Seizures in the pediatric population in the prehospital setting are important because they have a relatively high prevalence and potential for morbidity when prolonged. While there is debate about how long a patient can be in status epilepticus before the patient begins to suffer neurological damage, 15% of seizures lasting 30 minutes or longer in children can be complicated by focal neurological deficits, cognitive impairment, behavior problems, airway compromise, or other adverse events. The incidence of status epilepticus is approximately 20 per 100,000, with the most common cause being prolonged febrile seizures. It has been estimated that 2% to 5% of children experience febrile seizures at some point in their lives. Seizures account for 15% of all pediatric emergency medical services (EMS) calls in the USA, making it the second most prevalent condition in EMS pediatric transports, after traumatic injury. Since seizures are a common cause of EMS transports for pediatric patients, utilization of best practices for the management of seizures is essential.

The EMS for Children program has been a significant driver for identifying best practices for prehospital and hospital-based emergency care through research, education, and advocacy. In addition, EMS for Children has been a national leader in the development of prehospital evidence-based guidelines. Since the management of pediatric seizures in the prehospital setting is an important topic, the EMS for Children program, in collaboration with the National Highway Traffic Safety Administration (NHTSA), chose this topic as the first guideline to be developed using the National Prehospital Evidence-Based Guideline Model Process. This guideline, along with others on air medical transport and pain management in the setting of trauma have been recently published. In addition, guidelines such as these...
have the potential to be incorporated into national resources that are in development, including the collaboration between the National Association of State EMS Officials and NHTSA to create a set of Model Clinical EMS Guidelines.

Some controversy exists over the optimal management of prehospital seizures, especially regarding medication choice, dosing, and routes of administration. The guideline developed through the collaboration between EMS for Children and NHTSA addresses these controversies and identifies topics needing further study. The three anticonvulsant medications most commonly studied in the treatment of pediatric seizures are diazepam, midazolam, and lorazepam. These medications have been compared in the medical literature in varying doses and routes of administration, including intravenous (IV), intraoosseous (IO), intramuscular (IM), rectal (PR), buccal, and intranasal (IN).

Several themes become apparent upon review of the literature regarding anticonvulsant use for pediatric seizures in the prehospital environment. First, IV access is not necessary for timely seizure cessation or minimization of adverse events. Second, rectal is the route that is least preferred by EMS personnel when compared to the IN, IM, and buccal routes. The literature also provides guidance on issues related to medication-induced respiratory depression, the timing of medication administration, the use of glucometry, and medication dosing.

### CHOICE OF MEDICATION

There are numerous studies that have compared several benzodiazepines given by several routes (Table 1). The studies comparing different benzodiazepines in the prehospital setting do not show a definite benefit of one medication over the other in terms of efficacy. Rainbow studied 107 children presenting to an emergency department (ED) in status epilepticus, comparing diazepam to midazolam, and found that the two drugs had similar efficacy. Another prehospital study compared how much the concentration of diazepam, lorazepam, and midazolam had degraded at 30 day intervals when stocked on an ambulance. Diazepam and midazolam showed minimal degradation at 120 days, while lorazepam had degraded to 90% and 86% of the original potency at 90 and 120 days respectively, demonstrating significant, progressive degradation over time. This outcome may have cost implications when selecting which medication to stock in an ambulance, especially in the setting of nationwide shortages of many medications commonly used by EMS, including benzodiazepines.

### TABLE 1. Studies comparing therapy for acute seizure management.

<table>
<thead>
<tr>
<th>Medication comparisons</th>
<th>Study author (year of publication)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV vs non-IV medication comparisons</td>
<td></td>
</tr>
<tr>
<td>IV diazepam vs buccal midazolam</td>
<td>Talukdar (2009, 21</td>
</tr>
<tr>
<td>IV midazolam vs IM midazolam</td>
<td>Muchohi (2008, 19, Vilk (2002, 18</td>
</tr>
<tr>
<td>IV lorazepam vs IM lorazepam</td>
<td>Muchohi (2008, 19</td>
</tr>
<tr>
<td>IV lorazepam vs PR diazepam</td>
<td>Chin (2008, 34</td>
</tr>
<tr>
<td>IV lorazepam vs IN lorazepam</td>
<td>Arya (2011, 40</td>
</tr>
<tr>
<td>IV lorazepam vs IM midazolam</td>
<td>Silbergliet (2012, 20</td>
</tr>
<tr>
<td>Non-IV to non-IV medication comparisons</td>
<td></td>
</tr>
<tr>
<td>IM midazolam vs IN midazolam</td>
<td>None</td>
</tr>
<tr>
<td>IM Midazolam vs buccal midazolam</td>
<td>None</td>
</tr>
<tr>
<td>IN midazolam vs buccal midazolam</td>
<td>None</td>
</tr>
<tr>
<td>IV vs IV medication comparisons</td>
<td></td>
</tr>
<tr>
<td>IV valproic acid vs IV phenytoin</td>
<td>Agarwal (2007, 44</td>
</tr>
<tr>
<td>IV/IM midazolam (pooled) vs IV/PR diazepam (pooled)</td>
<td>Rainbow (2002, 13</td>
</tr>
</tbody>
</table>
Intravenous vs Alternative Routes of Administration: Is Vascular Access Necessary?

Obtaining vascular access in children is often difficult for EMS providers, who sometimes go months without placing an IV in a pediatric patient. This skill is made even more difficult when the patient is actively seizing. Paramedics at times cite difficulty in obtaining access as a reason for not treating a seizure in the prehospital setting. Attempting to obtain IV access in a seizing pediatric patient can lead to delays in medication administration, seizure cessation, and transport that could potentially lead to increased morbidity and mortality.

There have been various studies in the pediatric prehospital literature comparing the administration of benzodiazepines to seizure patients via the IV route versus the IM, IN, buccal, and PR routes. The literature suggests alternative routes of administration (specifically IM, IN, and buccal) have comparable efficacy and side effect profiles and should therefore be considered preferentially for children in the prehospital setting.

Evaluating studies that compare the IV route to each of the alternative routes is essential to understanding why obtaining IV access is unnecessary in these patients.

Intramuscular vs Intravenous

The studies that compare the administration of anticonvulsants via the IV route versus alternative routes (IM, IN, buccal, PR) generally demonstrate that alternative routes lead to faster medication administration, faster seizure cessation, and exhibit a similar safety profile. Rainbow demonstrated that IM midazolam was safe, rapidly absorbed, and easy to administer when compared to attempting IV access in a seizing pediatric patient in the prehospital environment.13 Another study by Chamberlain demonstrated that IM midazolam was equally safe when compared to IV diazepam and also led to faster medication administration and seizure cessation.16 A study by Shah of 115 children with seizures in the ED, pediatric ward, or the intensive care unit found significantly shorter time to seizure cessation (97 seconds) with IM midazolam than with IV diazepam (250 seconds) when a patient did not have previous IV access. In addition, there were no significant side effects seen in this study with either IM midazolam or IV diazepam.17 While there are several studies suggesting that IV benzodiazepines are superior to IM benzodiazepines in the treatment of pediatric seizures, most of these studies have significant limitations relative to those that demonstrate equivalent efficacy.18,19

However, the highest quality study to date comparing IM to IV therapy was the multi-center RAMPART (Rapid Anticonvulsant Medications Prior to Arrival Trial) study by Silbergleit et al. This was a randomized controlled trial of IM midazolam, delivered via an autoinjector device, vs IV lorazepam in prehospital seizure patients, including children. Though designed to merely demonstrate noninferiority, the study demonstrated superior efficacy of IM midazolam over IV lorazepam. There was a 73% rate of seizure cessation at the time of arrival to the ED with IM midazolam (95% confidence interval [CI], 69.3-77.5), compared to a 63% rate of cessation with IV lorazepam (95% CI, 4.0-16.1; P < .001 for both noninferiority and superiority). Both treatment arms had similar rates of respiratory distress; 14% in each group needed endotracheal intubation. Rates of recurrent seizures and other safety measures were also similar in both arms. IM midazolam was associated with a shorter time to seizure cessation than the IV lorazepam group (4.5 vs 6.4 minutes).20

Buccal vs Intravenous

There has also been research suggesting that the buccal route of anticonvulsant administration is as effective as the IV route. Talukdar conducted a randomized controlled trial of 120 pediatric seizure patients who received either buccal midazolam or IV diazepam. There was no significant difference in seizure cessation between the two groups: 85% with buccal midazolam versus 93% with IV diazepam (RR = 1.10, 95% CI, 0.97-1.25, P = .142). In addition, no significant side effects were witnessed with either medication.21

Intranasal vs Intravenous

Finally, there is also evidence that the IN route is as effective as the IV route. A study by Mahmoudian compared IN midazolam to IV diazepam in the treatment of seizures in 70 patients in a pediatric ED. IN and IV were found to be equally effective with similar side effect profiles.22 Similarly, a
randomized controlled trial by Lahat of 44 patients randomized to either IN midazolam or IV diazepam showed that both treatments were equivalent in terms of their efficacy, safety profile, and risk of seizure recurrence.²³ One challenge that EMS systems may face in implementing the use of IN medications, however, is the need to provide paramedics with training in utilizing a new route of delivery.

**RECTAL VS OTHER ALTERNATIVE ROUTES OF ADMINISTRATION**

Rectal administration of diazepam is frequently prescribed for patients to use at home in the event of a prolonged seizure at home. EMS providers often use rectal diazepam to treat seizures in the prehospital setting, however providers at times note their reluctance to use the rectal route due to the need to remove clothing and compromise patient modesty with rectally administered medication. Various studies in the literature have compared the rectal route to the other alternatives routes of administration, including the IM, IN, and buccal routes.

**IM vs Rectal**

A study by Rainbow compared 62 patients who received diazepam per rectum or IV versus 45 patients who received midazolam IM or IV.¹³ Both groups demonstrated similar efficacy and the midazolam group had a lower rate of respiratory depression. This study also demonstrated a preference of EMS providers for the IM route versus the rectal route of administration. Paramedics also had a preference for the IM route over attempting to obtain IV access in an actively seizing patient. The fact that both groups had similar efficacy and the IM group had less respiratory depression suggest that the IM route is as safe and effective as the rectal route.¹³ A similar study by Warden compared 45 pediatric prehospital seizure patients treated with rectal or IV diazepam to 48 patients treated with IM or IV midazolam. The 2 groups had similar efficacy and safety, and use of midazolam was associated with a higher rate of non-IV route of administration (65% vs 42%; P = .02), perhaps suggesting an EMS provider preference for the IM route over the rectal route.²⁴

**Buccal vs Rectal**

Buccal midazolam has been compared directly to rectal diazepam in the literature. Ashrafi compared buccal midazolam to rectal diazepam in 98 children with seizures and found that time to drug administration and time to drug effect were both significantly shorter with the use of buccal midazolam (P < .001), with similar efficacy in both treatment groups.²⁵ Another smaller study by Scott showed that buccal midazolam was as effective as rectal diazepam. Midazolam led to cessation of 75% of seizures, while diazepam led to cessation of 59% of seizures (P = .16).²⁶ However, a multicenter, randomized controlled trial by McIntyre comparing buccal midazolam to rectal diazepam in 219 episodes of seizures in 177 pediatric patients in the ED showed that buccal midazolam was actually more effective in causing seizure cessation compared with rectal diazepam (56% vs 27%) with a 29% absolute risk reduction in seizure cessation (95% CI 16%-41%) and lower risk of respiratory depression.²⁷

**Intranasal vs Rectal**

There have also been studies directly comparing IN midazolam to rectal diazepam, suggesting that IN is the superior route. A small study by Fisgin found that IN midazolam caused seizure cessation in 87% (20/23) of patients, whereas rectal diazepam caused seizure cessation in only 60% (13/22, P < .05).²⁸ Bhattacharyya compared physician administration of IN midazolam versus rectal diazepam in 188 seizure episodes in 46 children. Time to drug administration and to seizure cessation were faster with IN midazolam (P = .005), and there was less respiratory depression with IN midazolam.²⁹

A study by Holsti examined a population of 124 children with seizures brought to a pediatric ED by EMS. Thirty-nine of these patients were treated with IN midazolam and 18 patients were treated with rectal diazepam. A specific device was used to administer the IN medication, the intranasal mucosal atomization device (INMAD). Notably, mean seizure time was 19 minutes longer with rectal diazepam compared to INMAD midazolam (30 vs 11 minutes, P = .003). Compared with INMAD midazolam, rectal diazepam was also associated with higher rates of respiratory depression and ED intubation (odds ratio [OR] = 12.2; 95% CI, 2.0-75.4) and a higher rate of hospital admission (OR = 29.3; 95% CI, 3.0-288.6).² Another study by Holsti randomized 358 pediatric neurology clinic patients to use either INMAD midazolam or rectal diazepam as a home rescue medication for seizures lasting longer than 5 minutes. Median time to seizure cessation was 1.3 minutes less with INMAD (95% CI, 0.0-3.5 minutes; P = .09) compared to rectal
diazepam, showing that there was no significant difference in efficacy between IN midazolam and rectal diazepam. There was no significant difference in safety or complications either. Caretakers also preferred using the INMAD, feeling that it was easier to administer. In addition, giving an IN medication protects patients’ physical privacy better than a rectal medication. Finally, in this study the cost of a dose of IN midazolam was $12, whereas the cost of a dose of rectal diazepam was $212. These findings suggest that IN midazolam may be a superior drug to rectal diazepam in the treatment of home seizures, and that findings are relevant for EMS treatment of seizures in the field.

When a Route Other Than IV is Chosen, Rectal Is Least Preferred

The second important point that emerges when reviewing the literature on pediatric prehospital seizure management is that when a route other than IV is chosen, the rectal route is least preferred. This may seem counterintuitive to some, as rectal diazepam is quite frequently prescribed to families to administer to patients who are seizing at home for more than 5 minutes. Despite the historical preference for rectal medications to treat seizures, the evidence suggests that the use of IN, buccal, and IM benzodiazepines is superior to the rectal route.

TIMING OF DOSES

Another issue with regards to the prehospital management of pediatric seizures is the ideal timing of first and subsequent benzodiazepine doses. There has been much controversy regarding the definition of status epilepticus, and specifically, the time duration that a patient must be seizing to be considered to be in status epilepticus. Over the past two decades, this threshold has steadily declined from 30 to 5 minutes. With this level of uncertainty, and with the potential for morbidity and mortality associated with the failure to intervene for status epilepticus, many believe it is safe and prudent to treat any seizure lasting more than 5 minutes. Therefore, the EMS provider who arrives on scene should administer a benzodiazepine to a seizing child as quickly as is feasible, as in almost all responses it will take EMS more than 5 minutes from the 911 call to arrive on scene. Considering the onset of action of IV benzodiazepines, it would be reasonable to treat with a second dose of benzodiazepines for seizures that continue for persist for another 5-10 minutes after the initial dose in the prehospital setting. However, it is best to avoid giving more than 2 doses of benzodiazepines due to an increased risk of respiratory depression.

RESPIRATORY DEPRESSION

The most concerning adverse effects of benzodiazepines is respiratory depression, so it is important to compare the risk of respiratory depression among the various routes of administration of benzodiazepines. The evidence shows that non-IV routes of administration do not have an increased risk of respiratory depression when compared to IV administration. The study by Talukdar comparing buccal midazolam to IV diazepam showed no difference in adverse effects, including respiratory depression. The study by Mahmoudian comparing IN midazolam to IV diazepam similarly demonstrated that there was no increased risk of adverse effects or respiratory depression with IN midazolam. Finally the Silbergleit study also showed a similar rate of respiratory depression between IM midazolam and IV lorazepam.

The literature also suggests that there is no increased risk for respiratory depression with the IN or buccal routes when compared to rectal administration of benzodiazepines. The studies comparing the buccal and IN route to the rectal route also suggest that IN and buccal midazolam are noninferior and perhaps superior to rectal diazepam with regards to respiratory depression. The multicenter randomized trial by McIntyre showed decreased respiratory depression with buccal midazolam compared to rectal diazepam. Similarly, Holsti demonstrated that IN midazolam was associated with less respiratory depression when compared to rectal diazepam.

A study by Chin demonstrated that treatment with more than 2 doses of benzodiazepines is associated with a significantly increased risk of respiratory depression (OR = 2.9, 95% CI 1.4–6.1). Treatment with more than 2 benzodiazepines in the prehospital setting should likely only be done with online medical control assistance.

GLUCOMETRY

Many prehospital protocols for altered mental status recommend that field providers check blood glucose; ongoing seizures or the post-ictal state can be considered a subset of altered mental status. Richard’s study of 1377 pediatric EMS calls included 162 (11.8%) for the diagnosis of seizures. In these seizure calls, EMS providers checked the patient’s blood glucose by glucometry 70% of the time. A study by Kumar showed that capillary blood glucose...
values measured by glucometer best approximate venous blood glucose values from the laboratory and can be used effectively to guide clinical decisions in the field. A review article on pediatric seizures by Friedman recommends rapid, point of care glucometry in all actively seizing pediatric patients. Hypoglycemia is an infrequent but important cause of pediatric seizures, and can be cheaply, easily, and quickly identified via the use of point of care glucometry; therefore routine glucometry is recommended in all seizing patients.

**DOsing OF BENZODIAZEPINES**

More research is needed to determine the optimal dosage of benzodiazepines in the pediatric population, maximizing efficacy while at the same time minimizing respiratory depression. While uncertainty exists, Table 2 notes the dosages that have been reported in the literature. In the prehospital environment, patient safety and care efficiency are maximized with the establishment of standardized doses that are easy for EMS providers to remember and use for calculation. Based on present data, a reasonable approach would be to dose IM, IN, and buccal midazolam at 0.2 mg/kg and to dose IV diazepam, lorazepam, and midazolam at 0.1 mg/kg.

**UNANSWERED QUESTIONS**

There are questions that remain unaddressed with regards to buccal and IN administration of benzodiazepines for the treatment of pediatric seizures. There have been no studies directly comparing buccal, IN, and IM benzodiazepines in the treatment of pediatric seizures in order to determine which route is superior in which clinical settings. In addition, questions remain about whether or not upper respiratory infection symptoms and copious nasal secretions decrease the efficacy of IN benzodiazepines. Finally, Holsti’s studies regarding IN benzodiazepine use looked at a particular device, the INMAD, and it is not clear if the results of these studies can be generalized to other approaches to IN delivery.

**SUMMARY**

Though there is a paucity of research regarding the prehospital management of pediatric seizures, the development of an evidence-based guideline for pediatric prehospital seizure management through the collaboration between the EMS for Children program and NHTSA has identified the existing literature from which an evidence-based guidance for EMS personnel has been created. Based on the existing literature, several conclusions can be drawn. First, it seems that midazolam and diazepam may be advantageous to lorazepam in the prehospital setting due to their longer shelf life. Second, it is not necessary to obtain IV access, as this may delay time to administration of anticonvulsant medications, may be difficult for prehospital providers to perform, and medications given via other routes are equally efficacious. Specifically, the evidence indicates that the IN, IM, and buccal routes are as effective as the IV route and are not associated with any increased risk of adverse effects. Third, when choosing a route of administration of benzodiazepines other than IV, rectal medications are least preferred since the latter is associated with prolonged time to seizure cessation and more adverse effects. More research needs to be done to

<table>
<thead>
<tr>
<th>Route</th>
<th>Medication</th>
<th>Dosage</th>
<th>Proposed standardized prehospital dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM</td>
<td>Midazolam</td>
<td>0.2 mg/kg</td>
<td>0.2 mg/kg&lt;sup&gt;18&lt;/sup&gt;</td>
</tr>
<tr>
<td>Buccal</td>
<td>Midazolam</td>
<td>0.2-0.5 mg/kg</td>
<td>0.2 mg/kg&lt;sup&gt;21,27&lt;/sup&gt;</td>
</tr>
<tr>
<td>IN</td>
<td>Midazolam</td>
<td>0.2 mg/kg</td>
<td>0.2 mg/kg&lt;sup&gt;22,23,30&lt;/sup&gt;</td>
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<tr>
<td>IV</td>
<td>Midazolam</td>
<td>0.15-0.3 mg/kg</td>
<td>0.1 mg/kg&lt;sup&gt;18,45&lt;/sup&gt;</td>
</tr>
<tr>
<td>IV</td>
<td>Lorazepam</td>
<td>0.05-0.1 mg/kg</td>
<td>0.1 mg/kg&lt;sup&gt;34,42,46&lt;/sup&gt;</td>
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<tr>
<td>IV</td>
<td>Diazepam</td>
<td>0.1-0.3 mg/kg</td>
<td>0.1 mg/kg&lt;sup&gt;23,47&lt;/sup&gt;</td>
</tr>
<tr>
<td>PR</td>
<td>Diazepam</td>
<td>0.2-0.5 mg/kg</td>
<td>0.2 mg/kg (least preferred route)&lt;sup&gt;27,47&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
determine optimal dosing and timing, and to
determine which non-IV routes of administration
are preferable in the prehospital setting. The EMS
for Children program continues to offer funding to
address knowledge gaps in the prehospital care of
children. In addition, the recent increase in priority
that emergency care research has received at the
federal level has the potential to address these
treatment uncertainties.

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