Research Paper

Treatment of Neonatal Seizures: Comparison of Treatment Pathways From 11 Neonatal Intensive Care Units

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Objective: Seizures are a common neonatal neurologic emergency. Many centers have developed pathways to optimize management. We evaluated neonatal seizure management pathways at level IV neonatal intensive care units (NICUs) in the United States to highlight areas of consensus and describe aspects of variability.

Methods: We conducted a descriptive analysis of 11 neonatal seizure management pathways from level IV NICUs that specialize in neonatal neurocritical care including guidelines for electroencephalography (EEG), monitoring, antiseizure medication (ASM) choice, timing, and dose.

Results: Study center NICUs had a median of 70 beds (interquartile range: 52-96). All sites had 24/7 monitoring, with conventional EEG initiation, monitoring, and review capability. Management pathways uniformly included prompt EEG confirmation of seizures. Most pathways included a provision for intravenous benzodiazepine administration if either EEG or loading of ASM was delayed. Phenobarbital 20 mg/kg IV was the first-line ASM in all pathways. Pathways included either fosphenytoin or levetiracetam as the second-line ASM with variable dosing. Third-line ASMs were most commonly fosphenytoin or levetiracetam, with alternatives including topiramate or lacosamide. All pathways provided escalation to

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Introduction

Neonatal seizures are common, occurring after approximately 1-3.5/1000 term births, and are most often associated with acute neurologic injury. No level 1 evidence exists to show that treatment of neonatal seizures is associated with improved long-term outcomes; however, clear evidence supports rapid and effective treatment of neonatal seizures as the standard of care. Preclinical studies strongly support the detrimental effects of seizure in young brains, and clinical studies demonstrate that higher seizure burden is independently associated with imaging markers of neuronal injury and with increased morbidity and neuro-developmental disability. New evidence suggests rapid treatment of neonatal seizures identified on screening electroencephalography (EEG) increases the odds of successful treatment. In older children, rapid seizure treatment has been shown to minimize total seizure burden and decrease critical care needs. Among neonatal providers, there is agreement that rapid and effective treatment of acute symptomatic neonatal seizures is important. However, there is limited high-quality evidence regarding the choice of medications, optimal dosing, and duration of treatment.

Evidence from multiple treatment paradigms has demonstrated that standardization of care using a management pathway allows for focused quality improvement and improves treatment timeliness and effectiveness of management. Many institutions have created standardized management pathways for neonatal seizures. Owing to the paucity of high-quality evidence, the 2011 International League Against Epilepsy neonatal seizure management guideline offered limited guidance on specific medications or dosing. The development of evidence-based neonatal seizure guidelines has been hampered by the lack of sufficient randomized controlled trials and the difficulty inherent in conducting rigorous trials of neonatal seizures. This has led to neonatal seizure treatment which is driven in large part by physician and local experience and preference. Individual centers have worked with local neonatologists, neurologists, neurophysiologists, EEG technologists, pharmacists, and nursing teams to create customized pathways that operationalize the available resources and evidence. Multiple historical and contemporary studies have documented significant intercenter variability in neonatal seizure management, including varying choice of second-line antiseizure medication (ASM), the number of ASMs administered, and duration of ASM treatment.

It is not known how much of this variance is secondary to differences in standardized management pathways as opposed to variation in individual provider care.

We evaluated and descriptively compared neonatal seizure pathways at 11 level IV neonatal intensive care units (NICUs) in the United States. We described the range of current approaches, including areas of similarity and aspects of heterogeneity which support the need for further study.

Materials and Methods

We conducted a descriptive analysis of 11 neonatal seizure management pathways collected between November 2020 and March 2021 from tertiary and quaternary care hospitals in the United States. Participating institutions were recruited based on participation in neonatal seizure-focused research, neonatal seizure sessions at the Child Neurology Society 2020 conference, or participation in the Neonatal Seizure Registry (NSR). Inclusion criteria were as follows: (1) use of a neonatal seizure pathway or guideline of care and (2) intended use in at least one level IV NICU. Additional data regarding the hospital context for which each pathway was designed and the process of pathway development and approval were gathered by survey and small group discussions with a designated institutional representative for each pathway. The pathways included in this study are represented by the authors of this study. This study was reviewed and approved as exempt by Seattle Children’s institutional Review Board.

The main findings of the survey data and pathway analysis were summarized with descriptive statistics. Survey data were presented as medians with ranges. Survey data were presented as medians with ranges (StataCorp, TX). We assessed and summarized each pathway for inclusion and exclusion criteria, timing, dosing, and medication recommendations. Components addressed in each pathway were included as an aggregate count of pathways addressing each recommendation.

Results

Context

In total, 11 pathways were included in this analysis. Pathways were drawn approximately equally from institutions in the northeast, midwest, and western regions. All pathways were designed primarily for a level IV NICU. Seven institutions indicated that associated level III NICUs also utilized their pathway to initiate treatment of neonatal seizures with escalation to level IV care as needed. Five of the level IV NICUs served exclusively outborn neonates, with six serving a mix of inborn and outborn neonates. The median size of the NICU was 70 beds (range: 32-140 beds). All level IV NICUs were capable of initiating and reviewing continuous video EEG 24 hours a day as needed. Pathways were designed for on-call consultation from neurology, with all NICUs having access to both a neurology resident (three in-house and eight via home call) and to either a child neurology or neonatal neurology attending. Pathways were designed primarily for use by the child neurology team (11 pathways) and the NICU team (9 pathways). Two pathways were explicitly designed for widespread use by staff throughout the hospital; both included a recommendation for early and urgent child neurology consultation. Pathways were reviewed and approved by a variety of teams including child and neonatal neurologists, neurophysiologists, neonatologists, nurses, pharmacists...
and less commonly executive committees, cardiac intensive care unit (CICU) or pediatric intensive care unit (PICU) teams, and EEG Technologist teams.

**Composite pathway summary**

Pathways were manually reviewed and incorporated varying levels of detail depending on the intended audience and institutional practice. Figure 1 summarizes the recommendations, although not all pathways address each included recommendation. Three pathways explicitly specified that the pathway was intended for neonates between aged 35 or 36 weeks and less than 44 weeks postmenstrual age (Fig 1). No other exclusion or inclusion criteria were stated. Pathways universally prioritized expedited EEG in high-risk neonates or for confirmation of suspected seizures, with several citing literature noting high frequency of clinical misidentification for neonatal seizures.20,21 Eight of 11 pathways included criteria for providing benzodiazepine seizure rescue medications before an ASM load; criteria for administration varied from strong suspicion for seizure while awaiting EEG confirmation to giving only after seizure confirmation if ASM administration was delayed. All pathways agreed on the use of phenobarbital load as the first-line ASM followed by repeated load 30 to 60 minutes later if needed for persistent seizure activity. Nine of 11 pathways recommended initial treatment escalation for any electrographic seizure. Ten of 11 pathways included initiation of phenobarbital maintenance, either after the first phenobarbital load (four pathways) or after the requirement for repeated phenobarbital load (six pathways). Ten of 11 pathways included periodic serum phenobarbital level monitoring in their pathway.

Escalation to a second-line ASM 30 to 60 minutes after the second phenobarbital load was recommended for any electrographic seizure in eight of 11 pathways, with the remaining three having slightly higher thresholds for ASM escalation. The recommended second-line ASM was split between fosphenytoin (5/11) and levetiracetam (2/11), with the remaining four pathways recommending decision-making based on co-occurring clinical circumstance including concerns for hemodynamic instability, cardiac arrhythmia, and respiratory instability that may be differentially worsened by fosphenytoin administration. Of the eight pathways that discussed fosphenytoin maintenance, five recommended initiation of maintenance fosphenytoin for any fosphenytoin load, while three pathways only recommended bolus dosing. In the seven pathways that discussed maintenance medication after levetiracetam loading, six pathways recommended maintenance initiation. Eight pathways included a provision for use of the alternative ASM (either levetiracetam or fosphenytoin) as a third-line medication if clinically appropriate, while two pathways recommended proceeding directly to an infusion medication after failure of a second-line ASM. Alternative second- or third-line medications included topiramate (four pathways) and lacosamide (three pathways), with particular discussion of preferential consideration for alternative medications with suspected genetic epilepsy or an underlying etiology expected to have a prolonged course. In eight pathways, a pyridoxine trial was included after failure of second- or third-line ASMs or with persistently abnormal EEG background.

All pathways included an option to escalate to midazolam infusion if seizures persisted, with lidocaine cited as an alternative infusion medication in three pathways. Criteria for infusion initiation varied from any seizure after optimization of second- or third-line ASM to greater than 10% seizure burden after third-line ASM with provision for early use in refractory status epilepticus. All eight pathways that discussed EEG discontinuation recommended monitoring at least 12 hours and, more typically, 24 hours after last electrographic seizure or infusion medication discontinuation. Nine pathways discussed consideration for early discontinuation of maintenance ASMs for acute symptomatic seizures with recommended timing varying from as early as after 24 hours of seizure freedom to consideration of discontinuation at 2-4 weeks.

**Dosing**

Dosing was relatively consistent among pathways for rescue benzodiazepine therapy, phenobarbital, and fosphenytoin (Table 2). Lorazepam and midazolam were both dosed at 0.1 mg/kg IV with an option for repeat dosing included in two pathways. The initial phenobarbital loading dose was consistent at 20 mg/kg IV with some variation in infusion rate, and the recommended dose of repeat phenobarbital load ranged from 5 to 20 mg/kg IV. Recommended maintenance phenobarbital dosing varied between 3 and 5 mg/kg/day, with 9 pathways including target serum concentrations between 15 and 60 mcg/mL. Fosphenytoin loading dose was consistent at 5/11 across pathways.

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**Table 1.** Pathway Summary Characteristics

<table>
<thead>
<tr>
<th>Institutional Characteristics</th>
<th>Pathways (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institutional region* (# of pathways)</td>
<td>West (4), Midwest (4), Northeast (3)</td>
</tr>
<tr>
<td>Source of treated neonates at the NICU (# of pathways)</td>
<td>Outborn (5) and mixed inborn/outborn (6)</td>
</tr>
<tr>
<td>Bed size of NICU for which the pathway was designed, median (range)</td>
<td>70 (32-140)</td>
</tr>
<tr>
<td>Last pathway update (range)</td>
<td>8/2017-3/2021</td>
</tr>
<tr>
<td>Continuous conventional EEG initiation available 24 hours a day</td>
<td>100%</td>
</tr>
<tr>
<td>EEG review available as needed based on seizure frequency</td>
<td>100%</td>
</tr>
<tr>
<td>Neurology consultation availability overnight in the primary NICU (# of pathways)</td>
<td>Home call neurology resident (8), child neurology attending (9), neonatal neurology attending (5), in-house neurology resident (3)</td>
</tr>
<tr>
<td>Medications readily available in the primary NICU (# of institutions)</td>
<td>Lorazepam (11), phenobarbital (8), fosphenytoin (6), levetiracetam (4), midazolam (3)</td>
</tr>
<tr>
<td>Primary team(s) pathway designed to be used by (# of pathways)</td>
<td>Child neurology (11), NICU (9), all ICUs (2), all staff (2)</td>
</tr>
<tr>
<td>Teams involved in pathway creation or approval (# of pathways)</td>
<td>Child neurology (10), neonatal neurology (10), NICU (9), nursing (7), pharmacy (6), executive committee (3), CICU/PICU (2), EEG technologists (2), pediatric neurophysiology (1)</td>
</tr>
</tbody>
</table>

Abbreviations:
- CICU = Cardiac intensive care unit
- EEG = Electroencephalography
- ICU = Intensive care unit
- NICU = Neonatal intensive care unit
- PICU = Pediatric intensive care unit
- * Region based on the US census bureau 2020 region definition.
consistently recommended at 20 mg PE/kg IV in all pathways, but there was variation in recommended repeat loading boluses (5-10 mg PE/kg IV) and maintenance dosing (5-10 mg PE/kg/day), with target serum concentrations between 10 and 25 mcg/mL with use of free phenytoin levels or adjustment for abnormal protein levels as needed.
<table>
<thead>
<tr>
<th>Medication Category</th>
<th>Medication</th>
<th>Initial Bolus Dosing</th>
<th>Repeat Bolus Dosing</th>
<th>Target Serum Levels</th>
<th>Maintenance</th>
</tr>
</thead>
</table>
| Rescue therapy      | Lorazepam  | Range: 0.05-0.1 mg/kg IV
Most common: 0.1 mg/kg IV (6) | Range: None
Most common: 0.1 mg/kg IV (2) | Goal level 1-2 hours after final loading dose:
Range: 15-60 mcg/mL
Most common: 40-50 mcg/mL (3) | Range: 3-5 mg/kg/day
Most common: 5 mg/kg/day (6) |
| Midazolam           |            |                      |                     |                    |             |
| First-line therapy  | Phenobarbital | Range: 20-30 mg/kg IV
Most common: 20 mg/kg IV (10) | Range: 5-20 mg/kg IV
Most common: 20 mg/kg IV (5) | Goal level 1-2 hours after final loading dose:
Range: 10-25 mcg/mL
Most common: 10-20 mcg/mL (2) | Range: 5-10 mg PE/kg/day IV
Most common: 8-10 mg PE/kg/day IV (2) |
| Second- and third-line therapy | Fosphenytoin | 20 mg PE/kg IV (11) | Range: 5-10 mg PE/kg IV
Most common: 10 mg PE/kg IV (5) | Goal level 1-2 hours after final loading dose:
Range: 10-25 mcg/mL
Most common: 10-20 mcg/mL (2) | Range: 30-120 mg/kg/day IV/PO
Most common: 40 mg/kg/day IV/PO (3) |
| Levetiracetam       |            | Range: 40-60 mg/kg IV
Most common: 40 or 60 mg/kg IV (4 each) | Range: 20-60 mg/kg IV
Most common: 20 mg/kg IV (2) | Not used | Range: 50-100 mcg/kg/hr to 1000 mcg/kg/hr
Most common: 50 mcg/kg/hr increased by 40-60 mcg/kg/hr to 1000 mcg/kg/hr (2) |
| Topiramate          |            | Range: 2-10 mg/kg PO
Most common: N/A, 2-3 or 10 mg/kg PO (1 each) | 10 mg/kg PO repeated once in 24 hrs (1) | Not used | Range: 2-4 mg/kg/day IV/PO
Most common: 3 mg/kg/day PO, uptitrated QOD (2) |
| Pyridoxine related² | Pyridoxine | 100 mg IV (7) | Range: 100 mg IV repeated 2 to 5 doses
Most common: 100 mg IV repeated Q 5 min up to 500 mg IV (3) | Not used | Range: 15-30 mg/kg/day IV/PO
Most common: 30 mg/kg/day IV/PO (3) |
| Continuous infusion | Midazolam  | Range: 0.05-0.2 mg/kg
Most common: 0.2 mg/kg/dose IV (3) | Range: 0.1-0.2 mg/kg/dose IV
Most common: None - All pathways differ from each other | Not used | Range: 50 mg/kg/hr to 1000 mg/kg/hr
Most common: 50 mcg/kg/hr increased by 40-60 mcg/kg/hr to 1000 mcg/kg/hr (2) |
| Lidocaine           |            | 2 mg/kg/IV (2) |                     |                    |             |

**Abbreviations:**
- IV = Intravenous
- PE = Phenytoin equivalent
- PO = By mouth

² Summary ranges and most common dosing included in this table; more detailed dosing information can be found in the Supplementary Material.

³ Dosing information for pyridoxal 5 phosphate (PLP) and folinic acid (leucovorin) provided in the Supplementary Material.
FIGURE 2. Summary of pathway variation. * = The number of pathways addressing each recommendation included in parenthesis: PB, phenobarbital; BZD, benzodiazepine; FOS, fosphenytoin; LEV, levetiracetam; ASM, antiseizure medication. The color version of this figure is available in the online edition.

There was more variation in the recommended dosing for levetiracetam, topiramate, pyridoxine, and midazolam infusions (Table 2). Initial levetiracetam loading boluses varied between 40 and 60 mg/kg IV, with repeat boluses ranging between 20 and 60 mg/kg IV. Maintenance levetiracetam dosing was also widely variable, ranging from 30 to 120 mg/kg/day, with no centers utilizing serum concentrations for titration. Topiramate dosing was only included in three pathways but also had widely variable loading doses ranging from 2 to 10 mg/kg enterally with maintenance dosing of 2-4 mg/kg/day. Pyridoxine was uniformly loaded at 100 mg IV in all pathways, with four pathways including a provision for rapid repeated loading between two and five times. Maintenance pyridoxine therapy was included in five pathways varying between 15 and 30 mg/kg/day, and four pathways included variable accompanying pyridoxal 5' phosphate and folinic acid supplementation pending the return of reassuring biochemical testing. Midazolam infusion dosing varied with loading doses between 0.05 and 0.2 mg/kg IV with subsequent increases that included repeat bolus dosing between 0.1 and 0.2 mg/kg/hr. Maximum maintenance infusion rate varied between 0.3 and 1.0 mg/kg/hr.

Discussion

Neonatal seizure management pathways from 11 level IV NICUs specializing in neonatal neurocritical care had many areas of broad agreement, including the need to urgently evaluate, confirm, and treat neonatal seizures, use of phenobarbital as a first-line medication, and treatment escalation for ongoing electrographic seizures. Areas of heterogeneity remain regarding threshold for ASM escalation, choice of subsequent medication, and dosing (Fig 2).

Management pathways were written as flexible guidelines rather than rigid protocols, allowing for adjustments based on clinical circumstance and the burden and refractory nature of the seizures. Neonatal seizures occur as the presenting symptom of a variety of underlying etiologies and often coincide with dynamic multisystemic involvement requiring individualized patient care and early recognition of features, suggesting a neonatal epilepsy syndrome. Nonetheless, management pathways have been demonstrated to improve timeliness of treatment as well as clinical effectiveness and quality improvement efforts. Further work is needed to evaluate how to optimize and evaluate pathway implementation for the unique challenges presented by neonatal seizures.

Although explicit inclusion and exclusion criteria were present in only a minority of pathways, authors agreed that the general pathway outlined by each institution was focused on term neonates with acute symptomatic seizures. All pathways were designed for a clinical context in which child neurology consultation was readily available to facilitate customized care for neonates. This was reflected in the fact that all pathways were either intended primarily for child neurology team use or recommended early child neurology consultation. Several pathways were explicitly designed for neurology and neonatal teams to collaborate on rapid identification of neonates who would benefit from a tailored approach, including neonates with suspected genetic epilepsies.

Treatment initiation and escalation

In older children, rapid seizure treatment has been shown to minimize total seizure burden and decrease critical care needs. In neonates, new evidence supports that early seizure treatment is also likely more effective. However, this goal is complicated by the fact that most neonatal seizures are electrographic only and clinicians have a less than 50% accuracy differentiating neonatal seizures from other abnormal movements. In the pathways we studied, there was a strong consensus to urgently initiate EEG monitoring for high-risk neonates and those with a suspected clinical seizure, in accordance with the most recent International League Against Epilepsy and American Clinical Neurophysiology Society’s recommendations. All centers had EEG placement and monitoring available 24/7 at their level IV NICU. Eight pathways had a provision for temporizing treatment with benzodiazepines while awaiting EEG confirmation of seizure or ASM availability. However, the threshold for treatment initiation varied from relatively low threshold in the setting of strong clinical suspicion, to use of benzodiazepines for only EEG confirmed seizures while awaiting ASM treatment. Differences in threshold to initiate benzodiazepines for suspected seizures is likely multifactorial, including differences in ease of EEG confirmation ability, local geography and transport requirements, and an evolving understanding of neonatal seizure characteristics. Future research may help elucidate the risks and benefits of rescue medication in neonates with suspected seizures awaiting EEG confirmation.

Once seizures were confirmed on EEG, there was consensus to escalate therapy aggressively for continued seizures that were electroclinical or solely electrographic. As seizures became more refractory, the threshold for escalating to additional ASMs or a
continuous infusion varied, reflecting the desire to balance accumulating side effects with seizure control. While high seizure burden has been associated with increased morbidity and neurodevelopmental disability, the specific threshold that worsens outcome remains an area of active research. In current clinical practice, the decision to escalate therapy is often made after weighing individual risks and benefits for a particular neonate.

**ASM choice**

All pathways selected phenobarbital as the first line of treatment. However, the pathway recommendations were split between considering levetiracetam versus fosphenytoin as second-line treatment. While fosphenytoin has a well-established history as a neonatal ASM, it can be associated with cardiovascular complications including hypotension and/or cardiac arrhythmia. Maintaining consistent serum phenytoin levels may also be difficult in neonates. These concerns were reflected in pathway criteria for utilizing an alternative ASM. Levetiracetam is an attractive alternative as it has been shown to have few adverse effects in neonates, although a recent randomized controlled trial suggested poor efficacy compared with phenobarbital at the studied doses. The current split in pathway recommendations between fosphenytoin and levetiracetam suggests that future research directly comparing their effectiveness and safety as second-line neonatal ASMs remains imperative.

Alternative second-line ASMs, particularly topiramate, were most often recommended in the setting of neonatal-onset epilepsy or an underlying etiology where longer term ASM therapy was anticipated. Carbamazepine or oxcarbazepine is also utilized for several particular genetic neonatal-onset epilepsies including KCNQ2-related epilepsy.

When escalation to an infusion medication was indicated, all centers utilized midazolam, consistent with previous studies. Lidocaine was also included as an alternative for three centers if fosphenytoin had not been previously utilized, consistent with previous, predominately European, studies of efficacy in neonates.

Despite some minor variability among the centers with regard to ASM usage, the choice of ASMs for use in newborns remains limited as there have been very few trials of ASMs specifically for neonatal seizure treatment and the frequent need for IV administration limits testing of many ASMs with only enteral formulations. There remains an urgent need for development and rigorous clinical trial testing to expand the options available for neonatal seizure treatment.

**ASM dosing**

Phenobarbital and fosphenytoin both have a long history of neonatal use and well-studied neonatal pharmacokinetics resulting in widely consistent initial bolus dose recommendations with similar recommended maintenance dosing. The therapeutic and safe dosing range for levetiracetam has been reported as broad without a clear serum level correlate to efficacy, yielding more variable dosing recommendations. There are limited data available on the infusion dosing for midazolam in refractory neonatal seizures. Our data reflect the variability in dosing.

**ASM maintenance initiation and discontinuation**

The threshold to initiate maintenance ASMs varied by medication and center. There is little high-quality evidence to guide neonatal ASM maintenance administration, and the variability likely reflects the challenge of balancing support of seizure cessation with concern for both immediate side effects and long-term adverse effects of ASM exposure. Duration of ASM treatment after resolution of seizures remains variable, but accumulating evidence supports earlier discontinuation of ASM maintenance medications for acute symptomatic seizures in neonates as early discontinuation is typically not associated with either seizure recurrence, increased risk of childhood epilepsy, or worse neurodevelopmental outcomes. There was consensus in the pathway recommendations to strongly consider ASM discontinuation before hospital discharge, although exact timing remains variable.

**Opportunities for improvement**

One of the areas of opportunity identified was working to increase the speed with which neonatal seizures could be treated once they are identified or suspected. Three pathways specifically addressed how to rapidly access medications, including development of a seizure rescue protocol that brings a pharmacist to the bedside. Ready availability of at least first- and second-line drugs in decentralized medication dispensing systems such as BD Pyxis™ ES, or similar device could result in faster access and administration by nurses. In discussion with pathway authors, other approaches include preemptively ordering phenobarbital with all neonatal continuous EEGs to facilitate administration should seizures be identified. Additional approaches include working with institutions to include neonatal ASMs in decentralized medication dispensing systems. Previous quality improvement work in pediatric status epilepticus has demonstrated that implementing a bundle of interventions including nursing education and facilitating easy access to ASMs decreased subsequent critical care needs and intubations. Future work may focus on identifying barriers to rapid treatment of neonatal seizures and implementing similar bundled quality improvement measures in the NICU.

**Limitations**

We reviewed only pathways intended for United States level IV NICUs at academic institutions engaged in neonatal focused neurocritical research and care from the northeast, midwest, and western regions country. As care pathways are always formulated for a specific context and set of resources, this limits the generalizability of our findings. Although many of the included pathways have been recently updated, pathways continuously evolve as new evidence becomes available. The current review only addresses pathways as they existed in early 2021. Finally, we did not evaluate adherence to the pathways, but rather focused on describing the idealized pathways. Future work should focus on evaluating pathway adherence and relationship to outcomes, recognizing that standardization of clinical outcomes and the diverse underlying etiologies of neonatal seizures pose unique challenges.

**Conclusion**

We compared 11 pathways from institutions with a focus in neonatal neurocritical care that demonstrated broad similarities in the approach to treatment of neonatal seizures despite paucity of data from controlled trials regarding optimal neonatal seizure treatment, including routine utilization of continuous EEG monitoring and use of phenobarbital as initial treatment. Areas of heterogeneity suggest the need for further research, particularly with...
regard to second-line ASM choice, threshold to escalate ASM treatment for refractory seizures, ASM dosage, and timing of ASM discontinuation.

**Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2021.10.004.

**References**