the presence of evidence to inform diagnostic and therapeutic options, and persistent practice variation. An evidence-based medicine specialist trained the panel in the GRADE methodology for appraisal of a body of literature. The panel reached consensus on clinical questions framed in PICO (patient, intervention, comparison, outcome) format (Figure 1), which were then assigned to individual panel members for evidence retrieval and appraisal, followed by formulation of recommendations.

The scope of the evidence base drawn from the literature searches led to refinements or derivative PICO questions that more clearly represented the intent and full range of the original question (see Appendix A, available online); the derivative questions were also reviewed and approved by the panel. The panel updated and recorded their search terms and results in 2012 in order to identify relevant literature that had been published in the interim.

Each panelist created GRADE tables (evidence profiles) and drafted recommendations pertinent to his/her PICO question with proposals for strength of recommendation (strong or weak) and strength of the evidence (high, moderate, low, or very low). The panel reached consensus on the evidence quality, the prioritization of patient-centered outcomes, and the explicitly specified values and preferences; this helped the panel to reach consensus on the recommendations and their strength.
The panel drafted a patient care algorithm, which was subsequently approved and presented to stakeholders at the National Association of State EMS Officials (NASEMSO), FICEMS, NEMSAC, and the CDC Helicopter EMS (HEMS) Working Group. These organizations provided broad feedback, informing both this and subsequent implementation projects that applied the National Prehospital EBG Model. The updated literature searches for each PICO question, led to EBG revisions in several recommendations and modification of the algorithm, resulting in the need for the group to achieve consensus again in July 2012. In addition, the revised algorithm and recommendations were presented to the Pediatric Emergency Medicine Advisory Committee (PEMAC) of the Maryland Institute for EMS Systems, a statewide EMS oversight agency.

**RECOMMENDATIONS**

**Values and Preferences**

Timely and safe care is imperative in prehospital seizure management; thus the panel sought to ensure that the recommendations promoted timely seizure cessation while avoiding respiratory depression and seizure recurrence. In addition, prompt transport and minimizing scene time were also deemed to be important patient outcomes contributing to an understanding of values and preferences.

With respect to the EMS agencies, personnel, and health-care systems at large, minimizing cost to individual EMS agencies was taken into account in development of this prehospital guideline. Since many EMS agencies utilize a tiered dispatch approach, consideration of the scope of practice of both basic life support (BLS) and advanced life support (ALS) providers was also important to the panel. The panel attempted to factor in EMS provider preferences for ease of use of certain routes of medication, while also making recommendations that could be easily followed in a protocol algorithm format. Though the evidence quality may have been low or very low in many instances, the potential risks and harms were compelling in some cases and led the panel to make some strong recommendations.
Procedures: Glucometry

**Recommendation #1:**
We suggest that children with convulsive status epilepticus in the prehospital setting should have glucometry performed to assess for hypoglycemia, especially if they have diabetes.

*Evidence quality: Very low*

*Recommendation strength: Weak*

*Remarks: Glucometry in the pediatric prehospital patients has been successfully assessed by emergency medical technician (EMT)-basics, and abnormal results frequently prompt prehospital intervention.*

For long transports in which multiple doses of anticonvulsants, IV fluids, and/or other medications may be needed, IV or IO placement may be considered. Data demonstrate that ALS crews have a reasonable success rate in obtaining peripheral venous access on patients of all ages, with a relatively low complication rate. IO access is a good means of vascular access if it is absolutely needed, also with a relatively low complication rate. However, IV access may delay...
treatment and prolong scene time. Skill in obtaining IV and IO access can improve with simulation, and providers may benefit from continuing education for skill maintenance.

**Recommendation #6:**
We suggest that prehospital seizure management in children does not require IV placement to minimize seizure recurrence or adverse events.

*Evidence quality: Low*
*Recommendation strength: Weak*
*Remarks:* Studies show variable results for the rate of seizure recurrence with IV versus other routes of delivery of benzodiazepines. The evidence suggests that the rate of adverse events, including respiratory depression, is similar with either IV or alternative routes of delivery of benzodiazepines. Thus, placing an IV to deliver anticonvulsant therapy does not seem to confer greater safety. The effectiveness of non-IV routes and limiting the prolonged scene time associated with obtaining IV access drove this recommendation.

**Therapy: IV vs. Non-IV Treatment**

**Recommendation #7:**
We recommend that prehospital protocols for seizure management in children utilize alternative (non-IV) routes of drug administration as first-line therapy for treating children with status epilepticus.

*Evidence quality: Moderate*
*Recommendation strength: Strong*
*Remarks:* The evidence supports the use of alternative routes of administration as first-line therapy based on demonstrated equivalence or non-inferiority from randomized trials and prospective cohorts comparing IV vs. alternative routes of benzodiazepines used for patients in status epilepticus. One recent large multicenter study of children and adults with seizures treated in the prehospital setting demonstrated that intramuscular (IM) midazolam was not inferior to IV diazepam in terminating seizures prior to arrival in the emergency department.

Several authors have also assessed the time to seizure termination with IV vs. alternative routes of medication (intranasal (IN), IM, and buccal). In general, investigators have shown that while benzodiazepines delivered via an IV have a more rapid onset of action from dose delivery to seizure cessation, a greater amount of time is required to place the IV than to deliver the therapy by non-IV routes. Therefore, the total amount of time from the decision to treat with a benzodiazepine to seizure cessation is equivalent or less when alternative routes are used. Specifically, this has been shown for midazolam when delivered by the IM, IN, or buccal routes.

**Therapy: Non-IV vs. Non-IV Treatment**

**Recommendation #8:**
We recommend buccal midazolam over rectal (PR) diazepam for prehospital seizure cessation and control.

*Evidence quality: Low*
*Recommendation strength: Strong*
*Remarks:* Recently, two well-designed and well-executed randomized trials have suggested that the administration of buccal midazolam leads to more frequent seizure cessation than rectal (PR) diazepam. Comparatively, buccal midazolam also resulted in a greater reduction in the likelihood of seizure recurrence 1 hour after administration, with no difference in respiratory arrest or depression.

**Recommendation #9:**
We suggest IM midazolam over PR diazepam for prehospital seizure cessation and control.

*Evidence quality: Very low*
*Recommendation strength: Weak*
*Remarks:* Relative to the evidence for buccal midazolam, weaker evidence from one study suggests that IM/PR midazolam provides similar efficacy to IV/PR diazepam; however, subgroup analysis directly comparing IM midazolam and PR diazepam was not conducted. We identified no other studies of higher quality that compare IM and rectal benzodiazepines.

**Recommendation #10:**
We suggest intranasal (IN) midazolam over PR diazepam for prehospital seizure cessation and control.

*Evidence quality: Very low*
*Recommendation strength: Weak*
*Remarks:* Relative to the evidence for buccal midazolam, weaker but consistent evidence also suggests that intranasal (IN) midazolam may improve outcomes compared to rectal diazepam.

For recommendations #8–10: The recommendations for buccal, IN, and IM routes rather than PR were based both on efficacy data and anticipated parent and provider preference for these routes rather than PR. Each recommendation is distinctly stated, since the
evidence quality and the recommendation strength is uniquely based on the evidence comparing only two routes at a time, rather than an aggregate of the evidence comparing rectal to all other routes. The efficacy data to support buccal midazolam administration are the strongest. Algorithm simplicity for implementation, as opposed to comparative data from research, drove the recommendation to use a consistent dose of 0.2 mg/kg for any of these routes. There are currently no published studies comparing these specific alternative routes of delivering midazolam with each other.

**Therapy: IV vs. IV Treatment**

**Recommendation #11:**
We suggest IV diazepam, midazolam, or lorazepam as equivalent therapeutic options when IV benzodiazepines are administered.

*Evidence quality: Very low*
*Recommendation strength: Weak*

*Remarks:* There is no apparent difference in efficacy between IV midazolam and IV diazepam in terms of time to seizure cessation. The data are largely not from the prehospital setting, with studies demonstrating >90% seizure resolution with either medication. Intra, 66–68 Intravenous lorazepam has been compared to IV diazepam in a pediatric accident and emergency department, with similar efficacy.

Though data are limited, IV midazolam has been reported to have slightly higher rates of respiratory depression than diazepam. However, studies have had small sample sizes, resulting in imprecise estimates of respiratory depression. The available data describe respiratory depression from IV benzodiazepines in fewer than 20% of patients with much lower rates of resultant intubation.

**Recommendation #12:**
We suggest a dose of 0.05–0.1 mg/kg for IV diazepam (rate unknown).

*Evidence quality: Low*
*Recommendation strength: Strong*

*Remarks:* One prehospital study demonstrated that a dose of 0.05–0.1 mg/kg IV or PR diazepam had similar efficacy but less respiratory depression than 0.2–0.5 mg/kg of IV or PR diazepam. A small prehospital study also demonstrated that mean doses of 0.2 mg/kg of IV diazepam resulted in more respiratory depression than a mean rectal dose of 0.6 mg/kg.

**Recommendation #13:**
We suggest a dose of 0.05–0.1 mg/kg over 15–30 seconds for IV lorazepam.

*Evidence quality: Low*
*Recommendation strength: Weak*

*Remarks:* Intravenous lorazepam (0.05–0.1 mg/kg over 15–30 seconds) has been compared to IV diazepam (0.3–0.4 mg/kg over 15–30 seconds) in a pediatric accident and emergency department, with similar efficacy and less respiratory depression. Another study found no increase in respiratory depression using IV lorazepam 0.1 mg/kg when compared to IV diazepam 0.2 mg/kg. Studies in adults also found no difference in respiratory depression when comparing 2 mg IV lorazepam to 10 mg IV diazepam. Intravenous lorazepam at a dose of 0.05–0.1 mg/kg over 15–30 seconds, appears to be efficacious and safe for the termination of pediatric seizures without an increase in adverse side effects.

**Recommendation #14:**
We suggest a dose of 0.1 mg/kg for IV midazolam (rate unknown).

*Evidence quality: Very low*
*Recommendation strength: Weak*

*Remarks:* One study demonstrated that midazolam (both IV 0.1 mg/kg and IM 0.15 mg/kg) resulted in similar efficacy with less apnea than diazepam (IV 0.1 mg/kg and PR 0.5 mg/kg), but the rate of administration and whether one route accounted for more apnea than the other was not reported.

For recommendations #12–14, each recommendation is distinctly stated, since the evidence quality and the recommendation strength is uniquely based on the evidence comparing differing doses of a single medication, rather than an aggregate of the evidence comparing doses for all three benzodiazepines noted. Simplicity of the algorithm, no clear increase in efficacy with higher doses, and higher rates of respiratory depression at higher doses drove the recommendation to use a consistent dose and rate of 0.1 mg/kg over 30 seconds for all three IV benzodiazepines (midazolam, lorazepam, diazepam) reviewed.
Medical Direction

**Recommendation #15:**
We suggest that in children with convulsive status epilepticus requiring medication management in the prehospital setting, trained prehospital personnel should be allowed to administer medication without online medical direction.

**Evidence quality:** Very low  
**Recommendation strength:** Weak  
**Remarks:** There are few studies in the prehospital setting comparing the relative effectiveness and safety of offline medical direction to online medical direction for most conditions, including the treatment of pediatric seizures. The literature generally supports the use of offline medical direction in the form of written protocols to guide treatment by trained personnel. There is no literature that supports the need for online medical direction for medication management of a seizing pediatric patient. The literature favoring online medical direction acknowledged that prehospital providers infrequently made errors using offline protocols and infrequently failed to carry out orders already recommended in offline protocols.

**DISCUSSION**

This is the first use of the GRADE framework, of which we are aware, to develop an EBG for prehospital care. It is also the first attempt at testing a national model of guideline development that seeks to integrate evidence into standardized protocols for EMS providers. The scope of the project was guideline development using the Prehospital EBG Model Process; implementation and outcomes assessment were beyond the scope of this project. Although the vast majority of evidence was of low or very low quality, the GRADE methodology facilitated the explicit combination of the available evidence with consensus-derived patient and provider preference considerations in order to provide transparent recommendations. As expected, we found few relevant or higher quality studies conducted in the prehospital setting of seizure management in children, leading to a consistent “indirectness” of the available evidence and the need to rely mainly on emergency department-based studies or prehospital studies conducted on mainly adult patients. The result of this low quality evidence and indirectness led to a predominance of weak recommendations. The methodology used, however, aided the creation of a user-friendly management algorithm based on the best available evidence that will enable individual EMS agencies to openly discuss the recommendations of each step and tailor the implementation of the scheme to their local or regional circumstances.

The recommendations presented address controversies in the prehospital management of children with ongoing nontraumatic seizures, including the use of glucometry to check for hypoglycemia, the specific anti-epileptic medication to use, and the preferred route of administration. Hypoglycemia is the underlying etiology of convulsive status epilepticus in children in approximately 1–6% of cases. Our recommendations for use of glucometry were based on the limited evidence suggesting that glucometry can be validly and reliably performed in the prehospital setting and that treatment of hypoglycemia leads to decreased mortality. For children with seizures, no comparative data exist to determine whether the assessment of glucometry is preferred rather than empiric therapy for hypoglycemia.

Since prehospital providers frequently encounter a child who requires antiepileptic medication when dispatched for a pediatric seizure, the dilemma for medical directors in designing a seizure protocol lies in which specific medication(s) to use and via what route. The available evidence suggests that administration of benzodiazepines by nonparenteral routes leads to more rapid seizure cessation compared to the IV route, in large part because IV access can be time-consuming. Importantly, recent ED-based studies favor the use of buccal, intranasal, and IM midazolam rather than the most commonly used rectal diazepam, although further head-to-head comparisons are necessary.

While the work described herein represents a systematic approach to the development of an EBG applicable to one pediatric prehospital condition (i.e., status epilepticus), development of a guideline represents only part of the challenge in improving outcomes of care. Local and regional protocols that emerge from this guideline would allow an assessment of real-world application. In the absence of strategies for active dissemination of the guideline and tailoring to context, the evidence from the individual studies used to create this guideline may take over a decade to be translated into practice, without guarantee of an aggregate approach that aligns the science with care delivery. Implementation of the EBG through local protocols could form the shared baselines from which training of prehospital providers, standardization of supplies, and strategies for evaluation of outcomes can be undertaken.

Furthermore, it is important to note that the creation of this guideline was an iterative process, with guideline refinement over time to arrive at a more complete and up-to-date product. Indeed, this process highlighted the need for a plan to periodically update the evidence and recommendations. Additionally, the development of this guideline required a substantial commitment and hinged upon a large amount of experiential and fundamental knowledge from its...
participants, illustrating the importance of using a systematic approach such as GRADE and the need for large organizations (health-care systems/networks) and national/international agencies (e.g., U.S. Preventative Services Task Force) to take on these efforts. The steering committee for the FICEMS Technical Working Group oversaw the development of the National Prehospital EBG Model. Central organizations will become critically important to effective cataloging of EBGs, iterative completion of updates, dissemination of template protocols for local application, and defining best practices for implementation and outcomes assessment. The selection of future topics by other local, regional, or national organizations would ideally address issues in pediatric prehospital care based on criteria of high incidence, large resource consumption, associated morbidity and mortality, and known variation in practice.

LIMITATIONS
Although we used the GRADE framework, there are limitations to the specific approach we took to develop the seizure guideline. The selected panel had many PEM physicians and proportionally fewer EMS physicians and prehospital providers; no neurologists or parent representatives participated in the initial guideline creation. The lack of multiple randomized trials prevented the creation or evaluation of systematic reviews or meta-analyses to assess each PICO question. However, research specialists used standardized search terms in both the 2009 and 2012 literature searches to maximize consistency in the evidence retrieval process. Additionally, we neither conducted any data pooling to provide summary effect estimates nor performed any interobserver reliability assessments of study validity. Further, the preferences used in the guideline were consensus-derived from the study group, without the conduct of formal assessments of parents and prehospital providers. In addition, the pilot nature of this process required several years to obtain stakeholder and federal agency feedback, thus necessitating the updated literature search and guideline revision prior to initial publication. Development of this seizure EBG did not employ the last two steps of the National Prehospital EBG Model, which focus on implementation and evaluation of the protocol’s impact on patient and systems-centered outcomes. Future iterations of this guideline would be strengthened by such enhanced methodology.

CONCLUSIONS
Using the National Prehospital EBG Model and GRADE methodology, we have developed a pediatric seizure guideline that emphasizes the routine assessment of capillary blood glucometry and the use of buccal, IM, or intranasal benzodiazepines over IV or rectal routes for seizure cessation. This guideline can be customized by EMS agencies to develop local offline protocols for care. Guideline implementation and evaluation of its impact on patient and systems-centered outcomes are important next steps for this pilot work.

References
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50. Muchoho SN, Obiero K, Newton CR, Ogutu BR, Edwards G, Kokwaro GO. Pharmacokinetics and clinical efficacy of

**SUPPLEMENTARY MATERIAL AVAILABLE ONLINE**

Appendix A: PICO Questions and Evidence Summary
Appendix B: GRADE Tables

Supplemental content can be viewed and downloaded at [http://informahealthcare.com/pec](http://informahealthcare.com/pec).