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AN EVIDENCE-BASED GUIDELINE FOR PEDIATRIC PREHOSPITAL SEIZURE MANAGEMENT USING GRADE METHODOLOGY

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ABSTRACT

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 formu-

late 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. Future 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 sequelae can be substantial if not rapidly treated.¹ 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.²⁻⁸ Prehospital providers may have more difficulty in rapidly obtaining intravenous (IV) access in children relative to adults,^{9,10} and the stress of managing critically ill children poses an added challenge.^{11,12} While high quality studies are available to guide the management of adult patients with seizures in the prehospital setting,^{12,13} more research is needed to guide the practice of pediatric seizure management in the prehospital setting.¹⁴

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.^{15a,b,c,d,16,17} 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.^{16–19}

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 appropri-

ately 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.^{21b} 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.¹⁷ 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.^{16–21} 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.¹⁹

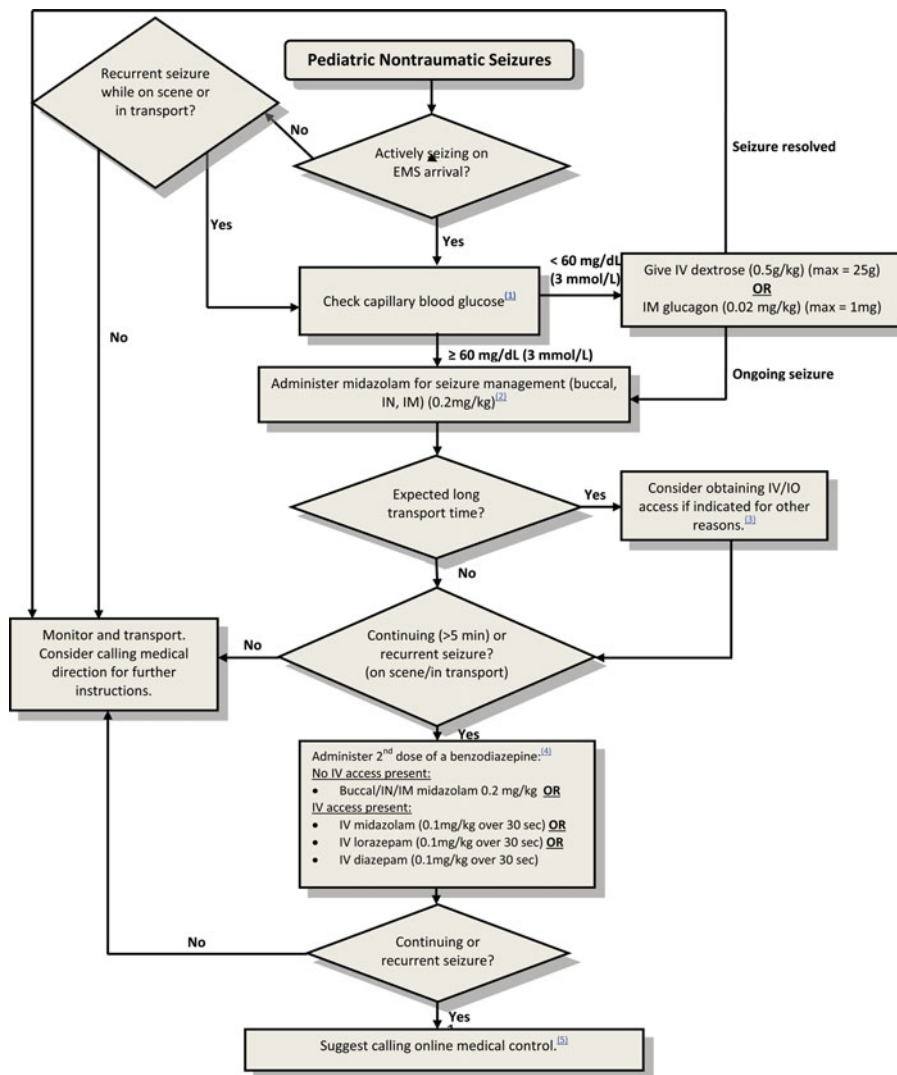


FIGURE 1. Patient care algorithm for an evidence-based guideline for pediatric prehospital seizure management.

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.²² The relatively low cost of the procedure, with respect to the potential delay in care or harm for not checking it, contributed to the recommendation. The guideline committee believed that there was benefit in systematically screening all seizing children for hypoglycemia, since the risks involved were minimal.

Recommendation #2:

We suggest that children with prehospital seizures should have blood glucose checked from a capillary source; a venous check would be a less preferred alternative to assess for hypoglycemia.

Evidence quality: Low

Recommendation strength: Weak

Remarks: It is noted that the correlation between bedside capillary and venous lab glucose tests is discordant based on various studies.^{23–26} Adults in the intensive care setting with poor perfusion are especially prone to have differing results between bedside capillary glucometry and venous lab glucose tests.^{27,29} In addition, venous samples may underestimate hypoglycemia.²⁷ Despite these limitations, the recommendation is supported by knowledge that the assessment of hypoglycemia by prehospital providers has 91% sensitivity and 92% specificity when compared to lab values in the hospital.²⁸

Recommendation #3:

We recommend that children with prehospital hypoglycemia (glucose <60 mg/dL or <3 mmol/L) should be treated with either intravenous (IV) dextrose or intramuscular (IM) glucagon.

Evidence quality: Low

Recommendation strength: Strong

Remarks: The use of prehospital protocols for seizures recommending IM glucagon or IV glucose for treatment of hypoglycemia is associated with decreased mortality.^{25,29} Additionally, the treatment of prehospital hypoglycemia has been demonstrated to be safe.^{25,30,31}

Recommendation #4:

We suggest that patients found to be hypoglycemic in the setting of a prehospital seizure should be transported to an emergency department, regardless of whether they return to baseline mental status after treatment.

Evidence quality: Low

Recommendation strength: Weak

Remarks: Even when treated in the prehospital setting, hypoglycemia, whose etiology is not entirely certain, can recur.³² Therefore, most children found to be hypoglycemic in the prehospital setting should be transported to an emergency department, regardless of whether they return to baseline mental status after treatment.³³

Procedures: IV Access

Recommendation #5:

We recommend that for children who are post-ictal upon arrival of EMS personnel in the prehospital setting, IV placement is not necessary if transport time is short, since alternative routes for administration of anticonvulsants should be utilized. If transport time is expected to be long, either precautionary IV or intraosseous (IO) needle placement may be considered as it may be useful for other aspects of patient care.

Evidence quality: Low

Recommendation strength: Strong

Remarks: The need to obtain and use IVs for seizure control appears to be very uncommon, because a large majority of seizures stop before EMS arrives^{33,34} or access is established. Therefore, few patients with seizures actually benefit from vascular access.^{35,36} Additionally, alternative routes of anticonvulsant administration may be more efficient and as effective. Despite the relatively low complication rate, the panel recommendations were based on the essential considerations of minimizing unnecessary procedures, the ease of administration of non-IV therapies by prehospital providers, and avoidance of prolonged scene time.

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,^{36–40} with a relatively low complication rate.⁴¹ IO access is a good means of vascular access if it is absolutely needed,⁴² also with a relatively low complication rate.^{42–44} However, IV access may delay

treatment and prolong scene time.⁴⁵ Skill in obtaining IV and IO access can improve with simulation,^{46,47} 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.^{13,48–50} The evidence suggests that the rate of adverse events, including respiratory depression, is similar with either IV or alternative routes of delivery of benzodiazepines.^{13,51–55} Thus, placing an IV to deliver anti-convulsant 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.^{13,51–53,55–57} 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.¹³

Several authors have also assessed the time to seizure termination with IV vs. alternative routes of medication (intranasal (IN), IM, and buccal).^{13,51,53,55,58,59} 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.^{13,55,59,60,61} 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.^{13,55,57–59,61}

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.^{60,61} 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.⁶² 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.^{63–65}

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.^{56,66–68} 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.^{65,69,71}

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.⁷⁰ 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.⁷¹

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.⁷² Another study found no increase in respiratory depression using IV lorazepam 0.1 mg/kg when compared to IV diazepam 0.2 mg/kg.⁷³ Studies in adults also found no difference in respiratory depression when comparing 2 mg IV lorazepam to 10 mg IV diazepam.^{74,75} 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.⁶⁵

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^{76,77} 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.⁷⁸ 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.^{79,80} 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.^{25,32} 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.⁴⁸ 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.^{62–67}

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.⁸¹ 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.¹⁷ 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.⁸²

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

1. Wheless JW. Treatment of status epilepticus in children. *Pediatr Ann.* 2004;33(6):376–83.
2. Gausche-Hill M. Pediatric continuing education for out-of-hospital providers: is it time to mandate review of pediatric knowledge and skills? *Ann Emerg Med.* 2000;36(1):72–74.
3. Glaeser PW, Linzer J, Tunik MG, Henderson DP, Ball J. Survey of nationally registered emergency medical services providers: pediatric education. *Ann Emerg Med.* 2000;36(1):33–38.
4. Gausche-Hill M, Henderson DP, Brownstein D, Foltin GL. The education of out-of-hospital emergency medical personnel in pediatrics: report of a national task force. *Prehosp Emerg Care.* 1998;2(1):56–61.
5. Su E, Mann NC, McCall M, Hedges JR. Use of resuscitation skills by paramedics caring for critically injured children in Oregon. *Prehosp Emerg Care.* 1997;1(3):123–127.
6. Su E, Schmidt TA, Mann NC, Zechnich AD. A randomized controlled trial to assess decay in acquired knowledge among paramedics completing a pediatric resuscitation course. *Acad Emerg Med.* 2000;7(7):779–786.
7. Lammers RL, Byrwa MJ, Fales WD, Hale RA. Simulation-based assessment of paramedic pediatric resuscitation skills. *Prehosp Emerg Care.* 2009;13(3):345–356.
8. Shah MN, Cushman JT, Davis CO, Bazarian JJ, Auinger P, Friedman B. The epidemiology of emergency medical services use by children: an analysis of the national hospital ambulatory medical care survey. *Prehosp Emerg Care.* 2008;12(3):269–76.
9. Sampalis JS, Lavoie A, Williams JI, Mulder DS, Kalina M. Impact of on-site care, prehospital time, and level of in-hospital care on survival in severely injured patients. *J Trauma.* 1993;34(2):252–61.
10. Lillis KA, Jaffe DM. Prehospital intravenous access in children. *Ann Emerg Med.* 1992;21(12):1430–4.
11. Lammers R, Byrwa M, Fales W. Root causes of errors in a simulated prehospital pediatric emergency. *Acad Emerg Med.* 2012;19(1):37–47.
12. Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, Gottwald MD, O'Neil N, Neuhaus JM, Segal MR, Lowenstein DH. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med.* 2001;345(9):631–7.
13. Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, Barsan W; NETT Investigators. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med.* 2012;366(7):591–600.
14. Foltin GL, Dayan P, Tunik M, Marr M, Leonard J, Brown K, Hoyle J, Lerner EB; Prehospital Working Group of the Pediatric Emergency Care Applied Research Network. Priorities for pediatric prehospital research. *Prehosp Emerg Care.* 2010;26(10):773–7.
- 15a. Institute of Medicine (U.S.) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. *Clinical Practice Guidelines We Can Trust.* Washington, DC: The National Academies Press; 2011.
- 15b. National Highway Traffic Safety Administration. National EMS Research Agenda. US Department of Transportation, Washington, DC, 2001. Available at www.ems.gov/pdf/EMSResearchAgenda.pdf. Accessed February 4, 2013.

- 15c. Institute of Medicine (U.S.) Committee on the Future of Emergency Care in the United States Health System. *Emergency Medical Services: At the Crossroads*. Washington, DC: The National Academies Press; 2006.
- 15d. Lang ES, Spaite DW, Oliver ZJ, Gotschall CS, Swor RA, Dawson DE, Hunt RC. A National model for developing, implementing and evaluating evidence-based guidelines for prehospital care. *Acad Emerg Med*. Feb 2012; 19(2): 201–9.
16. Brozek JL, Akl EA, Alonso-Coello P, Lang D, Jaeschke R, Williams JW, Phillips B, Lelgemann M, Lethaby A, Bousquet J, Guyatt GH, Schunemann HJ; GRADE Working Group. Grading quality of evidence and strength of recommendations in clinical practice guidelines, part 1 of 3: an overview of the GRADE approach and grading quality of evidence about interventions. *Allergy*. 2009;64(5):669–77.
17. Brozek JL, Akl EA, Jaeschke R, Lang DM, Bossuyt P, Glasziou P, Helfand M, Ueffing E, Alonso-Coello P, Meerpohl J, Phillips B, Horvath AR, Bousquet J, Guyatt GH, Schunemann HJ; GRADE Working Group. Grading quality of evidence and strength of recommendations in clinical practice guidelines, part 2 of 3: the GRADE approach to grading quality of evidence about diagnostic tests and strategies. *Allergy*. 2009;64(8):1109–16.
18. Guyatt GH, Oxman AD, Kunz R, Jaeschke R, Helfand M, Liberati A, Vist GE, Schunemann HJ; GRADE Working Group. Incorporating considerations of resources use into grading recommendations. *BMJ*. 2008;336(7654):1170–3.
19. Schünemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, Williams JW, Kunz R, Craig J, Montori VM, Bossuyt P, Guyatt GH; GRADE Working Group. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ*. 2008; 336(7653):1106–10.
20. Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328:1490–4.
- 21a. Jaeschke R, Guyatt GH, Dellinger P, Schunemann H, Levy MM, Kunz R, Norris S, Bion J; GRADE Working Group. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. *BMJ*. 2008;337:327–30.
- 21b. Brown KM, Macias CG, Dayan PS, Shah MI, Weik TS, Wright JL, Lang ES. The development of evidence-based prehospital guidelines using GRADE-based methodology. *Prehosp Emerg Care*. 2014; in press.
22. Vilke GM, Castillo EM, Ray LU, Murrin PA, Chan TC. Evaluation of pediatric glucose monitoring and hypoglycemic therapy in the field. *Pediatr Emerg Care*. 2005;21(1):1–5.
23. Funk DL, Chan L, Lutz N, Verdile VP. Comparison of capillary and venous glucose measurements in healthy volunteers. *Prehosp Emerg Care*. 2001;5(3):275–7.
24. Desachy A, Vuagnat AC, Ghazali AD, Baudin OT, Longuet OH, Calvat SN, Gissot V. Accuracy of bedside glucometry in critically ill patients: influence of clinical characteristics and perfusion index. *Mayo Clin Proc*. 2008;83(4):400–5.
25. Holstein A, Kuhne D, Elsing HG, Thiessen E, Plaschke A, Widjaja A, Vogel MY, Egberts EH. Practicality and accuracy of prehospital rapid venous blood glucose determination. *Am J Emerg Med*. 2000;18(6):690–4.
26. Kulkarni A, Saxena M, Price G, O’Leary MJ, Jacques T, Myburgh JA. Analysis of blood glucose measurements using capillary and arterial blood samples in intensive care patients. *Intensive Care Med*. 2005;31(1):142–5.
27. Kumar G, Sng BL, Kumar S. Correlation of capillary and venous glucometry with laboratory determination. *Prehosp Emerg Care*. 2004;8(4):378–83.
28. Jones JL, Ray VG, Gough JE, Garrison HG, Whitley TW. Determination of prehospital blood glucose: a prospective, controlled study. *J Emerg Med*. 1992;10(6):679–82.
29. Holstein A, Plaschke A, Vogel MY, Egberts EH. Prehospital management of diabetic emergencies – a population-based intervention study. *Acta Anaesthesiol Scand*. 2003;47(5):610–5.
30. Roberts K, Smith A. Outcome of diabetic patients treated in the prehospital arena after a hypoglycemic episode, and an exploration of treat and release protocols: a review of the literature. *Emerg J Med*. 2003;20(3):274–6.
31. Sporer KA, Johnson NJ. Detailed analysis of prehospital interventions in medical priority dispatch system determinants. *West J Emerg Med*. 2011;12(1):19–29.
32. Cain E, Ackroyd-Stolarz S, Alexiadis P, Murray D. Prehospital hypoglycemia: the safety of not transporting treated patients. *Prehosp Emerg Care*. 2003;7(4):458–65.
33. Richard J, Osmond MH, Nesbitt L, Stiell IG. Management and outcomes of pediatric patients transported by emergency medical services in a Canadian prehospital system. *Can J Emerg Med*. 2006;8(1):6–12.
34. Deasy C, Ryan D, O’Donnell C, Cusack S. The impact of a prehospital medical response unit on patient care and emergency department attendances. *Ir Med J*. 2008;101(2):1–2.
35. Babl FE, Vinci RJ, Bauchner H, Mottley L. Pediatric pre-hospital advanced life support care in an urban setting. *Pediatr Emerg Care*. 2001;17(1):5–9.
36. Schwartz D, Amir L, Dichter R, Figenberg Z. The use of a powered device for intraosseous drug and fluid administration in a national EMS: a 4-year experience. *J Trauma*. 2008;64(3):650–5.
37. Liberman M, Mulder D, Sampalis J. Advanced or basic life support for trauma: meta-analysis and critical review of the literature. *J Trauma*. 2000;49(4):584–99.
38. Hartholt KA, van Lieshout EM, Thies WC, Patka P, Schipper IB. Intraosseous devices: a randomized controlled trial comparing three intraosseous devices. *Pediatr Emerg Care*. 2010;14(1):6–13.
39. Gerritse BM, Scheffer GJ, Draaisma JM. Prehospital intraosseous access with the bone injection gun by a helicopter-transported emergency medical team. *J Trauma*. 2009;66(6):1739–41.
40. Gerritse BM, Schalkwijk A, Pelzer BJ, Draaisma JM. Advanced medical life support procedures in vitality compromised children by a helicopter emergency medical service. *BMC Emerg Med*. 2010;10:6.
41. Zarate L, Mandlco B, Wilshaw R, Ravert P. Peripheral intravenous catheters started in prehospital and emergency department settings. *J Trauma Nurs*. 2008;15(2):47–52.
42. Frascone RJ, Jensen J, Wewerka SS, Salzman JG. Use of the pediatric EZ-IO needle by emergency medical services providers. *Pediatr Emerg Care*. 2009;25(5): 329–32.
43. de Caen A. Venous access in the critically ill child. *Pediatr Emerg Care*. 2007;23(6):422–7.
44. Tobias JD, Ross AK. Intraosseous infusions: a review for the anesthesiologist with a focus on pediatric use. *Anesth Analg*. 2010;110(2):391–401.
45. Nicholl J, Hughes S, Dixon S, Turner J, Yates D. The costs and benefits of paramedic skill in pre-hospital trauma care. *Health Technol Assess*. 1998;2(17):1–72.
46. De Lorenzo RA, Abbott CA. Effect of a focused and directed continuing education program on prehospital skill maintenance in key resuscitation areas. *J Emerg Med*. 2007;33(3): 293–7.
47. Lamhaut L, Dagrón C. Comparison of intravenous and Intraosseous access by pre-hospital medical emergency personnel with and without CBRN protective equipment. *Resuscitation*. 2010;81(1):65–8.
48. Arya R, Gulati S, Kabra M, Sahu JK, Kalra V. Intranasal versus intravenous lorazepam for control of acute seizures in children: a randomized open-label study. *Epilepsia*. 52(4):788–93.
49. Muchohi SN, Kokwaro GO, Ogutu BR, Edwards G, Ward SA, Newton CR. Pharmacokinetics and clinical efficacy of midazolam in children with severe malaria and convulsions. *Br J Clin Pharmacol*. 2008;66(4):529–38.
50. Muchohi SN, Obiero K, Newton CR, Ogutu BR, Edwards G, Kokwaro GO. Pharmacokinetics and clinical efficacy of

- lorazepam in children with severe malaria and convulsions. *Br J Clin Pharmacol.* 65(1):12–21.
51. Mahmoudian T, Zadeh MM. Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children. *Epilepsy Behav.* 2004;5(2):253–5.
 52. Talukdar B, Chakrabarty B. Efficacy of buccal midazolam compared to intravenous diazepam in controlling convulsions in children: a randomized control trial. *Brain Dev.* 2009;31(10):744–9.
 53. Vilke GM, Sharieff GQ, Marino A, Gerhart AE, Chan TC. Midazolam for the treatment of out-of-hospital pediatric seizures. *Prehosp Emerg Care.* 2002;6(2):215–7.
 54. Lahat E, Goldman M, Barr J, Bistrizter T, Berkovitch M. Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomized study. *Br Med J.* 2000;321(7253):83–6.
 55. Shah I, Deshmukh CT. Intramuscular midazolam vs. intravenous diazepam for acute seizures. *Indian J Pediatr.* 2005;72(8):667–70.
 56. McMullan J, Sasson C, Pancioli A, Silbergleit R. Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: a meta-analysis. *Acad Emerg Med.* 2010;17(6):575–82.
 57. Chin RF, Neville BG, Peckham C, Wade A, Bedford H, Scott RC. Treatment of community-onset, childhood convulsive status epilepticus: a prospective, population-based study. *Lancet Neurol.* 2008;7(8):696–703.
 58. Mittal P, Manohar R, Rawat AK. Comparative study of intranasal midazolam and intravenous diazepam sedation for procedures and seizures. *Indian J Pediatr.* 2006;73(11):975–8.
 59. Chamberlain JM, Altieri MA, Futterman C, Young GM, Ochsen-schlager DW, Waisman Y. A prospective, randomized study comparing intramuscular midazolam with intravenous diazepam for the treatment of seizures in children. *Pediatr Emerg Care.* 1997;13(2):92–4.
 60. McIntyre J, Robertson S, Norris E, Appleton R, Whitehouse WP, Phillips B, Martland T, Berry K, Collier J, Smith S, Choonara I. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomized controlled trial. *Lancet.* 2005;366(9481):205–10.
 61. Mpimbaza A, Ndeezzi G, Staedke S, Rosenthal PJ, Byarugaba J. Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial. *Pediatrics.* 2008;121(1):e58–e64.
 62. Rainbow J, Browne GJ, Lam LT. Controlling seizures in the prehospital setting: diazepam or midazolam? *J Paediatr Child Health.* 2002;38(6):582–6.
 63. Fisgin T, Gurer Y, Tezic T, Senbil N, Zorlu, Okuyaz C, Akgun D. Effects of intranasal midazolam and rectal diazepam on acute convulsions in children: prospective randomized study. *J Child Neurol.* 2002;17(2):123–6.
 64. Bhattacharyya M, Kalra V, Gulati S. Intranasal midazolam vs rectal diazepam in acute childhood seizures. *Pediatr Neurol.* 2006;34(5):355–9.
 65. Holsti M, Dudley N, Schunk J, Adelgais K, Greenberg R, Olsen C, Healy A, Firth S, Filloux F. Intranasal midazolam vs rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy. *Arch Pediatr Adolesc Med.* 2010;164(8):747–53.
 66. Yoshikawa H, Yamazaki S, Abe T, Oda Y. Midazolam as a first-line agent for status epilepticus in children. *Brain Dev.* 2000;22(4):239–42.
 67. Galvin GM, Jelinek GA. Midazolam: an effective intravenous agent for seizure control. *Arch Emerg Med.* 1987;4(3):169–72.
 68. Papavasiliou AS, Kotsalis C, Paraskevoulakos E, Karagounis P, Rizou C, Bazigou H. Intravenous midazolam in convulsive status epilepticus in children with pharmacoresistant epilepsy. *Epilepsy Behav.* 2009;14(4):661–4.
 69. Hayashi K, Osawa M, Aihara M, Izumi T, Ohtsuka Y, Hagi-noya K, Kato I, Kaneko K, Sugai K, Takahashi T, Hamano S, Matsukura M, Miura H, Minagawa K, Yamano T, Yamamoto H, Yamanouchi H, Yoshikawa H; Research Committee on Clinical Evidence of Medical Treatment of Status Epilepticus in Childhood. Efficacy of intravenous midazolam for status epilepticus in childhood. *Pediatr Neurol.* 2007;36(6):366–72.
 70. Galustyan SG, Walsh-Kelly CM, Szewczuga D, Bergholte J, Hennes H. The short-term outcome of seizure management by prehospital personnel: a comparison of two protocols. *Pediatr Emerg Care.* 19(4):221–5.
 71. Alldredge BK, Wall DB, Ferriero DM. Effect of prehospital treatment on the outcome of status epilepticus in children. *Pediatr Neurol.* 12(3):213–6.
 72. Appleton R, Sweeney A, Choonara I, Robson J, Molyneux E. Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus. *Dev Med Child Neurol.* 1995;37(8):682–8.
 73. Sreenath TG, Gupta P, Sharma KK, Krishnamurthy S. Lorazepam versus diazepam-phenytoin combination in the treatment of convulsive status epilepticus in children: a randomized controlled trial. *Eur J Paediatr Neurol.* 14(2):162–8.
 74. Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, Gottwald MD, O'Neil N, Neuhaus JM, Segal MR, Lowenstein DH. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med.* 345(9):631–7.
 75. Leppik IE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA.* 249(11):1452–4.
 76. Holliman CJ, Wuerz RC, Vazquez-de Miguel G, Meador SA. Comparison of interventions in prehospital care by standing orders versus interventions ordered by direct (on-line) medical command. *Prehosp Disaster Med.* 1994;9(4):202–9.
 77. Wuerz RC, Swope GW, Holliman J, Vazquez-de Miguel G. On-line medical direction: a prospective study. *Prehosp Disaster Med.* 1995;10(3):51–4.
 78. Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill S, Liberati A, O'Connell D, Oxman AD, Phillips B, Schunemann H, Edejer TT, Vist GE, Williams JW; GRADE Working Group. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. *BMC Health Serv Res.* 2004;4(1):38.
 79. Lewena S, Pennington V, Acworth J, Thornton S, Ngo P, McIntyre S, Krieser D, Neutze J, Speldewinde D. Emergency management of pediatric convulsive status epilepticus: a multicenter study of 542 patients. *Pediatr Emerg Care.* 2009;25(2):83–7.
 80. Martin-Gill C, Hostler D, Callway CW, Prunty H, Roth RN. Management of prehospital seizure patients by paramedics. *Prehosp Emerg Care.* 2005;21(1):1–5.
 81. Balas EA, Boren SA. Managing Clinical Knowledge for Health Care Improvement. *Yearbook of Medical Informatics 2000: Patient-centered Systems.* Stuttgart, Germany: Schattauer; 2000:65–70.
 82. Chumpitazi CE, Barrera P, Macias CG. Diagnostic accuracy and therapeutic reliability in pediatric emergency medicine: the role of evidence-based guidelines. *Clin Pediatr Emerg Med.* 2011;12(2):113–20.

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>.