

Treatment of Seizures in the Neonate: Guidelines and Consensus-based Recommendations – Special Report from the ILAE Task Force on Neonatal Seizures

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Key Points

- This paper presents guidelines and recommendations on treatment of neonatal seizures by the ILAE (International League Against Epilepsy).
- The Clinical Practice Guideline group consisted of an international team of experts including neurologists, neonatologists, pediatricians, epileptologists, and a parent representative.
- Guidelines and recommendations are based on a systematic review, and if no sufficient evidence was available, on expert-based consensus via Delphi.
- An example of a suggested treatment pathway including doses and adverse events based on current evidence and expert recommendations is given.

Abstract

Seizures are common in neonates but there is substantial management variability. The neonatal task force of the International League Against Epilepsy (ILAE) developed evidence-based recommendations about antiseizure medication (ASM) management in neonates based on a systematic review, meta-analysis, and expert-based consensus in accordance with ILAE standards. Six clinical priority questions were formulated, a systematic literature review performed, and results reported following the PRISMA 2020 standards. Bias was evaluated using the Cochrane tool and ROBINS-I and certainty of evidence was evaluated using GRADE. If insufficient evidence was available from randomized controlled trials, expert opinion was sought using Delphi methodology. The strength of recommendations was defined according to the ILAE Clinical Practice Guidelines development tool. Main recommendations in neonates with seizures: phenobarbital should be the first-line ASM (evidence-based, moderate strength), regardless of etiology (expert agreement). In neonates with seizures not responding to first-line ASM, phenytoin, levetiracetam, midazolam, or lidocaine may be used as a second-line ASM (expert agreement); in neonates with cardiac disorders, levetiracetam may be preferred (expert agreement). Following cessation of acute provoked seizures (electroclinical or electrographic) without evidence for neonatal-onset epilepsy, ASMs should be discontinued before discharge, regardless of MRI or EEG findings (expert agreement). When channelopathies are suspected, sodium channel blocker (phenytoin or carbamazepine) should be used (expert agreement). Therapeutic hypothermia may reduce seizure burden in hypoxic-ischemic encephalopathy (evidence-based, weak strength). Successful treatment of electrographic seizure burden may be associated with improved outcome (expert agreement). A trial of pyridoxine (add-on to ASM) should be attempted in neonates with clinical features or EEG characteristics suggestive of pyridoxine-dependent epilepsy or with seizures unresponsive to second-line ASM without an identified etiology (expert agreement). Experts also agreed that neonatal centers should have standardized treatment pathway in place and that parents should be informed about treatment (including documentation of this in patient notes).

Abbreviations

ASM: antiseizure medication

CI: confidence interval

CPG: clinical practice guideline

EEG: electroencephalography

 aEEG: amplitude-integrated EEG

 cEEG: conventional video EEG

DEE: developmental and epileptic encephalopathy

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

ILAE: International League Against Epilepsy

IBE: International Bureau of Epilepsy

PICO: population, intervention, comparator, and outcome

PMA: post menstrual age

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO: International Prospective Register of Systematic Reviews

RCT: randomized controlled trial

RR: relative risk

WHO: World Health Organization

Introduction

Seizures are the most common neurological emergency in the neonatal period. Most seizures in newborns are acutely provoked, typically by hypoxic-ischemic encephalopathy, intracranial hemorrhage, arterial ischemic stroke, or intracranial infection.¹⁻³ In about 10-15% of infants, seizures are the manifestation of a neonatal epilepsy usually due to cortical malformations, genetic defects or inborn errors of metabolism.⁴⁻⁶ The 2022 International League Against Epilepsy (ILAE) classification of epilepsy syndromes with onset in neonates and infants addresses etiology-specific syndromes such as self-limited (familial) neonatal epilepsy, *KCNQ2* developmental and epileptic encephalopathy (DEE), pyridoxine-dependent (*ALDH7A1*)-DEE and pyridoxamine-5-phosphate deficiency (*PNPO*)-DEE.⁷

Electroencephalography (EEG or aEEG) is required for seizure diagnosis since most seizures in neonates have no clinical manifestations (electrographic-only),^{8,9} and differentiating between seizures and other abnormal movements is difficult.¹⁰ In addition, treatment with antiseizure medication (ASM) may cause electro-clinical uncoupling in which the clinical correlate ceases but electrographic seizures persist.^{11,12} EEG monitoring using conventional video EEG (cEEG) or amplitude-integrated EEG (aEEG) is recommended by multiple clinical practice guidelines and consensus statements,^{2,13-15} as well as clinical trials of neonatal seizure management.¹⁶

There is considerable variation in clinical practice regarding neonatal seizure management,¹⁷⁻²⁰ which can be explained by the paucity of available data. The most recent international guideline regarding neonatal seizure management was published in 2011 by the World Health Organization (WHO), ILAE and International Bureau of Epilepsy (IBE).¹³ It was intended for clinicians practicing in a wide range of healthcare facilities, and developed based on all published studies (including randomized controlled trials (RCT), quasi-randomized controlled trials, and observational studies) in full-term neonates with clinical and/or electrographic seizures in the initial 28 days. However, over the last decade, new evidence has emerged to inform updated recommendations. As a result, in 2015, the ILAE created a new task force to update the evidence-based recommendations about seizure management in term and preterm neonates based on a systematic review, and expert-based consensus when evidence was lacking in accordance with ILAE standards regarding clinical practice guideline (CPG) development.²¹

The aim of this article is to provide evidence and consensus based recommendations for six priority questions related to neonatal seizure management: (1) first-line ASM, (2) second-line ASM, (3) duration of ASM treatment, (4) impact of therapeutic hypothermia on seizure burden in hypoxic-ischemic encephalopathy, (5) impact of electrographic seizure treatment on outcome, and (6) administration of pyridoxine. The target users are clinicians who care for neonates with seizures, including neonatologists, pediatric neurologists, pediatricians, and pharmacologists.

Methods

The ILAE Commission for Pediatrics identified the need to update the original Neonatal Seizure Guideline published in 2011.¹³ Guideline development adhered to the ILAE handbook and toolkit.²²

Clinical practice guideline working group

Following consultation with ILAE's Executive Committee, a Clinical Practice Guidelines (CPG) working group was formed. The CPG working group was comprised of 26 members of the ILAE neonatal task force including 19 child neurologists and clinical neurophysiologists and three neonatologists representing all ILAE regions, two methodologists, one parent representative, and two senior advisors. Fifteen members declared no conflicts of interest, six members declared non-related conflicts of interest, and six members declared related conflicts of interests. Overall, 78% of the CPG working group were void of conflicts of interest and representation from the pharmaceutical and medical device industry.

Priority questions

Six clinical priority questions were formulated. Each question was developed following the PICO [population, intervention(s), comparator(s), and outcome(s)] format addressing first-line ASM, second-line ASM, duration of ASM treatment, impact of therapeutic hypothermia on seizures in hypoxic-ischemic encephalopathy, impact of seizure burden on outcomes (neurodevelopment and epilepsy), and use of pyridoxine to treat neonatal seizures (Table 1). For all questions on efficacy, only studies with EEG confirmed seizures were included, to reduce the risk of including events other than true epileptic seizures (i.e., inclusion of non-seizure events).

Systematic review

A systematic literature review was performed, and results reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards (PRISMA 2020).²³ The protocol was registered with PROSPERO (CRD42017071825). MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Both keywords and MeSH terms were included. Appendix A in the online supplementary material provides the search strategies for each database. The search was limited to seven languages (English, French, Italian, German, Spanish, Dutch, Portuguese) and years 2008–2017 as this was an update of the 2011 guideline (131 earlier references were included from the previous systematic review).¹³ Since therapeutic hypothermia was not included in the 2011 guideline, studies about therapeutic hypothermia for the treatment of neonatal seizures were searched from 2004–2017. The search was limited to humans. Case reports of less than five neonates and conference abstracts were excluded. Review articles were collated only to ensure that no key

references were missed. The first search was performed on August 14, 2017, and repeated on June 28, 2020.

All abstracts and full text articles were reviewed independently by two members of the CPG working group, with a third reviewer involved in the case of disagreement. Data extraction forms were drafted for all priority questions and pilot tested by members of the CPG working group.

Evaluation of evidence (GRADE)

Studies meeting inclusion criteria and considered relevant to a clinical priority question were included for further evaluation. The risk of bias was assessed using the Cochrane Risk of Bias tool (for RCT) and ROBINS-I (for non-RCT studies).^{24,25} GRADE was applied to questions on first-line ASM, second-line ASM, and the impact of therapeutic hypothermia on seizure burden in order to determine the quality of evidence which was rated as high, moderate, low, or very low. The quality was upgraded or downgraded for certain factors that could influence the quality of the evidence in line with the GRADE method.^{25,26} For the remaining questions (duration of ASM administration, impact of seizure burden on outcome, and use of pyridoxine), only uncontrolled studies were identified and so the certainty of evidence was judged to be very low.

Delphi Consensus Process

If no or insufficient evidence was obtained from RCT, then expert opinion was sought using the Delphi methodology.²⁷ In addition, questions addressing specific scenarios were included in the Delphi consensus process. Statements regarding the clinical priority questions were drafted by a core group consisting of seven child neurologists, one neonatologist, and one methodologist. All members of the CPG working group, except methodologists and the parent representative, were invited to anonymously respond to an online questionnaire (Survey Monkey, San Mateo, Ca, USA), thus assuring involvement of medical professionals from the relevant specialties (child neurology, epileptology, clinical neurophysiology, and neonatology), and from all ILAE regions. Each statement was evaluated using a 5-point Likert scale (completely agree, mostly agree, partially agree, mostly disagree, completely disagree). Consensus was achieved when at least 66% agreement (completely agree or mostly agree) or disagreement (mostly disagree or completely disagree) was reached. The Delphi consensus process consisted of five rounds of questionnaires.

Strength of recommendations and level of agreement

The strength of recommendations was defined according to GRADE and the ILAE CPG development tool.²² Specifically, besides the certainty of the evidence, clinical benefits and harms of the intervention were considered. If the certainty of evidence according to GRADE was at least moderate,

then the strength of the recommendation was considered 'strong'. If GRADE could not be applied but the Delphi process yielded an agreement of >66%, then a recommendation was made based on the Delphi process. If the level of agreement of >75%, then it was considered 'high' because of its clinical impact. If the agreement was 66-75%, then the level of agreement was considered 'moderate'.

Results

A total of 556 studies were identified as relevant to the clinical priority questions and underwent full text review (Figure 1). Of these, 35 were excluded because they were conference abstracts, 212 because diagnosis of neonatal seizures was not confirmed by EEG, and 136 because the full text review showed that the information given was not relevant for the priority questions. The remaining 218 studies were allocated to one or more priority questions.

Regarding clinical priority questions 1, 2 and 5, one or more randomized controlled trials were identified and GRADE could be used to evaluate the evidence regarding these clinical priority questions (Table 2). Figure 2 and Appendix B give the risk of bias for priority question 1 and 2.

Regarding clinical priority questions 3, 4 and 6, GRADE could not be applied.

The Delphi consensus process included 21 statements; consensus was reached for 10 (Figure 3).

Evidence based recommendations could be given regarding clinical priority questions 1 and 4, for all other questions, recommendations were based on consensus only.

Recommendations

Recommendations 1: First-line Antiseizure Medication

Evidence-based recommendation:

In neonates with seizures requiring antiseizure medication (ASM), phenobarbital should be the first-line ASM

Strength of Recommendation: **Moderate**

Consensus-based recommendations:

Phenobarbital should be the first-line ASM regardless of etiology (including hypoxic-ischemic encephalopathy, stroke, and hemorrhage).

Level of Agreement: **High**

If channelopathy is likely the cause for seizures due to family history then a sodium channel blocker should be the first-line ASM.

Level of agreement: **High**

Question 1:

Which is the preferred first-line ASM in neonates with seizures requiring pharmacological treatment (specifically regarding cessation of seizures and adverse effects)?

PICO: Table 1

Overview of Results:

- Studies allocated for full text review: 46
- Studies included after full text review: 11 (2 RCT, 3 prospective observational, 6 retrospective)
- Studies analyzed by GRADE: 2
- Evidence Level from GRADE: Moderate to low certainty (Table 2)

Delphi: Figure 3a

Forty-six studies evaluated first-line treatment of neonatal seizures and were selected for full text review. The most common reason for study exclusion was a focus on clinical seizures without EEG to diagnose seizures or assess response to therapy (see Figure 1). There were no placebo-controlled studies. Eleven studies were included (Table S1, Appendix C) assessing phenobarbital,^{12,28-35} phenytoin³², and levetiracetam^{29,33,36,37} as first-line treatment for neonatal seizures. Overall, phenobarbital was the most widely used first-line ASM in term and preterm infants with seizures, with a variable response rate.^{28,33}

Two RCT studies were included in the GRADE analysis (Table S1, Appendix C).^{32,33} The first study³² assessed the efficacy of phenobarbital and phenytoin for the treatment of seizures in term and preterm neonates with heterogeneous etiologies. Study inclusion required EEG-confirmed seizure(s) and efficacy was evaluated by EEG monitoring. Dosing of both ASMs was adjusted based on plasma levels, but the actual dosing was not stated. The primary outcome was complete seizure control within 24 hours. Seizures were controlled with phenobarbital in 13/30 (43%) and phenytoin in 13/29 (45%) neonates. There was no difference in efficacy between phenobarbital and phenytoin as first-line treatment (RR (relative risk) 0.97; 95%CI (confidence interval) 0.54-1.72). The level of evidence was downgraded due to confounding factors (Table 2). The second study³³ assessed the efficacy of phenobarbital and levetiracetam for the treatment of seizures in term neonates with heterogeneous etiologies. Seizures were assessed by EEG monitoring for eligibility and efficacy. Eighty-three neonates were included in the efficacy analysis while 106 treated patients were analyzed for safety data. Initial dosing was 20 mg/kg for phenobarbital and 40 mg/kg for levetiracetam. Neonates who continued to have seizures (assessed every 15 minutes) received an additional 20 mg/kg of phenobarbital or an additional 20 mg/kg of levetiracetam. The primary outcome was seizure cessation on EEG within 15 minutes and sustained seizure freedom on EEG for 24 hours after the infusion. Seizures were controlled with phenobarbital in 24/30 (80%) and levetiracetam in 15/53 (28%) neonates. Phenobarbital was more effective than levetiracetam as first-line treatment (RR 0.35; 95% CI 0.22–0.56); moderate certainty of evidence) (see Table 2). No studies evaluated efficacy of ASM according to etiology of acute symptomatic seizures.

Most studies (controlled and observational) did not report adverse events (n=9), but some (n=9) indicated that no adverse events were observed for phenobarbital, phenytoin and levetiracetam (Table S1). One RCT with phenobarbital and phenytoin reported that no adverse events were observed.³² Only one study with phenobarbital and levetiracetam used standardized adverse events tables and reported that there was a trend towards hypotension being more common with phenobarbital (n=17%) compared to levetiracetam (n=5%).³³

To determine whether the etiology of seizures should influence the choice of first-line ASM, five additional questions on first-line ASM were added to the Delphi survey (Figure 3). Results indicated that 78% completely or mostly agreed that irrespective of presumed etiology (hypoxic-ischemic encephalopathy, stroke, hemorrhage) of seizures, phenobarbital should be first-line ASM. In the Delphi survey, 91% completely or mostly agreed that if a channelopathy was considered as etiology due to positive family history, then a sodium channel blocker (phenytoin or carbamazepine) should be the first-line ASM.

Recommendations 2: Second-line Antiseizure Medication

Consensus-based recommendations:

In neonates with seizures not responding to first-line antiseizure medication (ASM), phenytoin, levetiracetam, midazolam, or lidocaine may be used as a second-line ASM for most etiologies (hypoxic-ischemic encephalopathy, stroke, or hemorrhage).

Level of agreement: **Moderate**

If channelopathy as an etiology for the seizures is suspected because of clinical or EEG features, then a sodium channel blocker should be used as a second-line ASM. This should be phenytoin or carbamazepine depending on the clinical state of the neonate (critically ill or otherwise well baby) and the regional availability of ASM and monitoring of drug levels.

Level of agreement: **High**

In a neonate with cardiac disorder(s), levetiracetam may be preferred as a second-line ASM.

Level of agreement: **Moderate**

Question 2:

Which is the preferred second-line ASM in neonates (specifically regarding cessation of seizures and adverse effects)?

PICO: Table 1

Overview of Results:

- Studies allocated for full text review: 43
- Studies included after full text review: 22 (3 RCT, 5 prospective observational, 14 retrospective)
- Studies analyzed by GRADE: 3
- Evidence Level from GRADE: Very low certainty (Table 2)

Delphi: Figure 3a and b

Seizures are often refractory to the first-line ASM, prompting use of a second-line ASM. Forty-three studies referred to the topic of second-line treatment of neonatal seizures and were selected for full text analysis (Table S2). There were no placebo-controlled studies. Additionally, all studies of second-line ASM were add-on design since there was no wash-out phase after the first-line ASM and often both ASMs were administered concurrently. Twenty-two studies were included; they assessed levetiracetam,^{33,38-42} phenobarbital,^{29,32,33} phenytoin,^{28,29,32,43} midazolam,⁴⁴⁻⁴⁹ lidocaine,^{44,46,49-52} clonazepam,⁴⁴ bumetanide,⁵³ topiramate,⁵⁴ paraldehyde,²⁸ diazepam,²⁸ and carbamazepine^{43,55} as second-line treatment. There was substantial variability in study methods including outcome measures, with substantial variability in efficacy across studies of the same ASM.

There were three RCT assessing phenytoin, midazolam, phenytoin, levetiracetam and / or lidocaine as second-line ASM (Table 2).^{32,33,44} One study assessed second-line therapy in neonates with seizures persisting after either phenobarbital or phenytoin.³² Seizures were controlled with phenobarbital in 5/13 (39%) and phenytoin in 4/15 (27%) neonates. There was no difference in efficacy between phenobarbital and phenytoin as second-line treatment (RR 1.44; 95%CI 0.49-4.27), but the sample size was small. A second study assessed second-line therapy in neonates with seizures persisting after either phenobarbital or levetiracetam.³³ Seizures were controlled with phenobarbital in 20/37 (54%) and levetiracetam in 1/6 (17%) neonates. There was no difference in efficacy between phenobarbital and levetiracetam as second-line treatment (RR 0.31; 95%CI 0.05-1.89). A third study assessed second-line therapy in neonates with seizures persisting after phenobarbital.⁴⁴ Seizures were controlled with lidocaine in 3/5 and midazolam in 0/3. There was no significant difference in efficacy between lidocaine and midazolam as second-line treatment (RR 4.67; 95%CI 0.32-68.03), but the sample size was too small. Many studies did not address adverse events,^{29,42,44-47,49} while some studies indicated that no adverse events were observed.^{32,38-41,43,55} Only two RCT used a systematic approach to adverse event assessment when assessing phenobarbital vs levetiracetam³³ and bumetanide.⁵³ (Table S2, Appendix C).

The level of certainty of the evidence was very low regarding second-line ASM because of imprecision of estimates due to the very small number of patients included; hence, the two RCTs included were not informative enough. Consequently, expert opinion was sought via the Delphi process. Specifically, we evaluated whether phenobarbital, phenytoin, levetiracetam, midazolam, or lidocaine should be used after no or insufficient response to first-line ASM and whether this choice should be influenced by etiology of seizures (hypoxic-ischemic encephalopathy, stroke, hemorrhage, channelopathy) or comorbidity (cardiac disorders) (Figure 3). Although experts agreed on which ASM could be used as second-line (phenytoin, levetiracetam, midazolam, or lidocaine), there was no agreement as to which was the best. Three rounds yielded no agreement for choice of second-line ASM so we concluded that all four ASMs may all be considered as second-line therapy for most etiologies (hypoxic-ischemic encephalopathy, stroke, or hemorrhage). There was, however, consensus that phenytoin or carbamazepine should be preferred for neonates with presumed channelopathy (>95% completely or mostly agreed); and levetiracetam should be preferred for neonates with cardiac disorder(s) (75% completely or mostly agreed) (Figure 3).

Recommendation 3: Duration of ASM treatment

Consensus-based recommendations:

Following cessation of acute symptomatic seizures (electroclinical or electrographic) without evidence for neonatal onset epilepsy, antiseizure medications should be discontinued before discharge home, regardless of MRI or EEG findings.

Level of agreement: **High**

Question 3:

Will continuation of ASM improve neurodevelopmental outcome and reduce the risk of developing subsequent epilepsy?

PICO: Table 1

Overview of Results:

- Studies allocated for full text review: 17
 - Studies included after full text review: 3 (0 RCT, 1 observational prospective, 2 retrospective trials)
- Studies analyzed by GRADE: 0
- Evidence Level from GRADE: Not applicable

Delphi: Figure 3a

Clinicians must determine how long to continue ASM administration after the acute management phase. There were 17 studies addressing this topic, and 3 studies were included for full text analysis, including two retrospective studies^{56,57} and one prospective observational study (Table S3, Appendix C).⁶ These studies reported that the risk of subsequent developmental delay,⁶ seizures recurrence,^{56,57} epilepsy,⁶ or neurologic impairment⁵⁷ was not different in patients with ASM (mostly phenobarbital) discontinued prior to discharge or continued after discharge.

As only insufficient evidence on duration of ASM from RCT or other controlled studies was found, expert opinion was evaluated by the Delphi process, specifically if ASM should be discontinued before discharge home, regardless of MRI or EEG findings. In the Delphi process, 87% completely or mostly agreed that following cessation of acute symptomatic seizures (electroclinical or electrographic) without indication for neonatal onset epilepsy, ASM should be discontinued before discharge (Figure2).

Similarly, 80% completely or mostly agreed that ASM should usually be discontinued before discharge independently of the presence or absence of MRI abnormalities, and 80% completely or mostly agreed that following cessation of acute symptomatic seizures in a neonate, ASM should usually be

discontinued before discharge independently of presence or absence of EEG background abnormalities. Some participants noted their responses was influenced by a prospective, observational, multicenter comparative effectiveness study published after completion of the systematic literature review that indicated neurodevelopment and risk for post-neonatal epilepsy at age 24 months was not different among children with acute systematic neonatal seizures whose ASM was discontinued or maintained at hospital discharge.⁵⁸

Recommendation 4: Impact of therapeutic hypothermia on seizure burden

Evidence-based recommendation:

Therapeutic hypothermia may reduce seizure burden in neonates with hypoxic-ischemic encephalopathy. However, the impact of therapeutic hypothermia as a specific seizure therapy was not assessed.

Strength of Evidence: **Weak**

Consensus-based recommendations:

Therapeutic hypothermia may reduce seizure burden in neonates with hypoxic-ischemic encephalopathy.

Level of agreement: **High**

Question 4:

In neonates with hypoxic-ischemic encephalopathy, does therapeutic hypothermia reduce seizure burden?

PICO: Table 1

Overview of Results:

- Studies allocated for full text review: 32
- Studies included after full text review: 9 (0 RCT, 6 observational prospective, 3 retrospective trials)
- Studies analyzed by GRADE: 3
- Evidence Level from GRADE: Low certainty

Delphi: Figure 3a

Therapeutic hypothermia (brain/body cooling) is a neuroprotective technique used for neonates with hypoxic-ischemic encephalopathy. Neonates with hypoxic-ischemic encephalopathy have a high risk for seizures, and EEG monitoring is often performed in neonates undergoing therapeutic hypothermia to identify electroencephalographic seizures. There were 32 articles addressing this topic, and while all

had access to comparison groups, none were RCTs. Nine studies fulfilled the recommended requirements for therapeutic hypothermia in the setting of term infants with hypoxic-ischemic encephalopathy (Table S4, Appendix C).⁵⁹⁻⁶⁷ Six studies were excluded because they focused on head cooling (EEG is not possible during selective head cooling),^{59,67} did not access continuous EEG,⁵⁹ or did not have comparators.^{62-64,66,67} Among the remaining three studies^{60,61,65} two had a historical control group comparators^{60,61} and one had both historical and real-time comparators.⁶⁵

GRADE assessment concluded with low certainty that seizure burden was higher in the normothermia groups for all three studies and that the mean seizure frequency was lower in the therapeutic hypothermia group of two studies (Table 2b and Table S4).^{60,65} There was very low certainty regarding reduced progression to status epilepticus (as defined by the researchers) in the therapeutic hypothermia group. Two studies did not find a difference in the occurrence of status epilepticus between non-hypothermia and hypothermia group^{61,65} while one study found a higher occurrence of status epilepticus in the non-hypothermia group compared to the hypothermia group (Table 2b).⁶⁰

Due to the lack of RCT, we aimed to confirm the weak evidence from observational studies via Delphi process. Nearly all (95%) completely or mostly agreed that therapeutic hypothermia may reduce seizure burden in neonates with hypoxic-ischemic encephalopathy.

Recommendation 5: Associations between electrographic seizure burden and outcome

Consensus-based recommendations:

Treating neonatal seizures (including electrographic-only seizures) to achieve a lower seizure burden may be associated with improved outcome (neurodevelopment, reduction of subsequent epilepsy).

Level of agreement: **Moderate**

Question 5:

Is a reduction of electroclinical and/or electrographic-only seizure burden in neonates associated with improved outcome (neurodevelopment, reduction of subsequent epilepsy)?

PICO: Table 1

Overview of Results:

- Studies allocated for full text review: 80

- Studies included after full text review: 10 (2 RCT, 4 observational prospective, 4 retrospective trials)
- Studies analyzed by GRADE: 0
- Evidence Level from GRADE: Not applicable

Delphi: Figure 3a

Seizure identification and effective management aims to reduce secondary brain injury and improve neurobehavioral outcomes. Ten studies were included after full text review (Table S5, Appendix C). Two studies randomized neonates to different approaches for seizure detection and management. One study⁶⁸ assessed outcome for the full cohort (not separating the different treatments), and the other study⁶⁹ assessed MRI before discharge (but not long-term outcome). Both studies were underpowered to assess outcomes (hence no GRADE assessment). The first RCT performed cEEG in term neonates with moderate or severe hypoxic-ischemic encephalopathy and randomized them to treatment of both electrographic and clinical seizures or treatment of only clinical seizures, and it demonstrated that seizure burden was lower with treatment of electrographic seizures.⁶⁸ As no differences were found between the two groups at two years of age, both groups were combined for outcome analysis (n=24), and higher seizure burden was associated with significantly worse neurodevelopmental outcome at 18-24 months. The second RCT randomized term neonates with moderate to severe hypoxic-ischemic encephalopathy and subclinical seizures on aEEG to treatment of both clinical and subclinical seizures (n=19) or treatment of only clinical seizures (n=14).⁶⁹ Treatment addressing subclinical seizures was associated with a trend toward lower seizure burden. For the whole group, lower seizure burden was associated with less severe injury on MRI. One study, published after the literature search,⁷⁰ randomized neonates to treatment of aEEG identified seizures versus clinical seizures. Death or severe disability assessed at two years were not significantly different between the two groups. Like the other two studies, this study was underpowered, and it did not change the conclusions drawn from the available literature.⁷⁰ Numerous studies have indicated that high seizure burden is associated with unfavorable outcomes.^{1,56,60,71-75} However, these studies focused on associations between seizure burden in neonates and outcome(s), as opposed to the impact of seizure reduction on outcome. Thus, based on the available data, we could not establish whether clinical efforts to reduce seizure burden are associated with improved neurodevelopmental outcome.

As there was no evidence from RCT or other controlled studies to inform our recommendations, expert opinion was evaluated using the Delphi process. Results indicated that 74% completely or mostly agreed that treatment of all seizures (electroclinical and electrographic-only) was associated with a better neurodevelopmental outcome and reduced the likelihood of epilepsy later in life.

Recommendations 6: Treatment with pyridoxine and pyridoxal 5'-phosphate

Consensus-based recommendations:

A trial of pyridoxine (add-on to antiseizure medication (ASM)) should be attempted in:

- Neonates presenting with clinical features or EEG characteristics suggestive of vitamin B6-dependent epilepsy.
- Neonates with seizures unresponsive to second-line ASM without an identified etiology.

Level of agreement: High

Question 6:

In neonates with seizures with unknown etiology, is the use of pyridoxine or pyridoxal 5'-phosphate effective and safe?

PICO: Table 1

Overview of results:

- Studies allocated for full text review: 16
- Studies included after full text review: 8 (0 RCT, 0 not randomized controlled, 8 retrospective studies)
- Studies analyzed by GRADE: 0
- Evidence Level from GRADE: Not applicable

Delphi: Figure 3a

At least six independent genetic disorders have been found to interfere with the bioavailability of pyridoxine and pyridoxal 5'-phosphate (PLP), resulting in vitamin B6-dependent epilepsy.^{76,77} These include ALDH7A1 or antiquitin deficiency, hypophosphatasia, hyperphosphatasia, pyridox(am)ine 5'-phosphate oxidase (PNPO) deficiency, and pyridoxal 5'-phosphate binding protein (PLPBP) deficiency (formerly called PROSC deficiency).⁷⁸ Neonates with vitamin B6-dependent epilepsy may initially present with features suggesting hypoxic-ischemic encephalopathy or systemic manifestations including lactic acidosis and acute abdomen.^{7,79} The systematic literature review did not identify any randomized or controlled studies investigating the effect of pyridoxine or PLP on neonates with seizures. Eight studies addressing safety of pyridoxine and PLP in neonates with seizures, and retrospective case series of neonates responding to pyridoxine or PLP were included after full text review (Table S6, Appendix C). Typical features of seizure semiology (myoclonic jerks, spasms), abnormal movements (eye movements, grimacing) and EEG (burst-suppression, discontinuity) were described in ALDH7A1 and PNPO deficient patients.⁷⁹⁻⁸¹ Whilst some neonates with vitamin B6-dependent epilepsy respond immediately to pharmacological doses of pyridoxine or PLP, delayed responses are described and therefore treatment with pyridoxine or PLP should be continued for at least 3-5 days before concluding that it is not effective.⁸² Other authors have suggested a trial with repeated doses of pyridoxine up to

total dose of 500 mg.⁷⁶ One retrospective study of 10 neonates with treatment resistant seizures reported that pyridoxine treatment led to immediate flattening of the EEG in 2/6 with ALDH7A1 variants vs 1/4 with undetermined seizure etiology.⁸³ Adverse effects of pyridoxine and pyridoxal 5'-phosphate included acute respiratory depression,⁷⁹ depression of EEG amplitude,⁸³ peripheral neuropathy with long-term high dose pyridoxine >500 mg/day,⁸⁴ and liver toxicity on high-dose PLP 50 mg/kg/day.⁸⁴ While it is reasonable to offer pyridoxine and PLP to neonates with seizures unresponsive to ASM while awaiting diagnostic information, it should be taken in account that these disorders are rare. The most common, PDE-ALDH7A1, has an estimated incidence of 1:65,000 - 1:396,000.^{85,86} Assuming a combined incidence of the independent genetic disorders presenting with vitamin B6-dependent epilepsy of 1:100,000 neonates, controlled studies of pyridoxine or PLP as first- or second-line therapy for neonatal seizures may not be feasible.

In the Delphi process, 100% completely or mostly agreed that a trial of pyridoxine (add-on to ASM) should be performed in a neonate or infant presenting with clinical features or EEG characteristics suggestive of vitamin B6 dependent epilepsy, and 96% completely or mostly agreed a trial of pyridoxine (add-on to ASM) should be attempted in all neonates with seizures without an identified etiology not responding to second-line ASM. The risk of apnea should be considered when a trial of pyridoxine is attempted. Neonates with PNPO-DEE may only respond to PLP. Therefore, if vitamin B6-dependent epilepsy is suspected, following an unsuccessful trial of pyridoxine, PLP treatment may be tried even though this product is not licensed as medication. If those metabolic disorders are suspected, treatment should not be delayed, as a therapeutic trial with either pyridoxine or PLP can be started before diagnostic samples are collected as this does not affect the results.

Additional Recommendations:

Need for standardized treatment pathways

Consensus-based recommendations:

A standardized treatment pathway for the management of neonatal seizures should be available in each neonatal unit.

Level of agreement: **High**

Delphi: Figure 3a

The treatment of neonatal seizures is time sensitive: studies have shown that neonates who are diagnosed and treated earlier respond better to treatment.^{30,87,88} Using standardized pathways for

diagnosis and etiology-specific treatment, protocols may improve the time to effective treatment. As assessed by the Delphi process, 100% completely or mostly agreed that neonatal units should have a standardized local or national pathway for the treatment of neonatal seizures.

Need for communication with parents/guardian

Consensus-based recommendations:

The parents of a neonate with seizures should be informed – within the scope of feasibility in an acutely ill neonate - about the nature of neonatal seizures, treatment options, including efficacy and potential adverse events of ASM that will be used and probable duration of treatment. This should be documented in the patient (medical) notes.

Level of agreement: **High**

Delphi: Figure 3a

Neonatal seizures, particularly in the context of acute brain injury, cause parental anxiety and concern about management and long-term prognosis.⁸⁹ The needs of parents and guardians of neonates with seizures have to be recognized and taken into account. Parents need to be informed about the nature of neonatal seizures, treatment options, including efficacy and potential adverse events of ASM that will be used and probable duration of treatment. However this has to be within the scope of feasibility of an actually ill child and must not delay treatment. The discussion with parents should be documented in the patient notes. As assessed by the Delphi process, 79% completely or mostly agreed with the above statement.

Discussion

Seizures are common in neonates, yet there is substantial variability in management.¹⁷⁻²⁰ These guidelines address the management of seizures in neonates based on the best available evidence and consensus-based expert opinion.

Recent monitoring guidelines have emphasized the need for EEG for the reliable diagnosis of neonatal seizures, as well as the importance of timely seizure identification through EEG-based approaches^{2,14,15} In this systematic review, only studies with EEG confirmed seizures were included as recommended by the International Neonatal Consortium,¹⁶ EMA,¹⁶ US FDA,¹⁶ Brighton Collaboration,² the ILAE,¹⁵ and ACNS.¹⁴ All these organizations agree that the validity of seizure outcome measures in drug trials is questionable if EEG is not used, including treating non-seizure events, underestimating

total electrographic seizure burden, and lack of ability to assess whether electrographic-only seizures cease. Our conclusions can be considered applicable to neonatal seizures in general, provided that diagnostic certainty for neonatal seizures as defined by Brighton collaboration² and ILAE¹⁵ is taken into account: conventional EEG (gold standard) and aEEG are considered reliable methods for clinical management, whereas with clinical observation alone only focal clonic and focal tonic seizures can be diagnosed if observed by an expert; all seizure types require confirmation with EEG or aEEG.

No guidelines have addressed seizure management since the WHO/ILAE/IBE guideline published in 2011.¹³ A systematic review in 2012 reviewed summarized pharmacokinetic data for second-line ASM and a systematic review in 2013⁹⁰ came to similar conclusions as the WHO/ILAE/IBE guideline. Four additional recent systematic reviews reviewed first-line treatment with phenobarbital and/or levetiracetam but without consensus based guidelines.⁹¹⁻⁹⁴

In comparison to the previous guidelines, there is now better evidence for the use of phenobarbital as the first-line ASM. Although more adverse effects were observed with phenobarbital in comparison to levetiracetam, this difference was not significant.³³ In addition, if a channelopathy is likely due to family history, then a sodium channel blocker (phenytoin or carbamazepine) should be the first-line ASM. In the absence of a positive family history, phenobarbital should be first-line so not to delay the start of treatment.

The choice of second-line therapy remains unclear, as there is little evidence from RCTs. However, there are important caveats regarding second-line ASM selection which have not been discussed in the previous guideline. If a channelopathy is suspected because of clinical and EEG features, then a sodium channel blocker (phenytoin or carbamazepine) should be the second-line ASM. Second, in a neonate with cardiac disorders, levetiracetam may be preferred as the second-line ASM. Third, a trial of pyridoxine (add-on to ASM) should be attempted in neonates presenting with clinical features or EEG characteristics suggestive of vitamin B6-dependent epilepsy, and neonates with seizures unresponsive to second-line ASM without an identified etiology. Further, if vitamin B6-dependent epilepsy is suspected, following an unsuccessful trial of pyridoxine, a trial of PLP should be considered.

We appraised the effect of therapeutic hypothermia on seizure burden and concluded that therapeutic hypothermia may reduce seizure burden in neonates with hypoxic-ischemic encephalopathy. Nevertheless, the impact of therapeutic hypothermia as a non-pharmacological treatment of seizure could not be assessed.

We reviewed evidence whether treatment of electrographic-only seizures may be associated with improved outcome(s) (neurodevelopment, reduction of subsequent epilepsy). However, since studies focused on associations between seizure burden and outcome, as opposed to the impact of seizure reduction on outcome, the available data could not establish whether clinical efforts to reduce seizure burden are associated with improved outcome. Given indirect evidence,^{30,68,69,71,73,88} experts agreed that treatment of electrographic seizure burden may be associated with improved outcomes.

Our evidence and consensus-based recommendations also specify that following cessation of acute symptomatic seizures (electroclinical or electrographic-only seizures) without evidence for neonatal onset epilepsy, ASM should be discontinued before discharge, regardless of MRI or EEG findings. This is in contrast to the prior WHO/ILAE/IBE guideline which recommended discontinuing ASM if seizure-free for >72 hours “in neonates with normal neurological examination and/or normal electroencephalography.”¹³ This conclusion is further supported by a study published after completion of the systematic review that indicated neither neurodevelopment nor epilepsy at age 24 months was different among children with acute symptomatic neonatal seizures whose ASM was discontinued or maintained at hospital discharge.⁵⁸

Based on our results, Figure 4 provides a sample neonatal seizure management pathway with suggested ASM doses (Table 3).^{18,95} As with all pathways, adaptation is needed based on individual patient characteristics and practice settings. All experts agreed that neonatal units should have a standardized pathway for the management of neonatal seizures.

The evidence and consensus-based recommendations identified several key limitations in the existing literature. First, many studies are small, lack EEG-based seizure diagnosis and ASM efficacy assessment, assess cohorts which are heterogeneous in terms of etiology and post-menstrual age, and only partially address confounding factors. Varied data approaches across studies made formal analyses combining the data across studies difficult. Development and implementation of more standard common data elements may improve these issues.¹⁵ Additionally, there are few dose finding studies or pharmacokinetic data available. Finally, studies have mostly assessed seizure cessation in response to ASM but not whether overall strategies to reduce seizure exposure (incorporating EEG-based diagnosis and optimized multi-faceted management approaches) improve long-term patient-centered neurobehavioral outcomes.

Research priorities for the treatment of neonatal seizures include (1) pharmacokinetic and pharmacodynamic studies specifically for term and preterm neonates; (2) appropriate dose finding

studies for new ASM, safety studies for new ASM and also old ASM if higher doses are used; and (3) RCT aiming to license further ASM in neonates.

The ILAE recommends that guidelines be updated every five years, and the ILAE Task Force on Neonatal Seizures is planning to develop an approach to periodically update these recommendations.

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Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Figure and tables

Figure 1 Systematic literature review PRISMA 2020 diagram

Figure 2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

- (a) First-line antiseizure medication
- (b) Second-line antiseizure medication.

Figure 3: Results of the Delphi consensus process using a 5-point Likert scale with two types of statements (A: agree-or-disagree statements and B: Choice of specific ASM).

- (a) Summary results for all type A statements
- (b) All type B statements.

* Indicates a consensus in the expert group (>66% agreement).

Figure 4: Suggested treatment pathway based on current evidence and expert recommendations. For doses and adverse events see Table 3

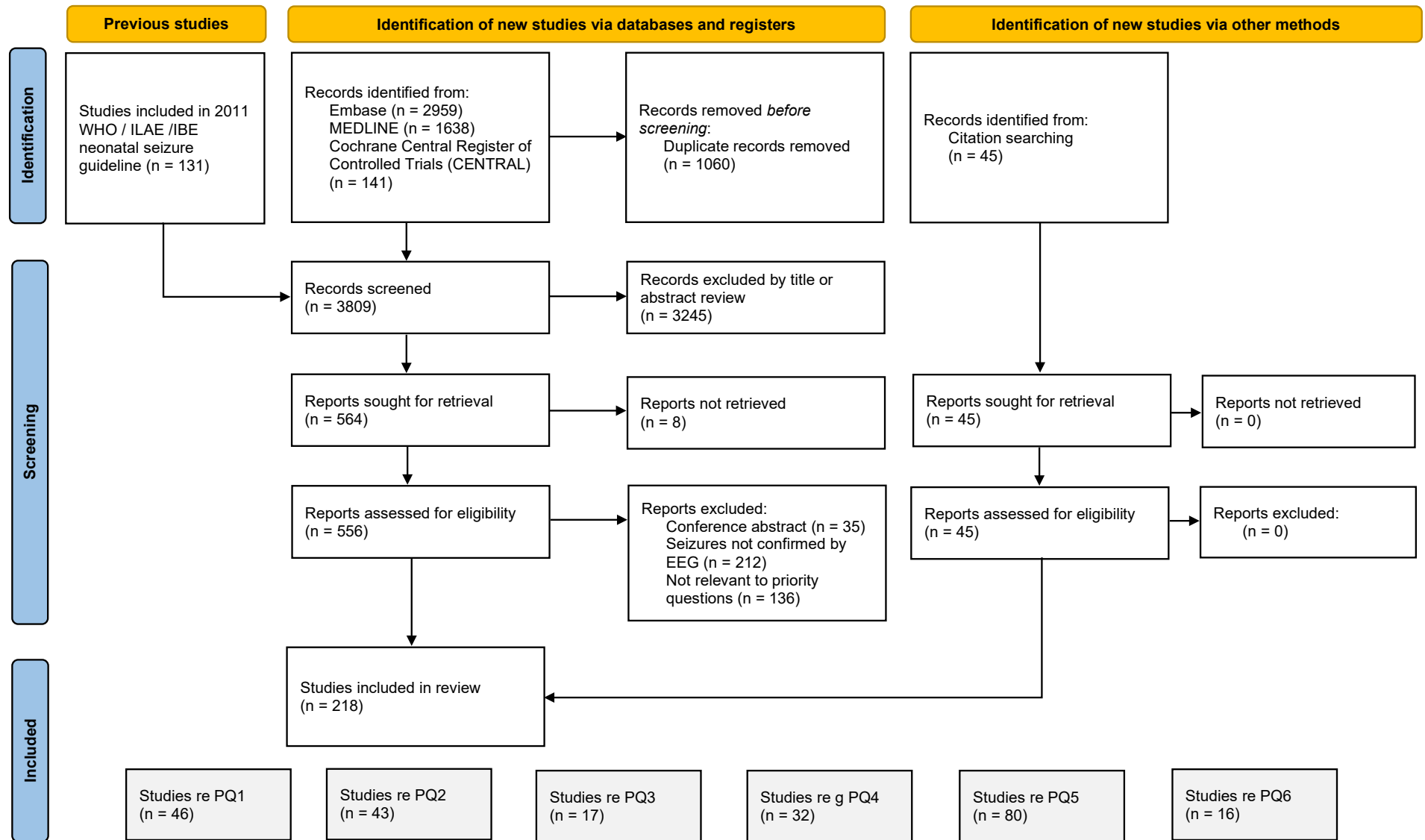
Table 1: Priority Question according to PICO [population, intervention(s), comparator(s), and outcome(s)] format

Table 2: GRADE Assessments.

- (a) Antiseizure medications for first-line and second-line pharmacotherapy
- (b) Hypothermia and Seizures.

Table 3: First and second-line antiseizure medications: examples of suggested doses and common adverse effects. Important note: The suggested doses have been derived from the available literature^{18,33,35,43,45,55,76,77,95-98} and personal experience of the authors and there are variations of opinions. Local / regional availability has to be taken into account.

Figure 1: Systematic literature review PRISMA 2020 diagram

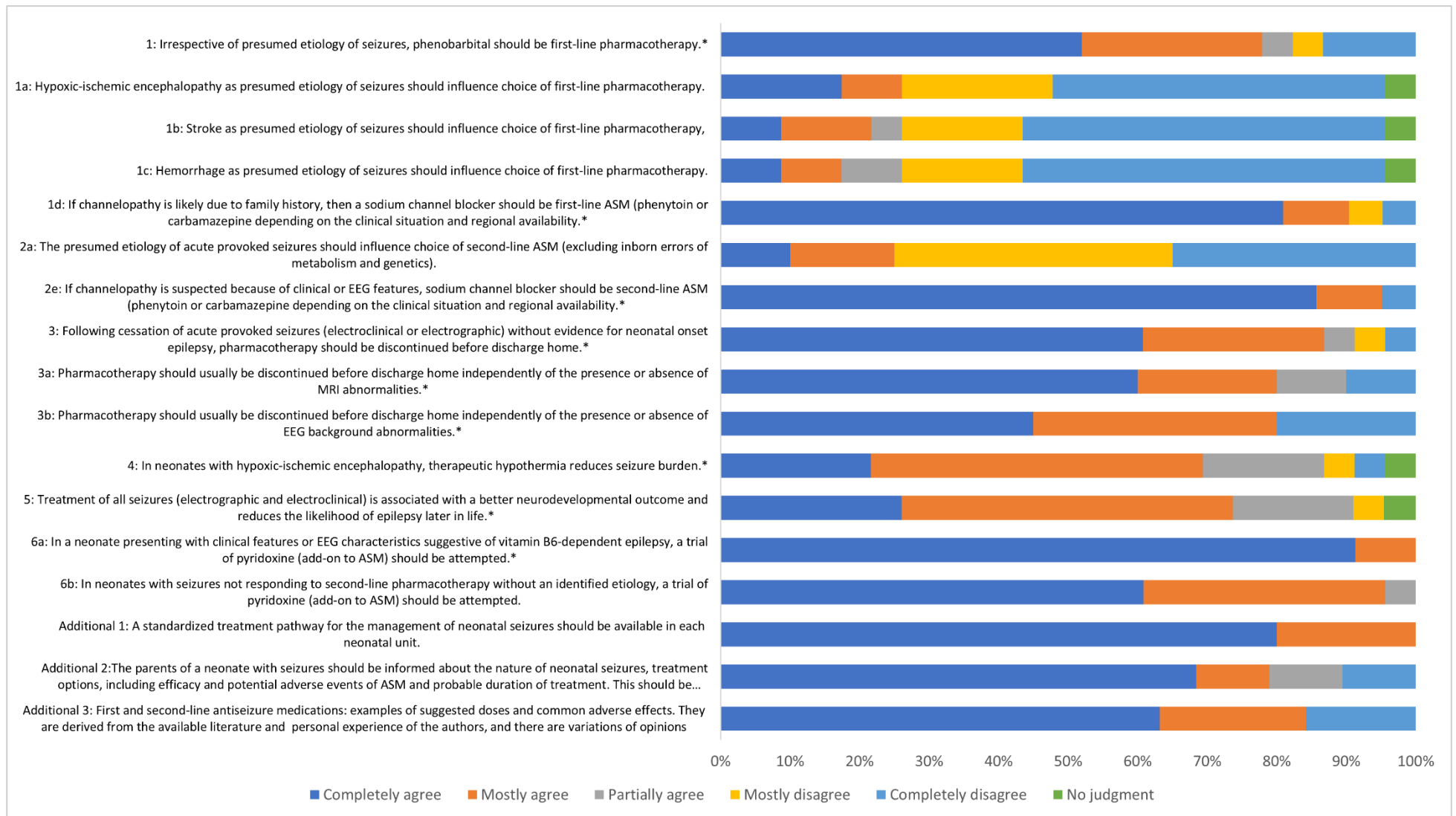


Legend: PQ: priority question, WHO: World Health Organization, ILAE international League Against Epilepsy, IBE: International Bureau for Epilepsy.

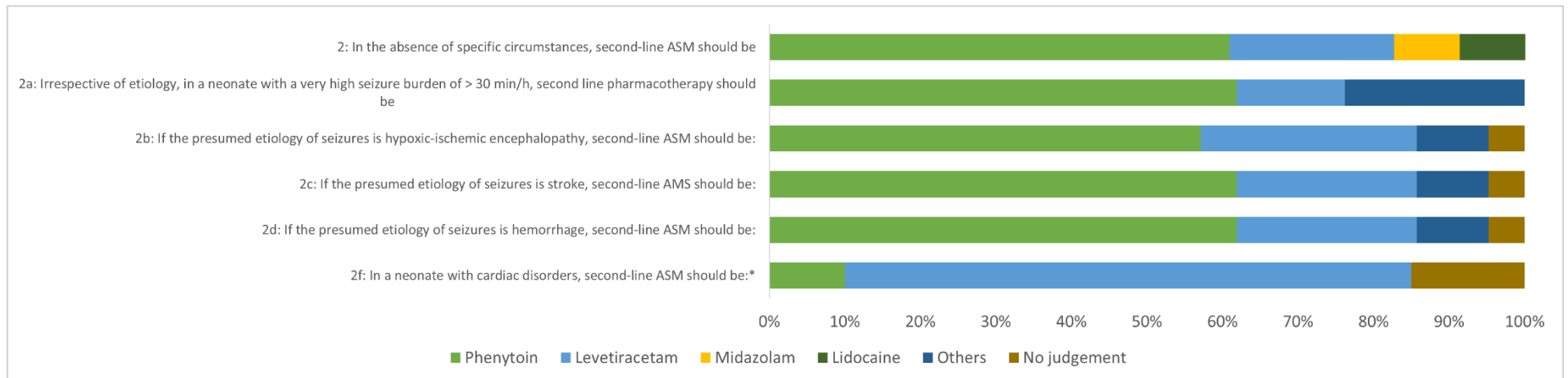
Figure 2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study. (a) First-line antiseizure medication and (b) second-line antiseizure medication.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
(a) Painter 1999	?	?	-	-	+	+	
(a) Sharpe 2020	?	?	+	+	?	+	
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
(b) Boylan 2004	?	?	-	-	+	+	
(b) Painter 1999	?	?	-	-	+	+	-
(b) Sharpe 2020	?	?	+	+	?	+	-

Figure 3: Results of the Delphi consensus process using a 5-point Likert scale with two types of statements (A: agree-or-disagree statements and B: Choice of specific ASM). (a) Summary results for all type A statements and (b) all type B statements. * Indicates a consensus in the expert group (>66% agreement).



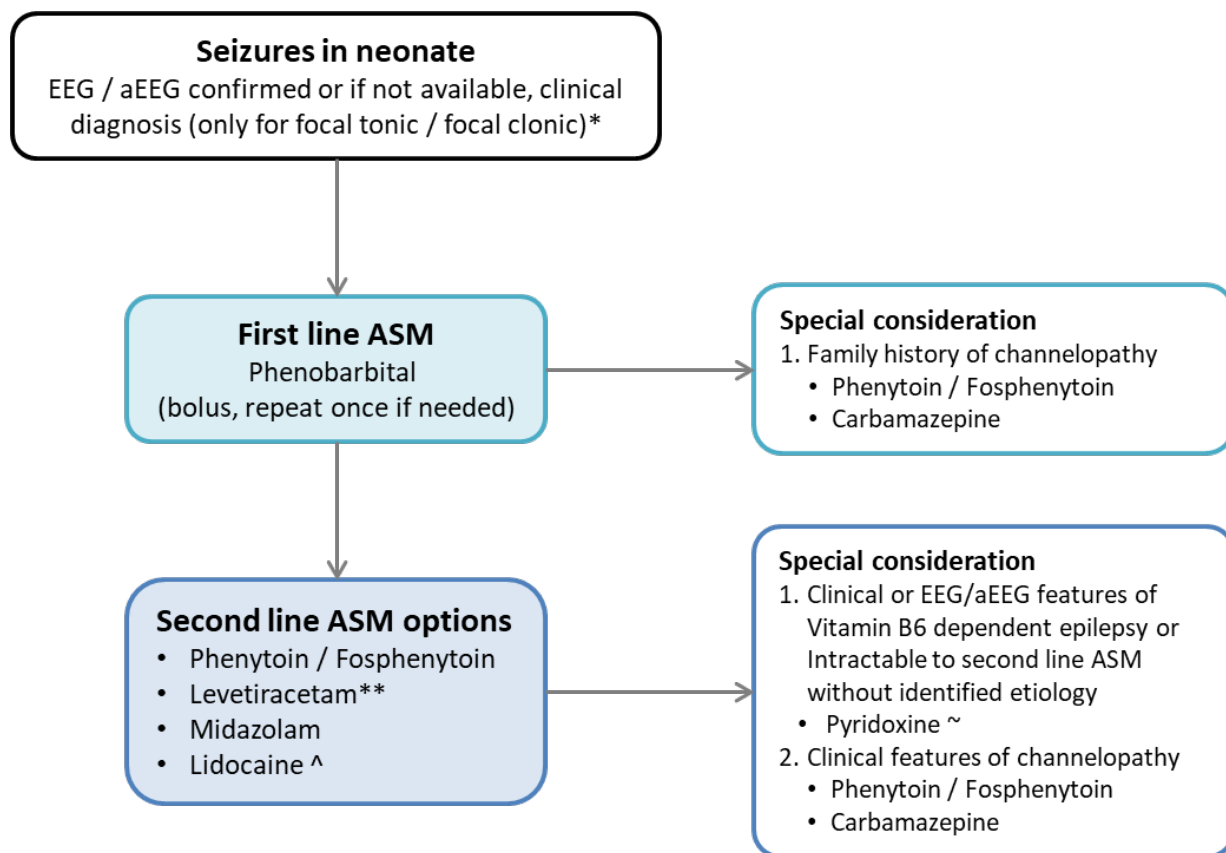
(a)



(b)

Legend: ASM: antiseizure medication

Figure 4: Suggested treatment pathway based on current evidence and expert recommendations. For doses and adverse events see Table 3.^{18,95}



Legend: ASM antiseizure medication, * Diagnostic certainty level 1 (confirmed by EEG), 2a (confirmed by aEEG) or 2b (observation by experienced clinician of focal clonic or focal tonic seizures)^{2,15}, ** Preferable for neonates with cardiac disorders, ^ Not to be used together with phenytoin and not in neonates with cardiac disorders, ~ Pyridoxal-5-phosphate may also be considered but note that it is not licensed as a medicinal product

Table 1: Priority Question according to PICO [population, intervention(s), comparator(s), and outcome(s)] format

Priority Question	P: population	I: indication	C: control	O: outcome
1. Which is the most efficacious ASM in neonates with seizures requiring pharmacological treatment (specifically regarding cessation of seizures and adverse effects)?	Neonates with EEG confirmed seizures	Pharmacologic treatment: phenobarbital, phenytoin, levetiracetam, midazolam, lorazepam	No or other pharmacological treatment	Cessation of seizure
2. Which is the most efficacious second-line ASM in neonates (specifically regarding cessation of seizures and adverse effects)?	Neonate with seizures not responding to first-line ASM treatment	Pharmacologic treatment: phenobarbital, phenytoin, levetiracetam, midazolam, lidocaine, lorazepam, topiramate, bumetanide, carbamazepine	No or other pharmacological treatment	Cessation of seizure
3. Will continuation of ASM improve neurodevelopmental outcome and reduce the risk of developing subsequent epilepsy?	Neonates after cessation of seizures	Medication withdrawal	Not discontinuing medication	Neurodevelopmental outcome and development of epilepsy
4. In neonates with hypoxic-ischemic encephalopathy, does therapeutic hypothermia reduce seizure burden?	Neonates with HIE	Therapeutic hypothermia	Neonate with HIE not undergoing therapeutic hypothermia	EEG Seizure burden (in min per hour)
5. Is a reduction of electroclinical and/or electrographic seizure burden in neonates associated with improved outcome (neurodevelopment, reduction of subsequent epilepsy)?	Neonates with seizures	Effective electrographic seizure treatment	No or ineffective electrographic seizure treatment	Neurodevelopmental outcome including epilepsy
6. In neonates with seizures, is the use of pyridoxine effective and safe?	Neonates with seizures not responding to antiseizure medication or clinical and EEG findings suggestive of vitamin B6-dependent epilepsy	Treatment with add-on pyridoxine or pyridoxal phosphate	No treatment	Cessation of seizures, safety, neurodevelopment

Legend: ASM: first-line antiseizure medication, EEG: electroencephalography, HIE: hypoxic-ischemic encephalopathy

Table 2: GRADE Assessments.

(a) Antiseizure medications for first-line and second-line pharmacotherapy

Question	Item	Certainty assessment							Number of Patients		Effect		Certainty	Importance
		Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			Relative (95%CI)	Absolute (95%CI)		
First-line	PBH vs. PHT	1 ³²	randomized trials	serious ^a	not serious	not serious	serious ^b	none	IV PBH 13/30 (43.3%)	IV PHT 13/29 (44.8%)	RR 0.97 (0.54 to 1.72)	13 fewer per 1,000 (from 206 fewer to 323 more)	⊕⊕○○ Low	Important
<p>a. Downgraded once. Random sequence generation and allocation concealment unclear (unclear risk of selection bias); single-blinded (high risk of performance and detection bias). GRADE assessment of study limitations: the proportion of studies from high risk of bias is sufficient to affect the interpretation of results. Considerations: Crucial limitation for one criterion, or some limitations for multiple criteria, sufficient to lower confidence in the estimate of effect. Final assessment: serious. See also: risk of bias table and summary.</p> <p>b. Downgraded once. 95% confidence interval overlaps no effect (it includes RR of 1) and fails to exclude important benefit.</p> <p>Comments: It is possible that randomization was ineffective in balancing unmeasured/unknown prognostic factors at baseline, given imbalance in some baseline variables (sex) and the small number of patients included No statistical power calculation.</p>														
First-line	IV LEV vs. IV PHB	1 ³³	randomized trials	serious ^a	not serious	not serious	not serious	none	IV LEV 15/53 (28.3%)	IV PHB 24/30 (80.0%)	RR 0.35 (0.22 to 0.56)	520 fewer per 1,000 (from 624 fewer to 352 fewer)	⊕⊕⊕○ Moderate	Important
<p>a. Downgraded once. Random sequence generation and allocation concealment unclear (unclear risk of selection bias); unclear risk of attrition bias. GRADE assessment of study limitations: most information is from studies at low or unclear risk of bias. Considerations: potential limitations are likely to lower confidence in the estimate of effect. Final assessment: serious. See also: risk of bias table and summary.</p>														
Second-line	IV PHB vs. IV PHT	1 ³²	randomized trials	very serious ^a	not serious	not serious	very serious ^b	none	IV PHB 5/13 (38.5%)	IV PHT 4/15 (26.7%)	RR 1.44 (0.49 to 4.27)	117 more per 1,000 (from 136 fewer to 872 more)	⊕○○○ Very low	Important
<p>a. Downgraded twice. Randomization was made at baseline (with random sequence generation and allocation concealment unclear), not after patients had received first-line treatment (high risk of selection bias); single-blinded (high risk of performance and detection bias). GRADE assessment of study limitations: the proportion of studies from high risk of bias is sufficient to affect the interpretation of results. Considerations: Crucial limitation for one or more criteria sufficient to substantially lower confidence in the estimate of effect. Final assessment: very serious. See also: risk of bias summary.</p> <p>b. Downgraded twice. Imprecision due to few events and 95% confidence interval is extremely wide, overlapping no effect (it includes RR of 1) and failing to exclude important benefits.</p>														

Second-line	IV LEV vs IV PHB	1 ³³	randomized trials	very serious ^a	not serious	not serious	very serious ^b	none	IV LEV 1/6 (16.7%)	IV PHB 20/37 (54.1%)	RR 0.31 (0.05 to 1.89)	373 fewer per 1,000 (from 514 fewer to 481 more)	⊕○○○ Very low	Important
<p>a. Downgraded twice. Randomization was made at baseline, not after patients had received first-line treatment (high risk of selection bias). GRADE assessment of study limitations: the proportion of studies from high risk of bias is sufficient to affect the interpretation of results. Considerations: Crucial limitation for one or more criteria sufficient to substantially lower confidence in the estimate of effect. Final assessment: very serious. See also: risk of bias summary.</p> <p>b. Downgraded twice. Imprecision due to few events and 95% confidence interval is wide, overlapping no effect (it includes RR of 1) and failing to exclude important benefit</p>														
Second-line	IV Lido vs IV MDZ	1 ⁴⁴	randomized trials	Serious ^a	not serious	not serious	very serious ^b	none	IV Lido 3/5 (60.0%)	IV MDZ 0/3 (0.0%)	RR 4.67 (0.32 to 68.03)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ Very low	Important
<p>a. Downgraded once. Random sequence generation and allocation concealment unclear (unclear risk of selection bias); single-blinded (high risk of performance and detection bias). GRADE assessment of study limitations: the proportion of studies from high risk of bias is sufficient to affect the interpretation of results. Considerations: Crucial limitation for one criterion, or some limitations for multiple criteria, sufficient to lower confidence in the estimate of effect. Final assessment: serious. See also: risk of bias summary.</p> <p>b. Downgraded twice. Imprecision due to few events and 95% confidence interval is extremely wide, overlapping no effect (it includes RR of 1) and failing to exclude important benefit.</p>														

(b) Hypothermia and Seizures.

Question	Item	Certainty assessment							Narrative description of the effect	Certainty	Importance
		Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
6	Seizure Burden	3 ^{60,61,65}	observational studies	serious ^a	not serious	not serious	not serious	strong association ^b	In all studies the seizure burden was higher in non-hypothermia group compared to hypothermia group: 203 min (range: 141 to 406) vs 60 min (range: 39 to 224), p=0.027 ⁶¹ ; 6.2 seizure burden (log) (SD: 0.9) vs 2.9 seizure burden (log) (SD: 0.6), p=0.003 ⁶⁵ ; 3.7 min/h (SD: 6.9) vs 0.2 min/h (SD: 0.4), p=0.003 ⁶⁰	⊕⊕○○ Low	Important

6	Seizure Frequency	3	observational studies	serious ^a	Serious ^c	not serious	not serious	none	No difference in the median number of seizures in the hypothermia group compared to the non-hypothermia group: median 75 (42-180, interquartile range, IQR) versus 41 (12-161); p=0.105. ⁶¹ More electrographic seizures in the non-hypothermia group compared to the hypothermia group (16/18, 88% versus 19/51, 37%). ⁶⁵ More seizures in the non-hypothermia group compared to the hypothermia group: 132 (range: 0-1580) vs 11 (0-186), p=0.013 (mean number of seizures); 47 (0-666) versus 1 (0-10), p=0.003 (mean number of electroclinical seizures); 85 (0-950) vs 10 (0-185), p=0.037 (mean number of electrical seizures) ⁶⁰	⊕○○○ Very low	Important
6	Status Epilepticus Occurrence	3	observational studies	serious ^a	serious ^c	not serious	serious ^d	none	Two studies did not find a difference in the occurrence of status epilepticus between non-hypothermia and hypothermia group (9/16 vs 4/15, p=0.095 ⁶¹ and 3/18 vs 5/51, p=0.434. ⁶⁵ One study found higher occurrence of status epilepticus in non-hypothermia group compared to hypothermia group (13/33, 39% vs 7/39, 18%, p=0.043) ⁶⁰	⊕○○○ Very low	Important
<p>a. Downgraded once, as most evidence comes from studies with moderate risk of bias (see results of ROBINS-I assessment in the corresponding table and the following judgments): GRADE assessment of study limitations: The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results. Considerations: Crucial limitation for one criterion, or some limitations for multiple criteria, sufficient to lower confidence in the estimate of effect. Final assessment: serious.</p> <p>b. Upgraded once for large effect (bias and confounding cannot possibly account for the results).</p> <p>c. Downgraded once due to inconsistency across study results.</p> <p>d. Downgraded once due to imprecision due to few events.</p>											

Table 3: First and second-line antiseizure medications: examples of suggested doses and common adverse effects. Important note: The suggested doses have been derived from the available literature^{18,33,35,43,45,55,76,77,95-98} and personal experience of the authors, and there are variations of opinions. Local / regional availability has to be taken into account.

Medication	Dosage	Common adverse effects	Remarks
Phenobarbital	Loading dose: 20 mg/kg iv Second loading dose: 10-20 mg/kg iv if required Maintenance: 5 mg/kg/day iv or orally in one dose	Respiratory depression Somnolence, depressed consciousness, and poor feeding Hypotension	If second loading dose of 20 mg/kg is given respiratory support should be available. Prolonged half-life first week of life and preterm. Renal and hepatic excretion can be affected in HIE. Consider plasma levels if on maintenance.
Phenytoin/ Fosphenytoin	Loading dose: 20 mg/kg PE iv over 30 min Maintenance: 5 mg/kg/day iv or orally in 2 divided doses, adjusted according to response and plasma concentration to max. per dose 7.5 mg/kg Target level 10-20 mcg/ml	Infusion site irritation / necrosis Hypotonia Arrhythmia, bradycardia Respiratory depression / arrest	Phenytoin has poor oral bioavailability. Levels likely higher in infants receiving therapeutic hypothermia, thus adjust dosage according to local target levels. Cardiac monitoring required. If used for channelopathies, switch to carbamazepine for maintenance once oral administration is possible.
Levetiracetam	Loading dose: 40 mg/kg iv Second loading dose: 20 mg/kg iv if required Maintenance: 40-60 mg/kg/day iv or orally in 3 divided doses	Mild sedation Irritability	Usually well tolerated but limited information regarding dosing and adverse effect for the neonatal population.
Lidocaine	Loading dose: 2 mg/kg iv over 10 min Maintenance: 7 mg/kg/hr iv for 4 hr, reduce to 3,5 mg/kg/h for 12 hr, reduce to 1,75 mg/kg/h for 12 hr, then stop Adapt dose for birth weight, PMA and therapeutic hypothermia ⁹⁶	Cardiac (arrhythmias, atrioventricular block, cardiac arrest) Hypotension Methemoglobinemia	Not to be given to a patient with congenital heart disease and/or on pro-arrhythmic drugs like phenytoin. Cardiac monitoring required.
Midazolam	Loading dose: 0.05-0.15 mg/kg, followed by Maintenance: 1 mcg/kg/min (=60 mcg/kg/hr) continuous infusion, titrate up in steps of 1 mcg/kg/min	Respiratory depression Somnolence, depressed consciousness, and poor feeding	Needs to be tapered when maintenance treatment has been used.

	(=60 mcg/kg/hr) to effect to max of 5mcg/kg/min (=300 mcg/kg/hr)*	Hypotension	
Carbamazepine	10 mg/kg/day orally in 2 divided doses**	Transient somnolence Gastrointestinal symptoms Hyponatremia and skin reactions reported in safety studies in children 1 month – 17 years	Usually well tolerated but limited information regarding dosing and adverse effect for the neonatal population.
Pyridoxine-HCL	Loading dose: 100 mg iv or orally, followed by 30 mg/kg/day iv or orally in 2 divided doses for 3-5 days	Respiratory depression Hypotension Prolonged treatment with high dosages may cause peripheral neuropathy	Ventilatory support should be available when loading dose is administered. If effective continue until genetic results are available.
Pyridoxal-5-phosphate	30 mg/kg/day orally in 3 divided doses for 3-5 days	Respiratory depression Hepatotoxic; cirrhosis described in prolonged use	Not licensed as medical product, but most promising approach in PNPO deficient patients. If effective continue until genetic results are available.

Legend: PE phenytoin equivalent, HIE hypoxic-ischemic encephalopathy, PMA post menstrual age, min minute, hr hour(s), mg milligram, kg kilogram, mcg microgram. * Higher doses (up to 18 mcg/kg/min = 1080 mcg/kg/hr) have been used by Castro Conde and co-workers⁴ without serious adverse effects. ** Higher doses (up to 20 mg/kg/day) have been used for KCNQ2 developmental and epileptic encephalopathies in some case series^{5,12,15}, but no safety studies have been performed in neonates. This table of recommended dosages was approved by the CGD group via Delphi (84% of experts mostly or completely agree).