Public Comment Draft – AES Infantile Epilepsy Guideline

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American Epilepsy Society Clinical Practice Guideline

Infantile Epilepsy

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Funding Statement: The evidence update and the development of this clinical guideline were funded by the American Epilepsy Society.

Acknowledgments: TBA

This publication includes data that were originally obtained through a Patient-Centered Outcomes Research Institute® (PCORI®) award [Contract No. 75Q80120D00002 from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services by the Patient-Centered Outcomes Research Institute (PCORI) through a memorandum of Agreement Amendment, number 20-603M-19]. The resulting AHRQ report and publications are referenced in the Methods section of this publication. The statements presented in this publication are solely the responsibility of the authors of this publication and do not necessarily represent the views of PCORI or AHRQ.

Abbreviations:
AES-American Epilepsy Society; AHRQ-Agency for Healthcare Research and Quality; ASMs-antiseizure medications; CCA-Council on Clinical Activities; CKD-classic ketogenic diet (CKD); CMSS-Council of Medical Specialty Societies; COE-confidence of effect; CoE-certainty of evidence; CPG-clinical practice guideline; CPT-carnitine palmitoyl transferase; DQ-developmental quotient; DRE-drug-resistant epilepsy; ELC-Epilepsy Leadership Council; GAC-Guidelines and Assessment Committee; ILAE-International League Against Epilepsy; LCAD-long-chain acyl dehydrogenase deficiency; LGIT-low-glycemic index treatment; LGS-Lennox-Gastaut syndrome; mAD-modified Atkins diet; MAE-myoclonic atonic epilepsy; MCAD- medium-chain acyl dehydrogenase deficiency; NNT-number needed to treat; PCORI-Patient-Centered Outcomes Research Institute; POLG- polymerase gamma related disorder; RD-risk difference; SCAD-short-chain acyl dehydrogenase deficiency; SUDEP-sudden unexpected death in epilepsy; SWS-Sturge-Weber syndrome; VNS-vagus nerve stimulation

Abstract

This practice guideline from the American Epilepsy Society (AES) provides evidence-based recommendations for pharmacological, dietary, and surgical therapies for epilepsy for infants and children from 1 month of age to less than 36 months. The multidisciplinary panel updated an existing systematic review which was funded by the Patient-Centered Outcomes Research Institute (PCORI) and conducted by ECRI (formerly the Emergency Care Research Institute) on behalf of the Agency for Healthcare Research and Quality (AHRQ). The updated review used the same search strategy, inclusion/exclusion criteria, and Grading of Recommendations Assessment, Development and Education (GRADE) methodology, and added studies from August 2021 through May 2023 that were not in the original systematic review. As with the previous review, West syndrome and infantile spasms are excluded from this guideline, as existing treatment guidance is already available for infantile epileptic spasms. While many of the recommendations are conditional due to low certainty of evidence, the panel made two strong recommendations: (1) hemispherectomy/hemispherotomy surgery is recommended for infants and children less than 36 months of age with drug resistant epilepsy (DRE) secondary to select underlying lesional pathologies, including hemimegaloencephaly, Rasmussen's encephalitis, Sturge-Weber syndrome (SWS), perinatal stroke, and hemispheric cortical dysplasia; and (2) intralobar, multilobar, or focal resections or posterior disconnections for drug-resistant focal or lesional epilepsy in this same age range. A treatment algorithm was developed based on the evidence and expert opinion as part of the guideline to help place pharmacological, dietary, and surgical recommendations in a clinical context. The limited number of studies and low certainty of evidence in this population underscores the need for higher quality data and etiology-specific treatments. More research is needed to evaluate effective therapies for infants with epilepsy, as well as the impact these therapies have on long-term developmental and mortality outcomes.

Introduction

Infancy represents a period with one of the highest incidences of epilepsy.[1-4] This incidence is driven by a wide range of risk factors such as perinatal injury, cortical malformations, and genetic etiologies.[5] These complex etiologies can lead to drug-resistant epilepsy (DRE), defined as persistent seizures despite two appropriately chosen antiseizure medications (ASMs), in an estimated 35-65% of infants with epilepsy. [6-8] Three primary categories of epilepsy treatment in infants are pharmacological, dietary therapy, and surgery. Typically, infants receive pharmacological treatment before the other interventions. As infants are in a critical period of brain development, the importance of effective treatment, and the balance between ongoing seizures and medication side effects, is heightened for both new-onset and drug-resistant epilepsy. Untreated seizures can have profound, lasting effects on cognitive and motor development.[9,10] Given the risk of sudden unexplained death in epilepsy (SUDEP), infants with DRE need to be evaluated for non-pharmacological treatments including surgery[11] and dietary therapies.

While there is some published treatment guidance for infantile epileptic spasms, limited treatment guidance exists for other forms of epilepsy in infants.[12] The 2015 International League Against Epilepsy (ILAE) report on infantile epilepsy noted a lack of evidence-based guidelines, with most recommendations coming from expert opinion.[13] We, therefore, sought to fill this critical gap with an evidence-based guideline.

The increasing availability of genetic testing has shifted the concepts of early childhood epilepsy etiology from largely idiopathic to etiology-specific epilepsies and syndromes.[14] Guidelines and publications on management of specific infantile and childhood syndromes, such as Dravet syndrome and Angelman syndrome, have recently been published.[15,16] Moreover, genetic testing is now recommended for all children with unexplained epilepsy,[14] opening the door for further, more detailed gene-specific treatment guidelines in the future. Despite these advances in epilepsy care, no comprehensive treatment guideline exists for infants with undifferentiated syndromic and non-syndromic epilepsy.

Guidelines have been shown to be effective at streamlining care[17] and may improve access to life-saving treatments such as epilepsy surgery.[18] The recommendations in this American Epilepsy Society (AES) guideline provide guidance on first- and second-line treatments for infants with epilepsy ages $\geq$1 month through <3 years, as well as when to consider dietary therapy or epilepsy surgery. Collectively, the recommendations provide a roadmap to guide care for patients with infantile epilepsy and to inform efficient, appropriate referrals to specialized pediatric epilepsy centers.

Rationale

This guideline was based on an update of a systematic review initially funded by the Patient-Centered Outcomes Research Institute (PCORI®) and conducted by ECRI in 2022 under contract to the Agency for Healthcare Research and Qualify (AHRQ).[19] The systematic review update reported here maintains the same PICO (population, intervention, comparator, outcome) questions and inclusion/exclusion criteria outlined for the AHRQ systematic review and incorporates studies published after the AHRQ review's literature search.

A notable exclusion in the AHRQ systematic review and in this update and guideline is the patient population with infantile spasms, including those meeting criteria for West syndrome. This exclusion was an intentional scope decision to enable appropriate focus on non-syndromic infantile epilepsy. While some treatment guidance is available for infantile spasms, limited treatment guidance exists for other forms of epilepsy in infants.

Guideline Recommendations Summary

Recommendations with brief remarks are summarized in Table I, Pharmacological Treatments; Table II, Dietary Treatments; and Table III, Surgical Treatments.

Evidence profiles on which the Recommendations are based, rationale details, and other implementation considerations noted by Work Group topic experts during Recommendation development are found in Supplement 5.

Table I-A.	Summary of Recommendations related to Pharmacological Treatments for infants (1 month to less than 36 months) diagnosed with new-onset epilepsy
Treatment Intervention and Comparator	**Recommendation**
I-A-1. levetiracetam compared with **no levetiracetam**	For infants and children 1 month to less than 36 months of age diagnosed **with new-onset epilepsy**, the AES guideline panel suggests treatment with levetiracetam rather than no levetiracetam. *Remarks:* - *In patients with a history of severe behavioral disorders, considering an alternative antiseizure medication rather than levetiracetam might be reasonable.* (**Conditional** recommendation, **Very Low** certainty of evidence)
I-A-2. valproate compared with **no valproate**	For infants and children 1 month to less than 36 months of age diagnosed **with new-onset epilepsy of uncertain etiology**, the AES guideline panel **suggests against** the use of valproate. *Remarks:* - *In patients with an unknown epilepsy etiology, genetic testing should be considered before the initiation of valproate in order to exclude pathogenic variants of polymerase gamma disorder (POLG).* - *When appropriate or if alternatives are not available, initiation of valproate might be reasonable if genetic testing demonstrates a lack of pathogenic variant in POLG.* - *There is an increased risk of hepatotoxicity associated with valproate use in children < 2 years of age, particularly those with underlying mitochondrial disorders.* **(Conditional** recommendation, **Very Low** certainty of evidence)

Table I-A.	Summary of Recommendations related to Pharmacological Treatments for infants (1 month to less than 36 months) diagnosed with new-onset epilepsy
Treatment Intervention and Comparator	**Recommendation**
I-A-3. oxcarbazepine compared with **levetiracetam**	For infants and children 1 month to less than 36 months of age diagnosed with **new-onset focal epilepsy**, the AES guideline panel suggests treatment with oxcarbazepine rather than levetiracetam. *Remarks:* - *Oxcarbazepine is contraindicated in generalized epilepsy and Dravet syndrome. Refer to Dravet Syndrome Foundation treatment guidance.*[15] - *Adverse events may be higher in patients with epilepsy due to sodium channel disorders who receive oxcarbazepine.* - *Use caution in patients with hypersensitivity reactions (Stevens-Johnson syndrome, HLA predisposition).* (**Conditional** recommendation, **Very Low** certainty of evidence)
I-A-4. levetiracetam compared with **phenobarbital**	For infants and children 1 month to less than 36 months of age diagnosed **with new-onset epilepsy**, the AES guideline panel **suggests for** the use of levetiracetam rather than phenobarbital. *Remarks:* - *In patients with a history of severe behavioral disorders, it might be reasonable to consider an alternative antiseizure medication rather than levetiracetam.* - *Prolonged use of phenobarbital is associated with potential neurotoxicity and adverse cognitive effects.* (**Conditional** Recommendation, **Low** Certainty of Evidence)

Table I-A.	Summary of Recommendations related to Pharmacological Treatments for infants (1 month to less than 36 months) diagnosed with new-onset epilepsy
Treatment Intervention and Comparator	**Recommendation**

I-A-5.
topiramate
compared with
carbamazepine
	For infants and children 1 month to less than 36 months of age diagnosed **with new-onset epilepsy**, the AES guideline panel **suggests** treatment with either topiramate or carbamazepine.
	Remarks:
	- *Topiramate is preferred in the following situations:*
	  - *When carbamazepine is contraindicated.*
	  - *In patients with a risk of hypersensitivity (e.g., rashes; HLA predisposition), as well as SCN1A disorders.*
	- *Carbamazepine is preferred in the following situations:*
	  - *Focal epilepsy or some channelopathies (KCNQ2, KCNQ3, SCN2A).*
	  - *Carbamazepine is contraindicated in children with certain generalized epilepsies or other channelopathies including Dravet syndrome; refer to Dravet Syndrome Foundation treatment guidelines.*
	(**Conditional** recommendation, **Very Low** certainty of evidence)

Table I-B.
Summary of Recommendations related to Pharmacological Treatments for infants (1 month to less than 36 months) diagnosed with focal or unknown drug-resistant epilepsy (DRE).

Treatment Intervention and Comparator	Recommendation
I-B-1. **valproate** compared with **no valproate**	For infants and children 1 month to less than 36 months of age diagnosed **with *drug-resistant* epilepsy**, the AES guideline panel **suggests** treatment with valproate rather than no valproate. *Remarks:* - *In patients with an unknown epilepsy etiology, genetic testing should be considered before the initiation of valproate in order to exclude pathogenic variants of POLG.* - *When appropriate, or if alternatives are not available, initiation of valproate might be reasonable if genetic testing demonstrates a lack of pathogenic variant in polymerase gamma disorder (POLG).* - *There is an increased risk of hepatotoxicity associated with valproate use in children < 2 years of age, particularly those with underlying mitochondrial disorders.*[20,21] - *Use of valproate concurrently with the ketogenic diet increases risk of carnitine and vitamin D deficiency. Serum levels of valproate, 25-hydroxyvitamin D, and carnitine should be monitored and supplemented accordingly.* (**Conditional** recommendation, **Very Low** certainty of evidence) **See also: Table I-A**, Recommendation **I-A-2**, a separate recommendation for treatment with valproate for infants with focal or unknown **new-onset** epilepsy.
I-B-2. **topiramate** compared with **no topiramate**	For infants and children 1 month to less than 36 months of age **diagnosed with *drug-resistant* epilepsy**, the AES guideline panel **suggests** treatment with topiramate rather than no topiramate. *Remarks:* - *In patients on the ketogenic diet, there is an increased risk of metabolic acidosis and kidney stones.* (**Conditional** recommendation, **Low** certainty of evidence).

Table I-B.
Summary of Recommendations related to Pharmacological Treatments for infants (1 month to less than 36 months) diagnosed with focal or unknown drug-resistant epilepsy (DRE).

Treatment Intervention and Comparator	Recommendation
I-B-3. **lamotrigine** compared with **no lamotrigine**	For infants and children 1 month to less than 36 months of age **diagnosed with *drug-resistant* epilepsy**, the AES guideline panel **suggests** treatment with lamotrigine rather than no lamotrigine. *Remarks:* - *Shared decision-making is needed to factor in time to effective dosing (long titration periods are needed for lamotrigine).* - *Use caution in patients with hypersensitivity reactions (Stevens Johnson syndrome). Risk increases with co-administration with valproate.* - *Lamotrigine is contraindicated in children with Dravet syndrome; refer to Dravet Syndrome Foundation treatment guidelines.*[15] (**Conditional** recommendation, **Very Low** certainty of evidence)
I-B-4. **rufinamide** compared with **no rufinamide**	For infants and children 1 month to less than 36 months of age diagnosed with **drug-resistant epilepsy**, the AES guideline panel **suggests** the use of rufinamide rather than no rufinamide. (**Conditional** recommendation, **Very Low** certainty of evidence)
I-B-5. **stiripentol** compared with **no stiripentol**	For infants and children 1 month to less than 36 months of age with **drug-resistant Dravet syndrome,** the AES guideline panel **suggests** treatment with stiripentol rather than no stiripentol for Dravet syndrome with concomitant clobazam treatment. *Remarks:* - *Refer to Dravet Syndrome Foundation treatment guidelines.* (**Conditional** recommendation, **Very Low** certainty of evidence)

Table II. **Summary of Recommendations related to Dietary Treatments for infants (1 month to less than 36 months) diagnosed with drug-resistant epilepsy.**	
Treatment Intervention and Comparator	**Recommendation**
II-A. **ketogenic diet** compared with **no ketogenic diet**	For infants and children 1 month to less than 36 months of age diagnosed with **drug-resistant epilepsy**, the AES guideline panel **suggests** a ketogenic diet rather than no ketogenic diet. *Remarks:* - *Classic ketogenic diet is recommended for children <24 months due to higher efficacy rates and need for more exact calculations to account for rapid growth during this time period. This allows for continued dietary adjustments to optimize efficacy and minimize side effects.* - *Dietary therapy may be considered as a first-line treatment in patients less than 36 months of age with a diagnosis of Glut 1 or PDH.* - *There are better response rates with the ketogenic diet when there is a genetic etiology.* (**Conditional** recommendation, **Low** certainty of evidence)
II-B. **modified Atkins diet** compared with **no modified Atkins diet**	For infants and children 1 month to less than 36 months of age diagnosed with **drug-resistant epilepsy**, the AES guideline panel **suggests** against the use of a modified Atkins diet. *Remarks:* - *Classic ketogenic diet is recommended for children <24 months due to higher efficacy rates and need for more exact calculations to account for rapid growth during this time period. This allows for continued dietary adjustments to optimize efficacy and minimize side effects.* - *Modified Atkins diet may be a reasonable alternative for patients unable to access or tolerate a classic ketogenic diet.* (**Conditional** recommendation, **Low** certainty of evidence)

Table II. **Summary of Recommendations related to Dietary Treatments for infants (1 month to less than 36 months) diagnosed with drug-resistant epilepsy.**	
II-C. **ketogenic diet** compared with **modified Atkins diet**	For infants and children 1 month to less than 36 months of age diagnosed with **drug-resistant epilepsy**, the AES guideline panel suggests a ketogenic diet rather than a modified Atkins diet. *Remarks:* - *Classic ketogenic diet is recommended for children <24 months due to higher efficacy rates and need for more exact calculations to account for rapid growth during this time period. This allows for continued dietary adjustments to optimize efficacy and minimize side effects.* - *In patients experiencing adverse events (e.g., constipation) or not tolerating the ketogenic diet, trying the modified Atkins diet might be reasonable. In all other instances, the ketogenic diet is preferred for this age group.* (**Conditional** recommendation, **Low** certainty of evidence)
II-D. **modified Atkins diet** compared with **low glycemic index treatment**	For infants and children 24 months to less than 36 months of age diagnosed with **drug-resistant epilepsy**, the AES guideline panel suggests either modified Atkins diet or low glycemic index treatment. *Remarks:* - *Classic ketogenic diet is recommended for children <24 months due to higher efficacy rates and need for more exact calculations to account for rapid growth during this time period. This allows for continued dietary adjustments to optimize efficacy and minimize side effects.* - *In populations >24 months to <3 years of age, any diet can be used.* (**Conditional** recommendation, **Low** certainty of evidence)

Table III.
Summary of Recommendations related to Surgical Treatments for infants (1 month to less than 36 months) diagnosed with specific types of drug-resistant epilepsy.

Treatment Intervention and Comparator	Recommendation
III-A. **hemispherectomy / hemispherotomy** compared with **no hemispherectomy / hemispherotomy**	For infants and children 1 month to less than 36 months of age diagnosed with **drug-resistant epilepsy**, the AES guideline panel made a **strong recommendation** for hemispherectomy/hemispherotomy surgery for appropriately chosen candidates who have been diagnosed with holohemispheric drug-resistant epilepsy secondary to select structural pathologies, including hemimegaloencephaly, Rasmussen's encephalitis, Sturge-Weber syndrome, perinatal stroke, and hemispheric cortical dysplasia. *Remarks:* - *Strong recommendation because of 1) the life-threatening nature of DRE secondary to select pathologies, and 2) the high risk of morbidity and mortality in children when left untreated, and 3) the greater potential for post-operative seizure-freedom compared with additional antiseizure medications.* (**Strong** recommendation, **Low** certainty of evidence)
III-B. **intralobar, multilobar, or focal resection, posterior disconnections** compared with **no resections**	For infants and children 1 month to less than 36 months of age diagnosed with **drug-resistant focal or lesional epilepsy**, the AES guideline panel **recommends** intralobar, multilobar, or focal resections or posterior disconnections rather than no intralobar, multilobar, or focal resections or posterior disconnections. *Remarks:* - *Strong recommendation driven by the life-threatening nature of drug-resistant focal or lesional epilepsy and the high risk of mortality in children when left untreated.* (**Strong** recommendation, **Very Low** certainty of evidence)

Table III.
Summary of Recommendations related to Surgical Treatments for infants (1 month to less than 36 months) diagnosed with specific types of drug-resistant epilepsy.

Treatment Intervention and Comparator	Recommendation
III-C. **supratentorial brain tumor resection** compared with **no resection**	For infants and children 1 month to less than 36 months of age diagnosed with **tumor-related epilepsy**, the AES guideline panel **suggests** for supratentorial brain tumor resection rather than no supratentorial tumor resection. *Remarks:* - *The biological character or grade of the tumor influences the decision calculus regarding undergoing surgery and tolerance for surgical complications.* (**Conditional** recommendation, **Very Low** certainty of evidence)

Methods

Overview

The overall guideline development process--including funding of the work, AES guideline work group formation, management of conflicts of interest, internal and external review, and organizational approval-- was guided by AES policies and procedures and overseen by the AES Guidelines and Assessment Committee.[22] Based on systematic reviews that assessed the evidence for treatment effectiveness, comparative effectiveness, and harms for each intervention, this clinical practice guideline was created by a panel of topic experts for each treatment category with patient family/caregiver or advocate representatives' input (Supplement 1). The work group used the GRADE approach to assess the supporting evidence contained in the reviews and develop the guideline recommendations.[23-25] An expanded methodology is provided in Supplement 2.

Guideline Funding

The evidence update and the development of this clinical guideline were funded by AES based on a prior systematic review, for which AES had nominated the topic. The prior systematic review was funded by PCORI®,[26] managed by the AHRQ, conducted under contract with AHRQ by the ECRI Institute, and published as an AHRQ final report[19,27] and two systematic review papers.[28,29]

Formulating Specific Clinical Questions and Determining Outcomes of Interest

Evidence reviews conducted with guidance from external methodology experts were based on the prior AHRQ high-quality systematic reviews. PICO questions, inclusion/exclusion criteria, and outcomes of interest align as closely as possible with those that guided the previously published AHRQ and ECRI work.[19,27] The current guideline recommendations are based on a synthesis of results from the previously reported systematic review and the current update.

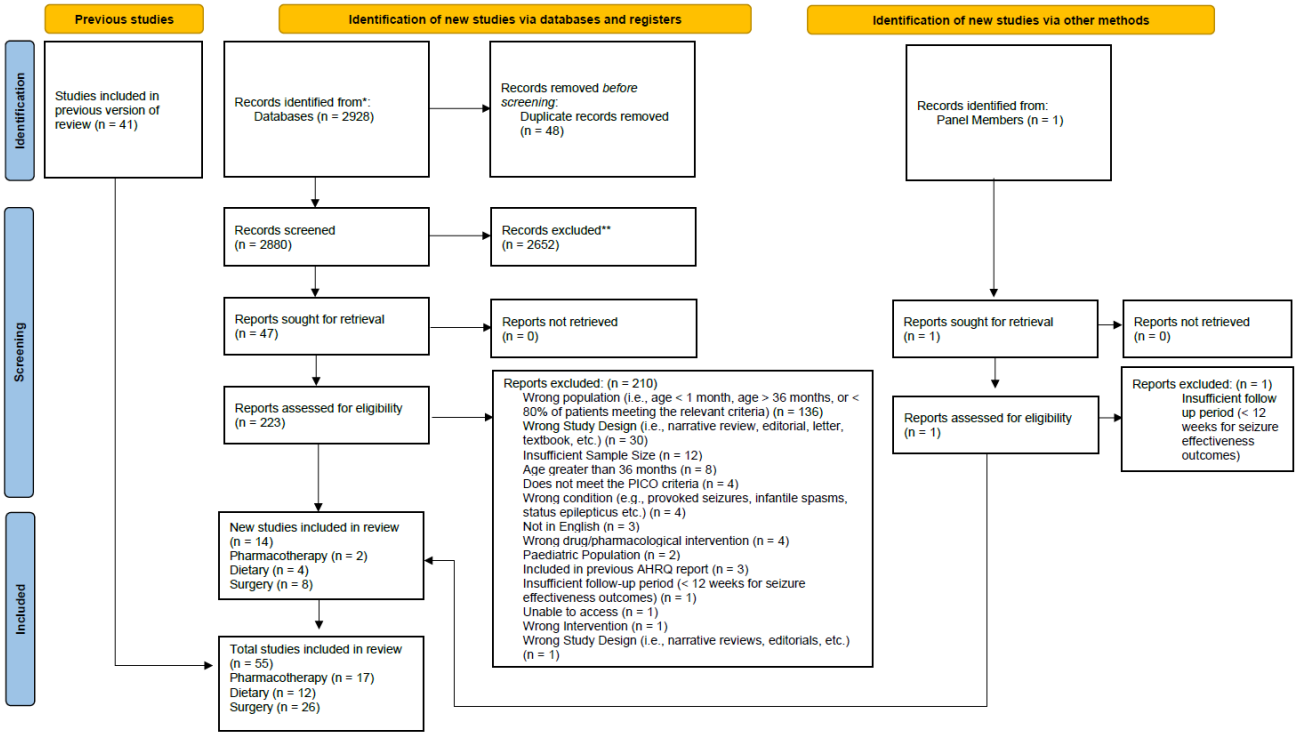
Each PICO question addressed in this guideline identifies a specific population (P), intervention (I), comparator (C), and the corresponding patient-important outcomes (O). Clinical questions and prioritized outcomes were identified *a priori* as part of the prior systematic review, with key informant and technical expert input, and consistent with principles of the GRADE approach of identifying priority patient- important outcomes specified in the protocol. The PICO questions of focus are detailed in Appendix A, as guided by the PCORI/AHRQ/ECRI reports. [21-23] and by new literature identified in the update.

Evidence Review and Development of Recommendations

Rigorous, high-quality systematic reviews were conducted to address each PICO question. An updated literature search using search strategies from the prior PCORI/AHRQ/ECRI systematic review[21,22] was conducted to identify new research published 2021 through May 18, 2023.

The newer data identified encompassed 2,882 studies. The PRISMA diagram (Figure 1) displays the update for the outcome of dual independent screening of Titles/Abstracts and Full Text. Data from studies included in the current update were synthesized with data from the 44 studies included in the prior systematic review to build a body of evidence informing this guideline. Results of these data syntheses are reported in detail in evidence profiles in Supplements 3 and 4.

Figure 1. Management of Infantile Epilepsies: Systematic Review Updates (PRISMA flow diagram).



Guideline Work Group members participated in dual independent literature screening, data extraction, and risk of bias assessments of included studies for the update, with guidance and assistance from the methodologists. The methodologists assessed the certainty of evidence[30] and developed concordant recommendations using the GRADE evidence-to-decision framework. Evidence profiles and certainty of the evidence for each PICO question are detailed in Supplement 5.

The certainty of the evidence relevant to each outcome was assessed using the GRADE approach based on the risk of bias, consistency, directness, precision, likelihood of publication bias, magnitude of effect, and dose-response relationship.[25] The certainty of the evidence for each outcome was rated from very low to high[26,31,32]

Recommendations are informed by data presented in the evidence profiles, certainty of evidence ratings, the balance of benefits and harms of the intervention and comparator, and patient values and preferences.

Interpretation of Strong and Conditional Recommendations

Recommendations are classified as either “strong” or “conditional.” The phrase “the guideline Work Group recommends” indicates a strong recommendation; the phrase “the guideline Work Group suggests” indicates a conditional recommendation.

Summary of the Evidence

I. Pharmacological Treatments

Recommendations, Evidence Summaries, and Discussions

Recommendations related to Pharmacological Treatments for infants (1 month to less than 36 months) diagnosed with focal or unknown new onset epilepsy

Recommendation I-A-1. For infants and children 1 month to less than 36 months of age diagnosed with new-onset epilepsy, the AES guideline panel **suggests** the use of levetiracetam rather than no levetiracetam.

(**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Remarks:

- In patients with a history of severe behavioral disorders, considering an alternative antiseizure medication rather than levetiracetam might be reasonable.

Summary of the evidence

One non-randomized study (n = 92) assessed the effect of treatment with levetiracetam compared with no levetiracetam for children with new-onset epilepsy (no prior ASM exposures) and reported on the outcomes of seizure freedom and adverse events leading to levetiracetam discontinuation.[33] An additional non-randomized study (n = 101) reported on the outcome of adverse events leading to levetiracetam discontinuation where a majority of the patients (60.4%) had been exposed to at least one prior ASM.[34]

Benefits, harms, and burden

Levetiracetam may increase seizure freedom compared with no levetiracetam (RR: 0.34, 95% CI: 0.2-0.45; Very Low CoE); however, the evidence is very uncertain due to concerns with the small sample size. The number needed to treat (NNT) to achieve seizure freedom with levetiracetam is 1.51 (95% CI: 1.32-1.77). In one study, 5 children (1%) were reported to have irritability and no patient discontinued therapy due to levetiracetam-related side effects.[33] In the other available study, levetiracetam-related adverse events were reported in 5 out of 101 patients and 7% (7 subjects) patients discontinued therapy due to adverse events, which included infantile spasms and respiratory disorders. The investigators felt the persistence of infantile spasms despite levetiracetam therapy was indicative of a lack of efficacy rather than an adverse event.[34]

Other considerations

Levetiracetam is widely available in different formulations and is inexpensive. Treatment with levetiracetam does not require routine laboratory testing but may require dosing adjustment in patients with renal dysfunction. Although only 1% of children in this study were reported to have irritability, other evidence suggests behavioral symptoms can occur in as many as 37.6% of pediatric patients.[35]

Conclusions and research needs for this recommendation

The guideline panel made a conditional recommendation for treatment with levetiracetam in infants and children 1 month to less than 36 months of age diagnosed with new-onset epilepsy. The panel recognized that the magnitude of the desirable effects may be moderate and that the undesirable effects may be small.

Recommendation I-A-2. For infants and children 1 month to less than 36 months of age diagnosed with *new onset* epilepsy, the AES guideline panel **suggests against** the use of valproate**.**

(**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Remarks:

- In patients with an unknown epilepsy etiology, genetic testing should be considered before the initiation of valproate in order to exclude pathogenic variants of polymerase gamma disorder (POLG).
- When appropriate or if alternatives are not available, initiation of valproate might be reasonable if genetic testing demonstrates a lack of pathogenic variant in POLG.
- There is an increased risk of hepatotoxicity associated with valproate use in children < 2 years of age, particularly those with underlying mitochondrial disorders.[20,21]

Recommendations I-A-2 and 1-B-1 are separate recommendations that address new-onset epilepsy (1-A-2) or DRE (1-B-1) populations. The Remarks for each recommendation differ, but the 2 recommendations share an evidence profile as well as sections addressing Summary of the evidence; Benefits, harms, and burden; Other Considerations; and Conclusions and research needs.

Summary of the evidence

One non-randomized study (retrospective chart review study) assessed the effect of treatment with valproate compared with no valproate for children with DRE (mean ASM exposure 2.8; median 3) and reported on the outcomes of seizure freedom, seizure frequency, and adverse events.[36] This study included 50 children below the age of 2 years, aged 3 months to 23 months. The mean age of starting valproate was 16 months. Thirty-two patients (64%) had more than 50% seizure improvement after valproate. Eleven patients (22%) were seizure-free. In these patients, the valproate was used as a second line ASM.

Benefits, harms, and burden

Valproate may increase seizure freedom compared with no valproate (RR: 0.78; 95% CI: 0.67, 0.91; Very Low CoE); however, the evidence is very uncertain due to concerns with small sample size. The NNT to achieve seizure freedom with valproate is 4.55 (95% CI; 2.99-9.51). Similarly, seizure frequency, as assessed with 50% or greater reduction, may be reduced (64% [32/50] participants experienced reduced seizure frequency; Very low CoE). Treatment with valproate compared with no valproate may increase the risk of the encephalopathy (risk difference [RD]: 4%) and elevated liver function measures of AST (RD: 4%) and GGT (RD: 10%). Valproate treatment may have little to no difference on ALT, alkaline phosphate, and bilirubin; however, the evidence is uncertain due to concerns about small sample size (Very low CoE).

Other considerations

Valproate is widely available and inexpensive. Treatment with valproate requires routine laboratory testing, which may decrease the acceptability and feasibility of the treatment for certain patients. Hepatotoxicity is a risk for children; therefore, children with unknown etiologies may require genetic testing.

Conclusions and research needs for this recommendation

The guideline panel made a conditional recommendation against valproate for new onset epilepsy patients and a conditional recommendation for treatment with valproate for DRE patients. The panel recognized that the magnitude of the desirable and undesirable effects would vary based on the patient population and made two separate recommendations for treatment with valproate. For patients with new-onset epilepsy, the panel determined that the desirable anticipated effects may be small. However, in refractory drug-resistant patients, the panel decided that the desirable anticipated effects may be moderate. Due to the risk of valproate-associated hepatotoxicity in patients with POLG, genetic testing is recommended prior to initiation of valproate. In patients with Dravet syndrome, treatment guidelines exist that recommend valproate as a first-line therapy.[15]

Recommendation I-A-3. For infants and children 1 month to less than 36 months of age diagnosed with new-onset focal epilepsy, the AES guideline panel **suggests** treatment with oxcarbazepine rather than levetiracetam.

(**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Remarks:

- Oxcarbazepine is contraindicated in generalized epilepsy and Dravet syndrome. Refer to Dravet Syndrome Foundation treatment guidance.
- Adverse events may be higher in patients with epilepsy due to sodium channel disorders who receive oxcarbazepine.
- Use caution in patients with hypersensitivity reactions (Stevens-Johnson syndrome, HLA predisposition).

Summary of the evidence

One non-randomized study (n = 161) compared clinical outcomes for children with new onset focal epilepsy treated with either levetiracetam or oxcarbazepine as first-line treatment.[37] Outcomes reported included seizure freedom and adverse events with more favorable seizure outcomes, but higher adverse events with oxcarbazepine.

Benefits, harms, and burden

Oxcarbazepine may increase seizure freedom compared with levetiracetam in children with new onset focal epilepsy with 74% achieving seizure freedom with oxcarbazepine compared with 41% with levetiracetam (RR 1.79, 95% CI:1.33 to 2.41) and reduced seizure relapse rates (27% vs 59%). The NNT to achieve seizure freedom with oxcarbazepine compared with levetiracetam is 3.08 (95% CO: 2.13-5.8). Adverse events were experienced by 6% of the study patients (8 with oxcarbazepine and 3 with levetiracetam), but all were mild and transient. One patient on oxcarbazepine developed hypersensitivity syndrome leading to discontinuation of therapy.

Other considerations

Both oxcarbazepine and levetiracetam are widely available in different formulations and are similar in cost. Treatment with oxcarbazepine may require routine laboratory testing and monitoring for hypersensitivity reactions. In addition, oxcarbazepine is contraindicated in generalized epilepsies and Dravet syndrome. Treatment with levetiracetam does not require routine laboratory testing but may require dosing adjustment in patients with renal dysfunction.

Conclusions and research needs for this recommendation

The guideline panel made a conditional recommendation that treatment with oxcarbazepine may be preferable to levetiracetam in infants and children 1 month to less than 36 months of age diagnosed with new- onset focal epilepsy. The panel recognized that the magnitude of the desirable effects may be moderate and that the undesirable effects may be small.

Future research is needed to further delineate response to oxcarbazepine based on etiology, as well as how to minimize risk of hypersensitivity reactions and other adverse events.

Recommendation I-A-4. In infants and children 1 month to less than 36 months of age diagnosed with new-onset epilepsy, the AES guideline panel **suggests for** the use of Levetiracetam rather than phenobarbital.

(**Conditional** Recommendation, **Low** Certainty of Evidence).

***Remarks*:**

- In patients with a history of severe behavioral disorders, it might be reasonable to consider an alternative antiseizure medication rather than levetiracetam.
- Prolonged use of phenobarbital is associated with potential neurotoxicity and adverse cognitive effects.[38,39]

Summary of the evidence

One prospective multicenter observational study that looked at 155 infants assessed the effect of treatment with levetiracetam compared with phenobarbital for children with new onset epilepsy (no prior ASM exposures) and reported on the outcomes of seizure.[40]

Benefits, harms, and burden

Levetiracetam was more likely to increase seizure freedom compared with phenobarbital with 40.2% (47/117) of infants on levetiracetam achieving seizure freedom at 6 months compared with 15.8% (6/38) on phenobarbital (OR: 4.2, 95% CI: 1.3-14; Low CoE); however, the evidence is uncertain due to concerns with the small sample size, particularly in the phenobarbital arm of the study, and possible differences in the populations. The NNT to achieve seizure freedom with levetiracetam compared with phenobarbital is 4.1 (95%CI: 2.45-10.23). While there were no statistically significant differences in the populations in terms of age or etiology, the authors speculated that patients started on phenobarbital may have had more severe clinical presentations prompting the use of phenobarbital over levetiracetam.

Other considerations

Levetiracetam is widely available in different formulations and is inexpensive. Treatment with levetiracetam does not require routine laboratory testing but may require dosing adjustment in patients with renal dysfunction.

Phenobarbital is widely used in neonatal seizures, and is inexpensive, but should be used with caution outside of this population due to the potential neurotoxicity and adverse cognitive effects.[41]

Conclusions and research needs for this recommendation

The guideline panel made a conditional recommendation for treatment with levetiracetam rather than phenobarbital in infants and children less than 36 months of age diagnosed with new-onset epilepsy. The panel recognized that the magnitude of the desirable effects may be moderate and that the undesirable effects may be trivial.

Future research is needed to further delineate response to levetiracetam based on etiology, particularly different genetic syndromes, as well as seizure classification (e.g., focal versus generalized) in this age group.

Recommendation I-A-5. For infants and children 1 month to less than 36 months of age diagnosed with new onset epilepsy, the AES guideline panel **suggests** treatment with either topiramate or carbamazepine.

(**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Remarks:

Topiramate is preferred in the following situations:

- When carbamazepine is contraindicated.

- In patients with a risk of hypersensitivity (e.g., rashes; HLA predisposition), as well as SCN1A disorders.

Carbamazepine is preferred in the following situations:

- Focal epilepsy or some channelopathies (KCNQ2, KCNQ3, SCN2A).
- Carbamazepine is contraindicated in children with certain generalized epilepsies or other channelopathies including Dravet syndrome; refer to Dravet Syndrome Foundation treatment guidelines.

Summary of the evidence

The evidence for this recommendation was based on a single, open- label observational study comparing topiramate to carbamazepine in children less than 2 years of age. The study reported on the outcomes of seizure freedom, seizure frequency, adverse events, and adverse events leading to discontinuation.[42]

Benefits, harms, and burden

The study found no clinically meaningful differences in seizure freedom rates between topiramate or carbamazepine (RR:1.06, 95%, CI: 0.78-1.44; very low CoE); however, the evidence is considered very low due to concerns with the small sample size and the confidence interval crossing the thresholds of benefit and harm. Given the low rate of side effects and small number of patients requiring discontinuation, the undesirable effect was determined to be small. Nevertheless, several expected adverse effects of both topiramate and carbamazepine were not reflected in the included studies. When considering the utility of topiramate or carbamazepine, several factors may impact the decision to start the medication, such as issues related to poor weight gain or weight loss, cognitive impairments, nephrolithiasis, risk of metabolic acidosis or rash, history of bone marrow abnormalities, and type of epilepsy.

Other considerations

Topiramate and carbamazepine are widely available with neither providing significant cost savings compared with the other. Topiramate is only FDA-approved for patients 2 years of age and older. Lab monitoring for topiramate and carbamazepine may raise a barrier to care in certain resource-limited settings. Some caregivers may express concerns about potential adverse effects, such as weight loss, cognitive impairment, or rash.

Topiramate would be preferred in situations where carbamazepine is contraindicated, such as generalized epilepsies or some channelopathies. There is a higher risk of Stevens-Johnson syndrome/Toxic Epidermal Necrolysis with carbamazepine use in patients with the HLA-B*1502 allele. Special consideration for patients on dietary therapy for epilepsy may need to be taken when considering topiramate initiation. Carbamazepine would be considered first-line therapy for focal epilepsy or certain channelopathies. Carbamazepine is contraindicated in Dravet syndrome; refer to the Dravet guidelines on management strategies.[15]

Conclusions and research needs for this recommendation

The AES guideline panel made a conditional recommendation for the use of either topiramate or carbamazepine in the treatment of infants and children 1 month to less than 36 months of age diagnosed with epilepsy. The certainty of the evidence is very low, and further research is needed to better understand the comparative efficacy and safety of these two antiepileptic medications in this patient population. Importantly, carbamazepine is contraindicated in Dravet syndrome. *Refer to Dravet Syndrome Foundation treatment guidance.*[13]

Evidence and Discussion - Recommendations related to Pharmacological Treatments for infants and children 1 month to less than 36 months diagnosed with focal or unknown drug-resistant epilepsy (DRE)

Recommendation I-B-1. For infants and children 1 month to less than 36 months of age diagnosed with drug-resistant epilepsy, the AES guideline panel **suggests** treatment with valproate rather than no valproate.

(**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Remarks:

- In patients with an unknown epilepsy etiology, genetic testing should be considered before the initiation of valproate in order to exclude pathogenic variants of POLG.
- When appropriate, or if alternatives are not available, initiation of valproate might be reasonable if genetic testing demonstrates a lack of pathogenic variant in POLG.
- There is an increased risk of hepatotoxicity associated with valproate use in children < 2 years of age, particularly those with underlying mitochondrial disorders.
- Use of valproate concurrently with the ketogenic diet increases risk of carnitine and vitamin D deficiency. Serum levels of valproate, 25-hydroxyvitamin D, and carnitine should be monitored and supplemented accordingly.

Recommendations I-A-2 and 1-B-1 are separate recommendations that address new-onset epilepsy (1-A-2) or DRE (1-B-1) populations. The Remarks for each recommendation differ, but the 2 recommendations share an evidence profile as well as sections addressing Summary of the evidence; Benefits, harms, and burden; Other Considerations; and Conclusions and research needs included in Recommendation 1-A-2.

Recommendation I-B-2. For infants and children 1 month to less than 36 months of age diagnosed with drug- resistant epilepsy, the AES guideline panel **suggests** treatment with topiramate rather than no topiramate.

(**Conditional** Recommendation, **Low** Certainty of Evidence).

Remarks:

- In patients on the ketogenic diet, there is an increased risk of metabolic acidosis and kidney stones.

Summary of the evidence

The evidence for this recommendation was based on two observational studies evaluating seizure freedom with topiramate in children with epilepsy less than 3 years of age.[43,44] Two randomized trials evaluated for adverse events including weight decrease, vomiting, and upper respiratory tract infection in children with epilepsy less than 3 years of age.[45,46]

Benefits, harms, and burden

The two observational studies found that treatment with topiramate increased seizure freedom compared to no topiramate (RR: 0.81, 95%, CI: 0.77-0.85; very low CoE); however, the evidence is considered very low certainty due to concerns with the small sample size.[43,44] The NNT to achieve seizure freedom with topiramate is 5.21 (95% CI: 4.25-6.73). One study reported that patients had been exposed to at least 1 prior ASM; the other study did not clarify past ASM exposures. The undesirable effects were small due to the low rate of side effects and small number of patients requiring discontinuation (RR: 0.66, CI: 0.13-3.46; low CoE). The two randomized trials also found dose-related increased rates of weight loss, vomiting, and upper respiratory tract infections; however the evidence is considered low due to small sample size and confidence interval crossing thresholds of benefit and harm.[45,46]

Other considerations

Topiramate is widely available. Topiramate is only FDA-approved for patients 2 years of age and older. Lab monitoring for topiramate may raise a barrier to care in certain resource limited settings. Regional

differences may influence how patients value the main outcome, as some caregivers may express concerns about potential adverse effects, such as weight loss, cognitive impairment, or rash. Topiramate should be used with caution in patients on the ketogenic diet due to the increased risk of metabolic acidosis and kidney stones.

Conclusions and research needs for this recommendation

The AES guideline panel made a conditional recommendation for the use of topiramate in the treatment of infants and children 1 month to less than 36 months of age diagnosed with drug-resistant epilepsy. The certainty of the evidence is very low and lacked detail on prior medication exposures. Further research is needed to better understand topiramate's response as initial treatment of epilepsy in this age group.

Recommendation I-B-3. For infants and children 1 month to less than 36 months of age diagnosed with drug resistant epilepsy, the AES guideline panel **suggests** treatment with lamotrigine rather than no lamotrigine.

(**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Remarks:

- Shared decision-making is needed to factor in time to effective dosing (long titration periods are needed for lamotrigine).
- Use caution in patients with hypersensitivity reactions (Stevens Johnson syndrome). Risk increases with co-administration with valproate.
- Lamotrigine is contraindicated in children with Dravet syndrome; refer to Dravet Syndrome Foundation treatment guidelines.

Summary of the evidence

Two studies assessed the effect of lamotrigine compared with no lamotrigine on children less than 36 months with epilepsy. One randomized controlled trial treated lamotrigine-naïve children (N=38) with lamotrigine as an adjuvant therapy and reported on the outcome of severe or serious adverse events.[47] One non-randomized study treated lamotrigine-naïve (n=79) and lamotrigine-exposed (n=125) children and reported on the outcomes of seizure freedom, seizure frequency, discontinuation due to adverse events and severe or serious adverse events.[48]

Benefits, harms, and burden

Lamotrigine may increase seizure freedom compared with no lamotrigine (RR 0.87; CI: 0.83, 0.92; Very Low CoE); however, the evidence is very uncertain due to concerns with the small sample size. The NNT to achieve seizure freedom with lamotrigine is 7.85 (95% CI: 5.77-12.24). In addition, lamotrigine-naïve and lamotrigine-experienced children treated with lamotrigine may have a greater reduction in seizure frequency, as measured by reduction of ≥50% seizure frequency from baseline, than children not treated with lamotrigine (126/204; 62% experienced a reduction ≥50% seizure frequency).

In terms of adverse effects, one non-randomized study reported 9% (18/204) discontinuation due to severe or serious adverse events or death during the long-term open-label phase.[47] This includes 7 deaths, none of which study authors considered to be related to the medication (Very low CoE). The panel members noted that the most common adverse events reported were pyrexia (45% of patients), upper-respiratory tract infection (28%), and ear infection (22%). While these side effects were reported, they were less likely directly related to medication effect. The only adverse event considered reasonably attributable to study medication in >2% of patients was irritability (n = 10; 5% of patients). No cases of serious rash were reported, and Stevens-Johnson syndrome was not reported in the study. One non-randomized study reported the following during the long- term open-label phase:

pneumonia: 8% (16/204); status epilepticus: 6% (12/204); focal with impaired awareness seizures: 6% (12/204); fever: 4% (12/204); convulsion: 3% (6/204); dehydration: 3% (6/204); and gastroenteritis: 3% (12/204).[48] (Very low CoE).

Other considerations

The panel recognized that lamotrigine is widely available in the United States. It is a daily oral medication that is taken 1 or 2 times daily with several formulations available (including liquid). It is available in most pharmacies and is covered by insurance as a generic drug.

The overall certainty of the evidence was very low. The panel recognized that the desirable effects were small to moderate due to the seizure frequency reduction by 50% and greater when compared with pre-lamotrigine baseline in 62% of the included patients (60% of the lamotrigine-naïve subgroup and 63% of the lamotrigine-experienced subgroup). The panel members noted the importance of a careful titration that is required when using lamotrigine. When initiating lamotrigine, caution should be taken in patients with hypersensitivity reactions due to the risk of Stevens-Johnson syndrome. Extra caution should be used for patients on concomitant valproate use.

Conclusions and research needs for this recommendation

The guideline panel made a conditional recommendation for treatment with lamotrigine for newly diagnosed epilepsy in infants and children 1 month to less than 36 months of age. The panel noted that the balance favors intervention if there is time to titrate to the optimal dose. Caution should be used in syndromes that worsen with sodium channel blocking agents and if there is a risk for Stevens-Johnson syndrome. Importantly, lamotrigine is contraindicated in children with Dravet syndrome.[15] Refer to Dravet Syndrome Foundation treatment guidance.[13]

Recommendation I-B-4. For infants and children 1 month to less than 36 months of age diagnosed with drug-resistant epilepsy, the AES guideline panel **suggests** the use of rufinamide rather than no rufinamide.

(**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Summary of the evidence

One non-randomized study (n = 103) assessed the effect of treatment with rufinamide compared with no rufinamide for children with DRE (2 or more ASMS prior to rufinamide) and reported on the outcomes of seizure freedom, seizure frequency per 30 days, and adverse events including those leading to rufinamide.[49]

Benefits, harms, and burden

Rufinamide may increase seizure freedom compared with no rufinamide (RR: 0.81, 95% CI: 0.73-0.89; Very Low CoE) as well as reduce seizure frequency per 30 days compared with no rufinamide (MD: 360 fewer seizures, 95% CI: 330.35-389.65 fewer seizures); Very Low CoE). The NNT to achieve seizure freedom with rufinamide is 5.15 (95% CI: 3.70-8.49).

Investigators reported response rates and percent seizure reduction of different seizure types and epilepsy syndromes with the highest reported seizure reductions in LGS, atonic and tonic seizure types. However, the evidence is very uncertain due to concerns with the small sample size.

In this study, 15 children (15%) were reported to have discontinued therapy due rufinamide-related side effects. Adverse events reported included somnolence in 12 children (12%) and irritability in 10 children (10%).

Other considerations

Rufinamide is FDA-approved for patients as young as 12 months of age. It is available in different oral formulations, including a pediatric-friendly commercially available suspension. Treatment with rufinamide does not require routine laboratory testing or dosing adjustment in patients with renal dysfunction. However, caution should be used in patients with hepatic dysfunction and certain cardiac abnormalities.

Conclusions and research needs for this recommendation

The guideline panel made a conditional recommendation for treatment with rufinamide in infants and children 1 month to less than 36 months of age diagnosed with drug-resistant epilepsy. The panel recognized that the magnitude of the desirable effects may be moderate and that the undesirable effects may be small.

Future research is needed to further delineate response to rufinamide as initial therapy in this age group. While the literature available did investigate response to rufinamide based on etiology, particularly different genetic syndromes as well as seizure classifications (e.g., focal versus generalized) and subtypes, further research is warranted with a larger sample size.

Recommendation I-B-5. For infants and children 1 month to less than 36 months of age with drug-resistant Dravet syndrome, the AES guideline panel suggests treatment with stiripentol rather than no stiripentol for Dravet syndrome with concomitant clobazam treatment.

(**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Remarks:

- Refer to Dravet Syndrome Foundation treatment guidelines.[15]

Summary of the evidence

One study evaluated the efficacy of stiripentol for use in patients with Dravet syndrome. This non-randomized, prospective study assessed patients with Dravet syndrome treated with stiripentol over the course of 104 weeks and reported on efficacy and safety.[50] While participant age ranged from 0.5-50 years of age, 95 patients (95/411) met inclusion criteria for our patient population.

Benefits, harms, and burden

Stiripentol use may result in seizure reduction (Very Low CoE); however, evidence is uncertain due to limitations of study design including the evaluation of seizure frequency in participants. In the population studied, 54.4% demonstrated marked or moderate improvement as described by physician assessment.

In the study, 61% of participants (58/95) reported side effects during stiripentol use. Side effects resulted in discontinuation for 17/411 patients and included somnolence, loss of appetite, worsening seizures, weight loss, ataxia/vertigo, and agitation. These were not reported specifically for our subpopulation. For those that were on concomitant clobazam or valproic acid, adjustments in these medication doses improved side effects.

Other considerations

The panel recognizes that stiripentol is a medication that must be dispensed from specialty pharmacies resulting in increased cost and decreased availability based on location in the United States. Stiripentol is available in tablet and powder formulation; however, the manufacturer's mixing instructions for stiripentol may result in a significant volume for some infants. The panel recognizes that some families have been able to mitigate this concern by administering with pudding or applesauce.

Stiripentol is FDA-approved for use in children with Dravet syndrome who are greater than or equal to 6 months of age with concomitant clobazam. Given this, there is an increased cost associated with the secondary medication, as well as routine labs needed for medication monitoring, as stiripentol

increased clobazam metabolites. There is controversy regarding whether measuring the metabolites adds anything to simple symptom monitoring and may not be easily available.

Conclusions and research needs for this recommendation

The guideline panel made a conditional recommendation for treatment with stiripentol for drug-resistant Dravet syndrome in infants and children 1 month to less than 36 months of age with concomitant clobazam treatment. Panel members noted that stiripentol should be considered in alignment with the International consensus on diagnosis and management of Dravet syndrome where it is a second-line medication.[15] Further research in this population is needed with specific attention to standardizing outcome measures.

Evidence and Discussion - Pharmacological Treatments for infants 1 month to less than 36 months diagnosed with focal or unknown epilepsy for which no recommendation is made.

Phenytoin. For infants and children 1 month to less than 36 months of age diagnosed with epilepsy, the AES guideline panel **makes no recommendation** on the use of phenytoin rather than no phenytoin **(Knowledge Gap).**

Summary of the evidence

There is no GRADE Evidence Profile, as no evidence met the eligibility criteria for the review.

The panel decided that this question is a Knowledge Gap, as there is no direct evidence to inform the comparison.

Panel members voted to exclude this from the guideline since the drug and condition do not meet the guideline's scope. This decision was based on 60 of the 82 patients receiving intravenous phenytoin for status epilepticus and therefore the study population was not applicable.[51]

Remarks:

- Phenytoin is an old ASM that is uncommonly used in infants due to poor oral absorption and known chronic adverse effects. The primary use for this medication is intravenous fosphenytoin for acute treatment of status epilepticus which is beyond the scope of this guideline.
- Adverse events may be higher in patients receiving phenytoin with risk of hypersensitivity reactions (e.g., rashes; HLA predisposition) as well as sodium disorders.
    - Stevens-Johnson syndrome and toxic epidermal necrolysis induced by carbamazepine and phenytoin is strongly and moderately associated with HLA-B*15:02 in patients
    - Phenytoin is contraindicated in Dravet syndrome; refer to the Dravet guidelines on management strategies.[15]

Vigabatrin. For infants and children 1 month to less than 36 months of age diagnosed with epilepsy, the AES guideline panel **makes no recommendation** on the use of vigabatrin rather than no vigabatrin **(Knowledge Gap)**

Summary of the Evidence

There is no GRADE Evidence Profile, as no evidence met the eligibility criteria for the review.

The panel decided that this question is a Knowledge Gap, as there is no direct evidence to inform the comparison.

One study reported on treatment with vigabatrin for children with epileptic spasms as well as other seizure types.[52] The panel decided to exclude this study as the population of interest was outside of the scope of this guideline since 94 of the 103 subjects had epileptic spasms.

Eleven panel members voted on the inclusion/exclusion of vigabatrin from this guideline because epileptic spasms were outside the scope of the present guideline.

Levetiracetam plus valproate. For infants and children 1 month to less than 36 months of age diagnosed with epilepsy, the AES guideline panel **makes no recommendation** on the use of levetiracetam plus valproate rather than levetiracetam alone.

Summary of the evidence

Treatment with levetiracetam plus valproate compared with valproate alone may increase seizure freedom (RR: 1.45; 95% CI: 0.75, 2.81; Low CoE).[53] In addition, the combination of levetiracetam plus valproate compared with valproate alone may increase quality of life as measured by a Barthel Index score of 84 compared with 60 (Low CoE).

Conclusions and research needs for this recommendation

Although the panel determined that the use of this combination in new-onset infantile epilepsy was not recommended, the panel noted the following points for future research:

- The comparison of levetiracetam + valproate vs levetiracetam alone in infantile epilepsy is a more beneficial question.
- The comparison of other combination ASMs is beneficial.

II. Dietary Treatments

Special considerations for all dietary therapies

Dietary therapies for epilepsy are complex nonpharmacological interventions that require a multidisciplinary team of specialists including dietitian, physician, nurse, and social work. Several variations of dietary therapies for epilepsy include classic ketogenic diet, medium chain triglyceride diet, modified Atkins diet (mAD), and low-glycemic index treatment (LGIT). Dietary therapy requires precise calculation of macronutrients, measurements of ingredients and supplementation of vitamins and minerals to maintain adequate nutrition. Due to metabolic shifts and micronutrient limitations of diet therapy, frequent lab monitoring is recommended. Medications have to be switched to the lowest carbohydrate formulation, often having to be compounded, which can increase costs. Limitations on what a child can receive for nutrition can have psychosocial impact and affect nutrition-related costs. Insurance coverage for specialty formulas, food, and micronutrient supplements to support diet therapy varies significantly by patient location and insurance plan. This creates a financial barrier to access treatment and affects equity of care. The cognitive ability of the caregiver may also limit the ability to provide dietary therapy. Family religious and cultural celebrations, food allergies, and dietary preferences are important considerations when planning dietary therapy.

Dietary therapy is recommended to be considered after failure of two appropriate ASMs, or earlier--even first-line--in some epilepsy syndromes such as GLUT-1DS or PDH.[40,54] Contraindications to dietary therapy include:[40]

- Carnitine deficiency (primary)
- Carnitine palmitoyl transferase (CPT) I or II deficiency
- Carnitine translocase deficiency
- β-oxidation defects
    - Medium-chain acyl dehydrogenase deficiency (MCAD)
    - Long-chain acyl dehydrogenase deficiency (LCAD)
    - Short-chain acyl dehydrogenase deficiency (SCAD)
    - Long-chain 3-hydroxyacyl-CoA deficiency
    - Medium-chain 3-hydroxyacyl-CoA deficiency.
- Pyruvate carboxylase deficiency
- Porphyria

Recommendations, Evidence Summaries, and Discussion

Recommendation II-A. For infants and children 1 month to less than 36 months of age diagnosed with drug-resistant epilepsy, the AES guideline panel **suggests** a ketogenic diet rather than no ketogenic diet.

(**Conditional** Recommendation, **Low** Certainty of Evidence)

Remarks:

- Classic ketogenic diet is recommended for children <24 months due to higher efficacy rates and need for more exact calculations to account for rapid growth during this time period.
- This allows for continued dietary adjustments to optimize efficacy and minimize side effects.
- Dietary therapy may be considered as a first-line treatment in patients less than 36 months of age with a diagnosis of Glut 1 or PDH.
- There are better response rates with the ketogenic diet when there is a genetic etiology.[55]

Summary of the evidence

Seven non-randomized studies were reviewed to assess the efficacy of ketogenic diet therapy in patients who had already failed greater than 3 medications. Outcomes reported included the impact on seizure freedom and seizure reduction at intervals of 3, 6, and 12 months. In the 4 studies with 6- and 12-month follow-up, medical ketogenic dietary therapy failed to achieve seizure freedom in 74% and 82.3% of patients respectively (6-month RR: 0.74, 95% CI: 0.66-0.82; 12-month RR 0.82, 95% CI: 0.74-0.91; low CoE). The NNT to achieve seizure freedom at 12 months with ketogenic diet is 5.65 (95% CI: 4.63-7.24). In addition, this response was reported to be sustained post discontinuation of treatment.[56,57]

Benefits, harms, and burden

Side effects noted included hypoglycemia, acidosis, constipation, vomiting and reflux, hypercalciuria, dyslipidemia, and vitamin and mineral deficiency. Note that these have also been reported in some patients prior to initiation.[55] Side effects did not impact the ability to continue treatment and patients are able to be managed medically.

Ketogenic treatments can be implemented in patients at this age that eat food by mouth, via tube, or even via ketogenic parenteral nutrition. The formulation of treatments can include breastmilk, commercially available formula, and blended foods calculated to meet the individual needs for growth and development and therapeutic ketogenic ratio of fat: protein and carbohydrate.

Limited treatment availability and increased cost to the family affects equity and feasibility of care.

Ketogenic diets may increase seizure freedom compared with not utilizing ketogenic treatment over one year.

Other considerations

For patients who are breastfeeding, the mothers will have to supplement their milk either when it is expressed or while nursing.

Ketogenic ratios can be adjusted for improved tolerability and management of side effects.

Conclusions and research needs for this recommendation

Ketogenic therapy is a unique and effective dietary treatment, but the feasibility as well as accessibility are limiting factors to its utilization. The guideline panel made a conditional recommendation to treat with a ketogenic diet in infants and children 1 month to less than 36 months of age diagnosed with drug-resistant epilepsy. The panel recognized the magnitude of the desirable effects may be moderate and that the undesirable side effects are small. Due to the many factors involved in dietary treatment,

initiating dietary treatment as a feasible modality must be a shared clinical decision between the clinician and family.

Future research is needed in larger sample sizes in this age group to continue to optimize outcome both short- and long-term.

Recommendation II-B. For infants and children 1 month to less than 36 months of age diagnosed with drug-resistant epilepsy, the AES guideline panel **suggests against** the use of a modified Atkins diet.

(**Conditional** Recommendation, **Low** Certainty of Evidence).

Remarks:

- Classic ketogenic diet is recommended for children <24 months due to higher efficacy rates and need for more exact calculations to account for rapid growth during this time period. This allows for continued dietary adjustments to optimize efficacy and minimize side effects.
- Modified Atkins diet may be a reasonable alternative for patients unable to access or tolerate a classic ketogenic diet

Summary of the evidence

One case-control study (n=30) compared modified Atkins Diet to a regular diet and reported on the outcomes of seizure frequency and severity at 3 and 6 months, as well as adverse events.[58] Seizure frequency decreased in 6/15 (40%) patients in the modified Atkins Diet group at 3 months and 8/15 patients in the modified Atkins group at 6 months. Seizure severity decreased in 14/15 (93.33%) patients in the modified Atkins group leading to mean decrease of 16.03± 7.06 three months from baseline and 37.63± 4.75 six months from baseline. Patients in the regular diet group (n=15) showed a mean decrease of 0.45 ± 4.91 at 3 months and 1.79 ± 7.94 at 6 months.[58]

Benefits, harms and burden

In the case-control study reviewed, the modified Atkins Diet group (n=15) showed vomiting in 30.8%, constipation in 15.4%, diarrhea in 15.4%, and dysphagia in 23.1% of patients. Two out of 15 patients in the modified Atkins Diet group could not tolerate the diet and suffered significant weight loss.[58]

Other considerations

There is limited evidence on the use of modified Atkins Diet in this age group. This may be due to classic ketogenic diet being more commonly used as infant formulas are calculated according to classic ketogenic diet ratio of macronutrients.

Conclusions and research needs for this recommendation

No substantial body of evidence reports on the use of modified Atkins Diet in this age group. The panel suggests against use of modified Atkins Diet in this population due to limited evidence (one non-randomized study with 30 total participants). More robust evidence supports the use of the classic ketogenic diet in this age group. The panel recognized the magnitude of the desirable effects may be small and the undesirable effects may be small. Future research is needed to increase sample size and certainty, and to further delineate response to modified Atkins Diet in this age group.

Recommendation II-C. For infants and children 1 month to less than 36 months of age diagnosed with drug-resistant epilepsy, the AES guideline panel **suggests** a ketogenic diet rather than a modified Atkins diet.

(**Conditional** Recommendation, **Low** Certainty of Evidence).

Remarks:

- Classic ketogenic diet is recommended for children <24 months due to higher efficacy rates and need for more exact calculations to account for rapid growth during this time period. This allows for continued dietary adjustments to optimize efficacy and minimize side effects.
- In patients experiencing adverse events (e.g., constipation) or not tolerating the ketogenic diet, trying the modified Atkins diet might be reasonable. In all other instances, the ketogenic diet is preferred for this age group.

Summary of the evidence

One randomized study (n = 104) assessed the effect of treatment with the classic ketogenic diet versus a modified Atkins Diet in drug-resistant childhood epilepsy and reported on the outcomes of seizure freedom, seizure reduction, and adverse events leading to diet discontinuation.[59] An additional case-control study (n = 40) reported on the outcome of adverse events in general and up to and including diet discontinuation in drug-resistant childhood epilepsy.[58]

Benefits, harms, and burden

A ketogenic diet may increase seizure freedom compared with a modified Atkins Diet (at 3 months, RR: 2.65, 95% CI: 0.99-7.08; Low CoE; at 6 months, RR: 2.12, 95% CI: 0.88-5.11; Low CoE); however, the evidence is uncertain due to small sample size.[59] In both studies reviewed, fewer patients discontinued diet therapy in the ketogenic diet treatment group (RR: 0.94, 95% CI: 0.59-1.49; Low CoE).[58,59] In one study, the modified Atkins Diet (n = 15) showed vomiting in 30.8%, constipation in 15.4%, diarrhea in 15.4%, and dysphagia in 23.1% of patients when compared with 0%, 25%, 12.5%, and 12.5% in the classic 4:1 ketogenic diet group (n = 10). Adverse effects were all noted to be minor and treatable. The panel notes in this study the ketogenic diet group was solely formula fed while the modified Atkins Diet was provided via food.

Other considerations

Equity and availability of diet therapy vary based on socioeconomic status and geographic location. Treatment with the ketogenic diet or modified Atkins Diet requires a multidisciplinary team, routine laboratory testing, and possible increased out-of-pocket costs for families due to variable insurance coverage for formula, food, or supplements.

Conclusions and research needs for this recommendation

The guideline panel made a conditional recommendation for treatment with the ketogenic diet rather than the modified Atkins Diet in infants and children 1 month to less than 36 months of age diagnosed with drug-resistant epilepsy. The panel recognized that the magnitude of the desirable effects may be moderate and that the undesirable effects may be trivial.

Future research is needed to increase sample size and certainty, and to further delineate response to diet therapy based on etiology in this age group

Recommendation II-D. For infants and children 24 months to less than 36 months of age diagnosed with drug- resistant epilepsy, the AES guideline panel **suggests** either modified Atkins diet or low glycemic index treatment.

(**Conditional** Recommendation, **Low** Certainty of Evidence)

Remarks:

- Classic ketogenic diet is recommended for children <24 months due to higher efficacy rates and need for more exact calculations to account for rapid growth during this time period. This allows for continued dietary adjustments to optimize efficacy and minimize side effects.
- In populations >24 months to <3 years of age, any diet can be used.

Summary of the evidence

One randomized open label control trial (n = 60) compared the efficacy of mAD and LGIT in infants with drug-resistant epilepsy.[60] At 12 weeks 16.6 % of mAD vs 6.6% of LGIT patients achieved seizure freedom (RR 2.50, 95% CI: 0.53 to 11.89, low COE) and 30% of mAD vs 13.3% of LGIT patients achieved >90% seizure reduction. The patients on LGIT had a percentage of 73.3% vs 43.3% mAD that achieved 50-90% reduction in seizures, although with a small effect size.

Benefits, harms, and burden

Lethargy was the most common reported side effect and was higher in those receiving the LGIT (66.7%) versus 53.3% in mAD. Modified Atkins had a higher reported side effect rate of constipation (50 vs 30%) and vomiting (16.7 vs 10%). Two patients from each group had significant weight loss and severe respiratory tract infection that required hospitalization.

Other considerations

A similar study comparing all three-- classic ketogenic diet, modified Atkins Diet, and LGIT-- in a population with ages ranging from 1 to 15 years found no significance in outcome. A lower side effect profile was seen in those treated with a LGIT. Food acceptability varies based on age and food tolerance. Choice of diet between modified Atkins Diet vs LGIT may depend on the child's dietary pattern.

Conclusions and research needs for this recommendation

The guideline panel made a conditional recommendation of either the use modified Atkins Diet or LGIT in infants aged 24 months to less than 36 months. The panel recognized that the magnitude of the desirable effects may be small and that the undesirable effects are small.

Future research is needed to increase sample size and length of follow up to determine difference in efficacy rates based on dietary treatment modality

III. Surgical Treatments

Special considerations

There is a paucity of data in extensive surgical resection or disconnection in young infants with drug-resistance epilepsy. Over the last three decades, the landscape of ultra-early epilepsy surgery in children 36 months of age and younger has expanded significantly as both the detrimental effects of uncontrolled epilepsy on the developing brain and the safety of this surgery have been extensively studied.[61] Children in this age group with refractory epilepsy often have significant developmental malformations of the brain that are innately less responsive to ASMs. These patients are best evaluated early at epilepsy centers with expertise in caring for this age group. Recent data suggest 57-66% of patients can become seizure free and experience developmental improvement.[62]

Epilepsy surgery in infants and children 1 month to less than 36 months of age requires an experienced multidisciplinary pediatric team including neurosurgery, epilepsy neurology, anesthesia, neuroradiology, neuropsychology, neurocritical care, and nursing. For epilepsy surgery in infants and young children, ILAE Level 2 centers should be considered.[63] This is particularly important for more extensive procedures such as hemispherectomies, hemispherotomies. or any epilepsy surgery in children less than 12 weeks of age.

Recommendations, Evidence Summaries, and Discussion

Recommendation III-A. For infants 1 month to less than 36 months of age diagnosed with lateralizing drug-resistant epilepsy, secondary to select pathologies, the AES guideline panel makes a **strong**

recommendation for hemispherectomy/hemispherotomy surgery.
(**Strong** Recommendation, **Low** Certainty of Evidence)

Remarks:

- Strong recommendation because of 1) the life-threatening nature of DRE secondary to select pathologies, and 2) the high risk of morbidity and mortality in children when left untreated, and 3) the greater potential for post-operative seizure-freedom compared with additional antiseizure medications.

Summary of the evidence

Sixteen nonrandomized studies were reviewed to assess the surgical outcome of hemispherectomy/ hemispherotomy in infants and children 1 month to less than 36 months of age diagnosed with drug-resistant epilepsy..[16,61,64-77] Outcomes included seizure freedom (Engel 1a, ILAE 1), favorable outcome (Engel I or II; ILAE I-IV), developmental assessment, and surgical risk profile. Although not all studies looked at all three individual endpoints, they were included if both sample size and age range met the inclusion criteria. The body of evidence considered has notable heterogeneity; however, given the low incidence of included pathologies and hemispheric surgical interventions in this age group, the importance of the included literature is critical.

Benefits, harms, and burden

Hemispherectomies/hemispherotomies decrease the chance of failure to achieve seizure freedom compared with no hemispherectomy/hemispherotomy in patients with DRE (RR: 0.32, 95% CI: 0.19-0.55; Low CoE). However, the certainty of the evidence is limited by small sample sizes. The NNT to achieve seizure freedom with hemispherectomy/hemispherotomy is 1.42 (95% CI: 1.32-1.53). Hemispheric surgery for DRE offers substantial benefits, including high rates of seizure freedom and potential long-term control. Achieving seizure freedom in up to 70-90% of otherwise refractory DRE is significant, especially considering the possibility of cure in select cases.[61,62,78,79] Early surgery offers the potential for improved developmental outcomes, although there is need for further longitudinal studies.[80-82] The desired effects of hemispheric surgery stand in comparison to any other available medical treatment and the natural history of epilepsy risk of SUDEP.

Surgical intervention in this age group is considered safe and feasible when performed at comprehensive epilepsy centers[61]; surgery carries risks that this panel considers moderate.[83] Such risk is stratified to immediate perioperative management, as well as long-term risk of hydrocephalus and potential decline in degree of seizure control in subsequent years.

The certainty of evidence is low. Overall, the balance between desirable and undesirable effects favors the intervention due to the long-term benefits in seizure control, development, and overall quality of life.

Other considerations

The degree of burden imposed on health systems, families, and patients with such pathologies is significant. The decision to pursue surgery is driven by intent to improve seizure burden, development, and quality of life. While the risk of surgery is moderate, families may be motivated by the potential for improved outcomes despite challenges in decision making. Understanding patients' values and preferences is crucial for personalized treatment decisions, enhancing patient-centered care, and improving satisfaction and outcomes. Moreover, addressing disparities in access to surgical expertise is necessary to ensure equitable care across regions and populations to reduce surgical outcome variations.

Conclusions and research needs for this recommendation

In infants and children identified as meeting appropriate selection criteria, the AES guideline panel recommends for hemispheric surgery rather than medication.

No level 1 evidence exists for performance of hemispherectomy or hemispherotomy in this age group (infants and children 1 month to less than 36 months of age) for patients with select structural pathologies, including hemimegaloencephaly, Rasmussen's encephalitis, Sturge weber syndrome, perinatal stroke, and hemispheric cortical dysplasia. There is a paucity of data on the long-term impact of surgery on cognitive development. Further studies are needed to understand how surgery affects cognitive functions and developmental trajectories, which is crucial for patient outcomes and treatment planning. Research into the cost-effectiveness of hemispheric surgery, including different surgical techniques and postoperative care pathways, is needed to inform healthcare resource allocation and optimize healthcare delivery in this field.[84,85]

Recommendation III-B. For infants 1 month to less than 36 months of age diagnosed with drug-resistant focal or lesional epilepsy, the AES guideline panel **recommends for** intralobar, multilobar, focal resections or posterior disconnections rather than no intralobar, multilobar, focal resections or posterior disconnections.

(**Strong** Recommendation, **Very Low** Certainty of Evidence)

***Remarks**:*

- Strong recommendation is driven by the life-threatening risk of drug-resistant focal or lesional epilepsy and high baseline risk of morbidity in children when left untreated.[86]

Summary of the evidence

Ten non-randomized studies reported on seizure control and developmental outcomes as well as complications following focal resective epilepsy surgery (cumulative n = 164).[11,61,67,70,74,76,77,87-89] Favorable seizure control outcomes were reported either in Engel scale (Engel 1 and 2), ILAE scale (ILAE 1 to IV), or greater than 50% reduction in seizure frequency. Engel 1 and 2 seizure control outcomes were reported for 50-100% of patients at follow-up interval of 3 months to 6 years in 5 non-randomized studies[67,76,77,88,89]. One non-randomized study reported that 15 of 16 patients (94%) who had focal resection or lobectomy had ILAE I to IV seizure control outcomes.[61] Two non-randomized studies reported 83% (n=24) and 100% (n=10).[70,74]

Non-randomized studies ranged in postoperative complications from 4.5% of 44 patients who developed postoperative complications following focal resection[77] (3) to 1 stroke in 10 patients that underwent posterior quadrant disconnection[87] (1) to that 3 out of 10 patients who had cortical resection developed hydrocephalus.

One non-randomized study reported improvement in Developmental Quotient (DQ) from a preoperative median of 37 to a postoperative median of 49 (n=10).[70] Another non-randomized study reported that 44% (n=9) of patients had improvement in their preoperative developmental delay following focal resection.

Benefits, harms, and burden

Intralobar, multilobar, focal resections or posterior disconnections decrease the chance of failure to achieve seizure freedom compared with no resection in patients with DRE (RR: 0.42, 95% CI: 0.34-0.53: Very Low CoE). However, the certainty of the evidence is limited by small sample sizes. The NNT to achieve seizure freedom with intralobar, multilobar, focal resections, or posterior disconnections is 1.59 (95% CI: 1.42-1.80). Overall, the evidence favors resection over no resection.

The postoperative complication rates range from 1% risk of stroke with posterior quadrant disconnection[87] (1) to 4.5% overall risk[77] (3). A high incidence of postoperative hydrocephalus (30%) reported by one study appears to be an outlier, was not reported in other studies, and is not borne out by observations in clinical practice.

Some limited evidence suggests improvement in DQ following focal resection or disconnection.

Other considerations

Intralobar, multilobar, and posterior disconnections and focal resections have limited availability related to accessibility of appropriate surgical facilities and specific surgical expertise. However, although the upfront costs of surgery are large (imaging, ancillary investigations, procedure costs, hospitalization, rehabilitation), the procedures are cost effective when compared with the overall cost of a lifetime of medical management.[84,85]

Conclusions and research needs for this recommendation

The guideline panel made a strong recommendation for intralobar, multilobar, and posterior disconnections compared with no resection in infants and children 1 month to less than 36 months of age diagnosed with drug-resistant focal or lesional epilepsy. The panel also recognized that the magnitude of desirable effects is large and that of undesirable effects or complications is small to moderate.

No level 1 evidence exists for efficacy of resection in this age group, but one randomized controlled study in children and two RCTs in adults describe efficacy of surgical resection for focal epilepsy in children[90] and adults.[91,92]

Recommendation III-C. For infants and children 1 month to less than 36 months of age diagnosed with tumor-related epilepsy, the AES guideline panel **suggests for** supratentorial tumor resection rather than no supratentorial tumor resection.

(**Conditional** Recommendation, **Very Low** Certainty of Evidence)

Remarks:

- The biological character or grade of the tumor influences the decision calculus regarding undergoing surgery and tolerance for surgical complications.

Summary of the evidence

One non-randomized study (n=20) reported on the seizure control after resection of supratentorial brain tumors associated with epilepsy in children that are under 3 years of age with a follow-up of 1 year to 8 years.[93] Favorable seizure control outcomes were reported with 80% of patients being Engel I or II, at 1 year and 4 years after surgery and 76% of patients were still Engel 1 or II at 8 years following surgery. The grade of the tumors influenced seizure control outcomes as a higher number of patients with low-grade tumors had Engel I and II seizure control outcomes compared with patients with high-grade or malignant brain tumors ($p < 0.01$; $t = 2.84$).

Benefits, harms, and burden

Supratentorial brain tumor resection increases the chance of seizure freedom in children who are under 3 years of age with supratentorial brain tumors associated with epilepsy. The certainty of this evidence is significantly limited by the small sample size in this single non-randomized study. Rates of postoperative complications are not reported in this study, but there were no intraoperative deaths. Mortality was related to the grade of primary supratentorial tumor (low versus high grade). No deaths occurred in the patients with low-grade tumors for the duration of follow up. Also, the grade of the tumors influenced seizure control outcomes as a higher number of patients with low-grade tumors had Engel I and II seizure control outcomes.

Other considerations

Binary considerations exist in tumor resection in children who are under 3 years of age with supratentorial brain tumors associated with epilepsy: primary consideration is control or extirpation of the oncological entity, and the secondary consideration is seizure control. Thus, the biological character or grade of the tumor influences the decision calculus regarding undergoing surgery and tolerance for surgical complications. High grade (malignant) tumors have higher mortality from tumor progression or recurrence and have lower rates of Engel I and II seizure control outcomes. However, caregivers will opt for early surgery in high grade tumors to stop further tumor progression even if there is a high risk of complications while seizure control is a secondary consideration. On the other hand, caregivers may prefer to avoid surgery for low-grade tumors if there is a risk of complications and opt to continue with medical management.

Conclusions and research needs for this recommendation

The guideline panel made a conditional recommendation for resection of supratentorial brain tumors associated with epilepsy in infants and children 1 month to less than 36 months of age as it may increase the chance of seizure freedom. However, the evidence is uncertain due to the small sample size from a single study. The grade of the tumor (high or low grade) influences seizure control outcomes, long-term survival, and decision-making regarding surgery.

Evidence and Discussion – Surgical Treatments for infants and children 1 month to less than 36 months diagnosed with focal or unknown epilepsy for which no recommendation is made.

In infants and children 1 month to less than 36 months of age diagnosed with epilepsy, the AES guideline panel **makes no recommendation** on the use of vagus nerve stimulation (VNS).

Summary of the evidence

One single site retrospective chart review study of VNS in an ill-defined infant population has insufficient information upon which to draw meaningful conclusions regarding safety and efficacy of VNS in infants and children 1 month to less than 36 months of age.[94]

Benefits, harms, and burden

In infants and children 1 month to less than 36 months of age diagnosed with drug refractory epilepsy, there is insufficient data to draw meaningful conclusions regarding benefits and harm. However, the burden of epilepsy and risk of SUDEP make surgical interventions, such as VNS placement, to decrease the frequency of seizures a potential option. Implants in this age group carry innate risk due to wound healing and ability of tissue to receive the implant.

Other considerations:

Although there is insufficient data upon which to base a recommendation for palliative use of VNS in children, there is no data to suggest VNS should not be pursued.

Conclusions and research needs for this recommendation

One single site retrospective chart review study of VNS in an ill-defined infant population is in the literature. As such, there is insufficient information upon which to draw meaningful conclusions regarding safety and efficacy necessary for a recommendation.

The panel notes the need for future research in the way of prospective collection of observational data of VNS in well characterized patients who have drug-resistant epilepsy, who are not candidates for resective/curative surgery, with well delineated outcome measures and assessments. Future efforts should be aimed at gathering clinical data for this device in the infant DRE population.

Clinical Decision Tools

Figure 2. Overview of Infantile Epilepsy Management.

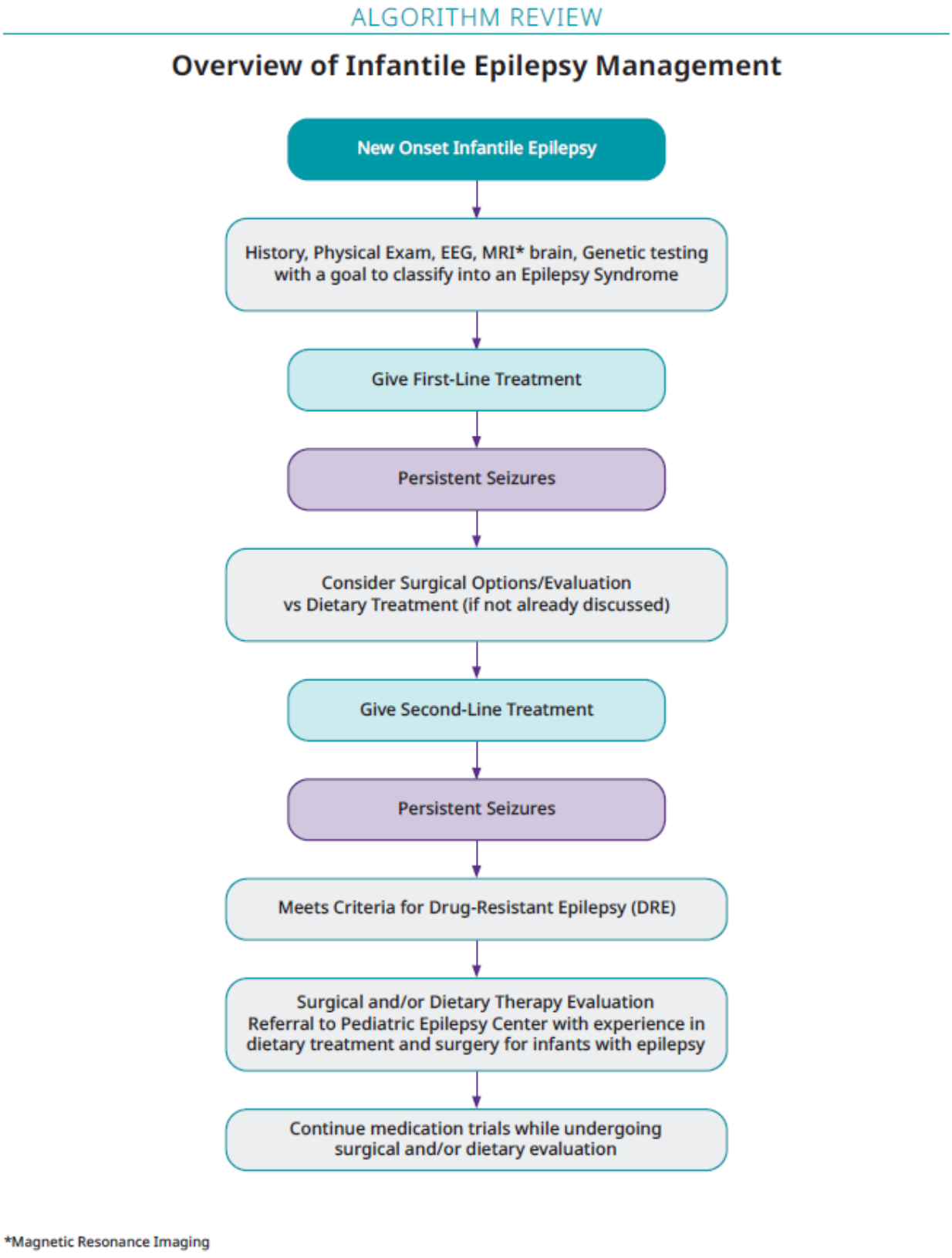


Figure 3. Antiseizure Medications.

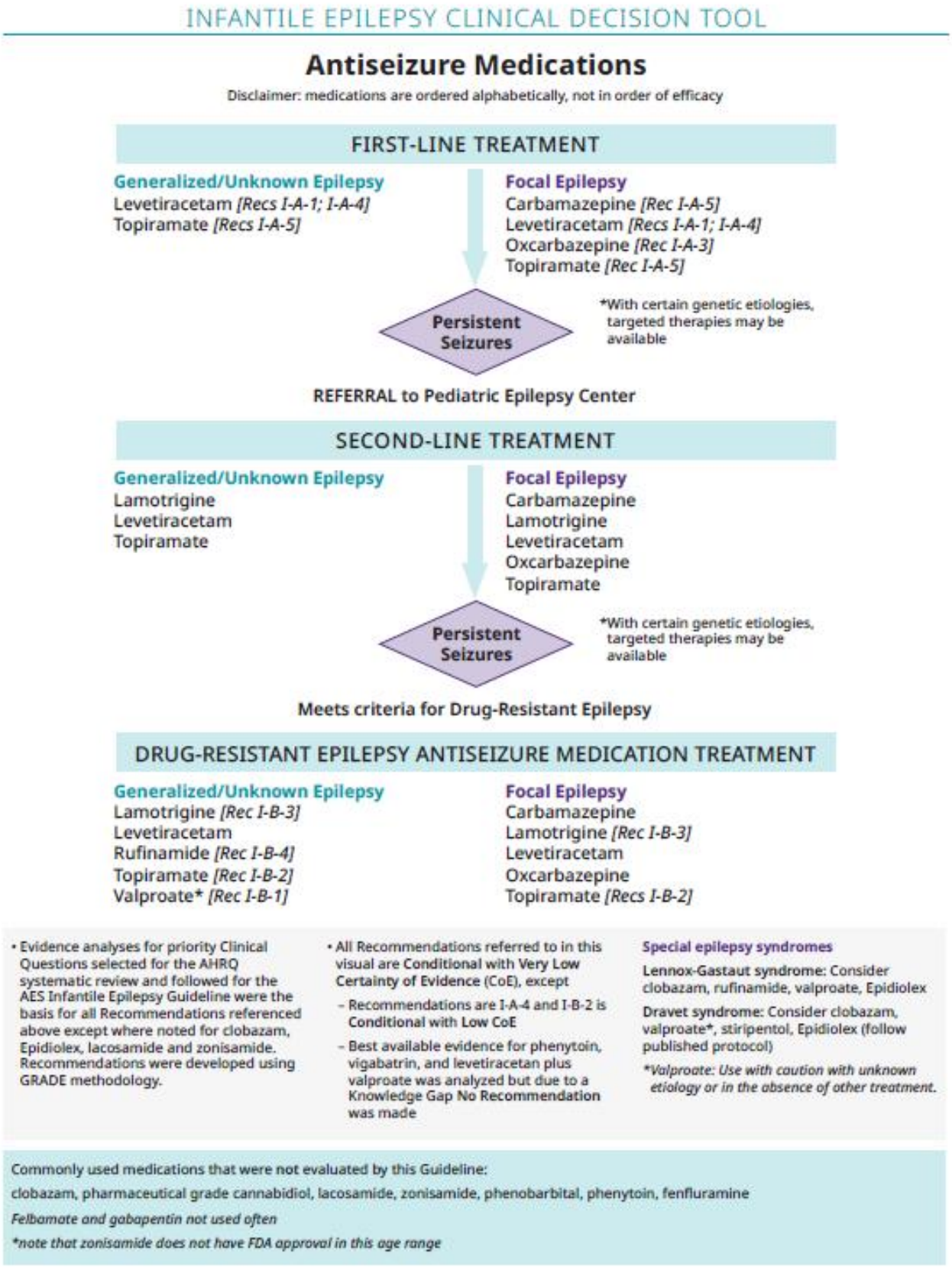
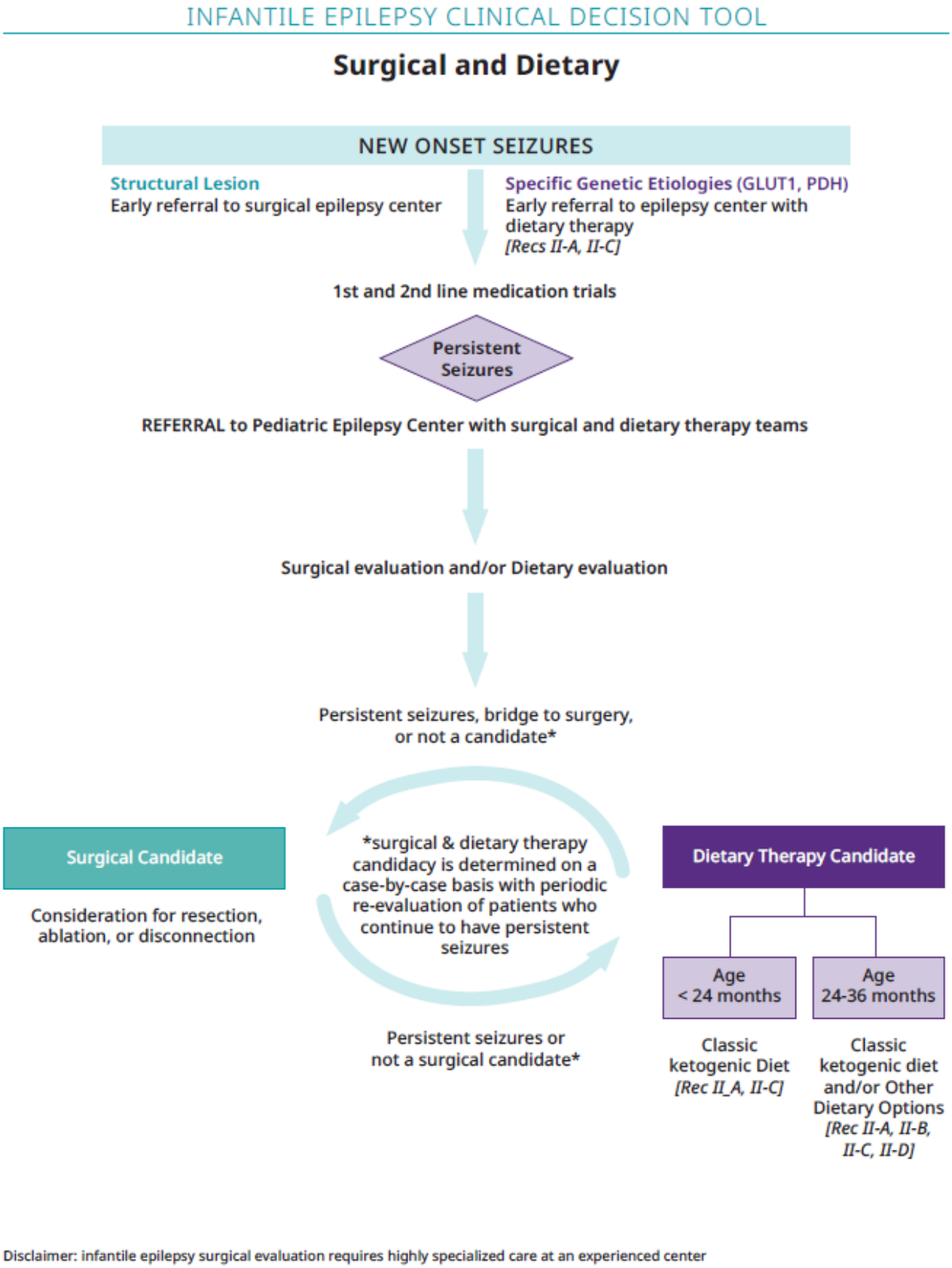


Figure 4. Surgical and Dietary.



Discussion

This paper presents the first published treatment guideline for infantile epilepsy. It is important to recognize that many of the recommendations are conditional and based on low-grade evidence. Clinicians should interpret and apply these recommendations with this understanding. The accompanying clinical algorithm is designed to assist in the management of seizures in this population, utilizing the highest level of available evidence alongside expert consensus. The guideline addresses three primary therapeutic interventions: pharmacological, dietary, and surgical approaches. Notably, many antiseizure medications frequently used in this age group are either off-label or lack sufficient evidence to be included in this systematic review.

A key objective of this guideline is to expedite referrals of DRE cases to specialized epilepsy centers for surgical evaluation and advanced therapeutic management. While specific treatment recommendations exist for defined epilepsy syndromes such as infantile spasms, the strength of this guideline lies in its approach to managing new onset and drug-resistant infantile epilepsy. However, this also represents a limitation, as the included PICOs focus solely on studies where more than 80% of participants were between 1 and 36 months of age, with infantile spasms explicitly excluded.

The literature on infantile epilepsy treatment remains limited, both in terms of the number of studies available and the quality of evidence. Clinical trials in this population often suffer from small sample sizes and methodological limitations, including randomized controlled trials, controlled trials, and single-arm studies. Consequently, the guideline panel was able to make only a limited number of strong recommendations. The two strong recommendations pertain to surgical interventions: (1) hemispherectomy/hemispherotomy for infants and children under 36 months with DRE due to select underlying pathologies, and (2) intralobar, multilobar, or focal resections, as well as posterior disconnections, for drug-resistant focal or lesional epilepsy in the same age range. Further research is essential to strengthen existing recommendations and explore etiologic-specific therapeutic approaches.

Several antiseizure medications with FDA approval for use in infants (e.g., lacosamide for partial-onset seizures in patients >1 month of age, clobazam as adjunctive therapy for seizures associated with Lennox-Gastaut syndrome in children >2 years) were not reviewed due to study inclusion criteria. Some clinical trials involving these medications did not meet the selection criteria for this analysis. Nevertheless, the treatment algorithm incorporates these medications due to their frequent use in clinical practice. Excluded medications based on trial criteria include clobazam, zonisamide, lacosamide, and pharmaceutical grade cannabidiol. As these medications were not formally evaluated, the Work Group does not make specific recommendations beyond those supported by FDA labeling. Additionally, due to a lack of sufficient studies, knowledge gaps remain regarding treatments such as VNS, preventing the Work Group from making certain therapeutic recommendations.

AES maintains a structured process for guideline review, occurring every 3–5 years. A priority in these reviews will be identifying new evidence that may influence or alter the recommendations. Based on these assessments, the AES Guidelines and Assessment Committee will determine whether the guideline should be affirmed, updated, replaced, or retired.

This guideline represents a significant milestone in the establishment of standardized treatment protocols for infantile epilepsy. However, it also underscores substantial research needs. Few studies focus specifically on infants aged 1 to 36 months, and even fewer address treatments tailored to specific etiologies. The urgent need for robust research is evident, particularly in evaluating first-line therapies for infants. Ethical concerns arise when considering randomized, placebo-controlled trials in this vulnerable population, but comparative effectiveness research provides a viable alternative for assessing treatment efficacy without exposing children to the risks of non-intervention. As genetic testing becomes increasingly routine in epilepsy diagnostics, future studies should prioritize targeted treatments that address the underlying genetic and structural causes of epilepsy. Disease-modifying therapies hold promise in altering the developmental trajectory of infantile epilepsy, reducing long-term neurological consequences, and minimizing the risk of SUDEP.

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Appendix

Appendix A. PICO Questions

PICO Questions for Pharmacological Treatments

- For infants and children 1 month to less than 36 months of age diagnosed with focal or new-onset epilepsy:
    - Levetiracetam compared with no levetiracetam
    - Valproate compared with no valproate in infants and children with:
        - Newly diagnosed epilepsy
        - Drug-resistant epilepsy
    - Lamotrigine compared with no lamotrigine in infants and children with:
        - Newly diagnosed epilepsy
        - Drug-resistant epilepsy
    - Oxcarbazepine compared with levetiracetam
    - Levetiracetam compared with phenobarbital
    - Topiramate compared with carbamazepine
- For infants and children 1 month to less than 36 months of age diagnosed with drug-resistant epilepsy:
    - Valproate compared with no valproate in infants and children with drug-resistant epilepsy
    - Topiramate compared with no topiramate
    - Lamotrigine compared with no lamotrigine in infants with drug-resistant epilepsy
    - Rufinamide compared with no rufinamide
    - Stiripentol compared with no stiripentol
- Pharmacological Treatments PICO Questions for which **No Recommendation** was made for infants and children 1 month to less than 36 months of age:
    - Phenytoin compared with no phenytoin, for infants and children diagnosed with epilepsy
    - Vigabatrin compared with no vigabatrin, for infants and children diagnosed with focal or unknown epilepsy
    - Levetiracetam with valproate compared with valproate, for infants and children diagnosed with focal or unknown epilepsy

PICO Questions for Dietary Treatments – For infants and children 1 month to less than 36 months of age diagnosed with drug-resistant epilepsy:

- Ketogenic Diet compared with No Ketogenic Diet
- Modified Atkins Diet compared with No Modified Atkins
- Ketogenic Diet compared with Modified Atkins Diet
- Modified Atkins Diet compared with Low Glycemic Index Treatment

PICO Questions for Surgical Treatments – For infants and children 1 month to less than 36 months of age diagnosed with drug-resistant epilepsy:

- Hemispherectomy/hemispherotomy compared with no hemispherectomy/ hemispherotomy for Infants diagnosed with unilateral drug- resistant epilepsy
- Intralobar, multilobar, or focal resections or posterior disconnections compared with no resections
- Supratentorial brain tumor resection v. no resection for tumor-related epilepsy.
- Vagus nerve stimulator (VNS) compared with no vagus nerve stimulator (VNS). [No Recommendation]

Supplemental Materials

Supplemental Materials 1. Author/Work Group Members, Credentials, Institutional Affiliations, Conflict of Interests (COI) Disclosures

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Supplemental Materials 2. Methodology

Overview

The overall guideline development process-- funding of the work, American Epilepsy Society (AES) Guideline Work Group formation, management of conflicts of interest, internal and external review, and organizational approval-- was guided by AES policies and procedures and overseen by the AES Guidelines and Assessment Committee.[22] Based on systematic reviews that assessed the evidence for treatment effectiveness, comparative effectiveness, and harms for each intervention, this clinical practice guideline was created by a panel of topic experts for each treatment category with patient family/caregiver or advocate representatives' input. The work group used the GRADE approach to assess the supporting evidence contained in the reviews and develop the guideline recommendations.[23-25]

Guideline Funding

The evidence update and the development of this clinical guideline were funded by AES, a 501(c)(3) nonprofit medical society, based on a prior systematic review for which AES had nominated the topic. The prior systematic review was funded by PCORI®,[26] managed by the AHRQ, conducted under contract with AHRQ by the ECRI Institute, and published as an AHRQ final report[19,27] and two systematic review papers.[28,29]

AES is a community of physicians, scientists, advanced practice providers, nurses, psychiatrists, psychologists, engineers, pharmacists, advocates, and other professionals engaged in the understanding, diagnosis, study, prevention, treatment, and cure of epilepsy. AES is dedicated to advancing knowledge and supporting evidence-based clinical practice to improve outcomes for persons with epilepsy and their families.[95] Methodological support for the guideline was provided by Evidence Foundation, a registered 501(c)(3) nonprofit organization, as a contracted service funded by AES.[96]

Management of Conflicts of Interest

Prior to the Work Group appointment, prospective members disclosed conflicts of interest via AAMC's Convey® Global Disclosure System (Washington, DC), with annual updates and clarifications via email follow-up as needed. Disclosures included financial and non-financial/intellectual interests, per AES guidelines policy.[22]

Conflicts of interest were reviewed for relevance and managed according to AES policies that incorporate guidance from AES Conflicts of Interest Policies, AES Principles for Industry Relationships, and the Council of Medical Specialty Societies' (CMSS) *Code for Interactions with Companies*[97] and *Principles for the Development of Specialty Society Guidelines*[98] per the AES manual. All are in alignment with principles for development of systematic reviews and clinical practice guidelines from the Institute of Medicine (now National Academy of Medicine).[99,100]

Conflict of interest disclosure information for AES Work Group participants is summarized in Supplement 1. None of the Evidence Foundation-affiliated researchers who contributed to the systematic review process or who supported the guideline development had any current material interest in a commercial entity with any product that could influence the guidelines. Of the 20 Work Group members, 7 reported relationships (35% of total Work Group members) that were deemed relevant to some aspects of the guideline. To manage conflicts of interest during meetings, Work Group members with a current, direct financial interest in a commercial drug or treatment that could be affected by the guidelines were asked to recuse themselves from pertinent steps.[22]

Organization, Work Group Composition, Planning, and Coordination

The Work Group's systematic review update and guideline development processes were coordinated by AES, with oversight provided by the AES Guidelines and Assessment Committee and Council on Clinical Activities.

The guideline Work Group co-leads were invited by GAC leadership based on their clinical practice and/or research focus on relevant populations and prior or current experience serving on the AES Guidelines and Assessment Committee. The co-leads in turn screened potential Work Group candidates with related expertise,

including some who had also provided expert guidance to the prior PCORI/AHRQ/ECRI systematic review. Clinical and research topic experts and family/caregiver/advocate patient representatives were recommended by the co-leads, with oversight by the Guidelines and Assessment Committee and by the AES staff liaison to the Epilepsy Leadership Council network. The patient representatives were active, voting members of the Work Group who are included as authors on this guideline in acknowledgment of the key family/caregiver role in management of epilepsy for these young patients.

Inclusion considerations included a balance of expertise related to the PICO question topics, diversity factors, and individual and overall group conflict of interest disclosure information. Most, but not all, Work Group members were AES members; topic expertise was prioritized. AES staff provided logistical support for the technical review, guideline development process, and manuscript preparation, but had no role in choosing the guideline questions or determining the recommendations.

The guideline Work Group membership and methodology advisors are described in Supplement 1. The Work Group included 14 topic experts (epileptologists, neurologists, pharmacists, dietitians, and neurosurgeons with clinical and research expertise in the management of infants and children with epilepsy): 9 with expertise related to pharmacological treatments, 2 with specific expertise related to dietary treatments, and 3 with specific expertise related to surgical treatments of the included population of patients with infantile epilepsy; and 4 family/caregiver/advocate patient representatives with lived experience and/or advocacy experience on behalf of the included patient populations.

Methodologists with expertise in evidence appraisal, GRADE methodology, and guideline development facilitated the guideline development process. The Work Group and methodologists met via a series of virtual meetings.

Members of the guideline Work Group served as volunteers and received no compensation. Patient representatives also served on a voluntary basis, in part related to their roles with patient advocacy organizations.

Formulating Specific Clinical Questions and Determining Outcomes of Interest

Evidence reviews conducted with guidance from external methodology experts were based on the prior AHRQ high-quality systematic reviews. PICO questions, inclusion/exclusion criteria, and outcomes of interest align as closely as possible with those that guided the previously published AHRQ and ECRI work.[19,27] The current guideline recommendations are based on a synthesis of results from the previously reported systematic review and the current update and followed the protocol developed for the PCORI/AHRQ/ECRI systematic review.

Each PICO question addressed in this guideline identifies a specific population (P), intervention (I), comparator (C), and the corresponding patient-important outcomes (O). Clinical questions and prioritized outcomes were identified *a priori* as part of the prior systematic review, with key informant and technical expert input, and consistent with principles of the GRADE approach of identifying priority patient- important outcomes specified in the protocol. The PICO questions of focus are detailed in Supplement 2, as guided by the PCORI/AHRQ/ECRI reports and by new literature identified in the update. [21-23]

Evidence Review and Development of Recommendations

Rigorous, high-quality systematic reviews were conducted to address each PICO question. An updated literature search using search strategies from the prior PCORI/AHRQ/ECRI systematic review was conducted to identify new research published 2021 through May 18, 2023.[21,22]

The newer data identified encompassed 2,882 studies. The PRISMA diagram displays the update for the outcome of dual independent screening of Titles/Abstracts and Full Text. Data from studies included in the current update were synthesized with data from the 44 studies included in the prior systematic review to build a body of evidence informing this guideline. Results of these data syntheses are reported in detail in GRADE evidence profiles in Supplement 3.

Guideline Work Group members participated in dual independent literature screening, data extraction, and risk of bias assessments of included studies for the update, with guidance and assistance from the methodologists. The methodologists assessed the certainty of evidence and developed concordant recommendations using the GRADE evidence-to-decision framework.[30] Evidence profiles and certainty of the evidence for each PICO question are detailed in Supplement 3.

The certainty of the evidence relevant to each outcome was assessed using the GRADE approach based on the risk of bias, consistency, directness, precision, likelihood of publication bias, magnitude of effect, and dose-response relationship.[25] The certainty of the evidence for each outcome was rated from very low to high (Table 1).[26,31,32] Guideline Work Group members received the evidence profiles prior to deliberating on recommendations and reviewed the included data for completeness. The Work Group developed recommendations during a series of virtual consensus meetings.

Work Group leaders volunteered to prepare for and lead full Work Group discussion, recommendation development, and consensus for each PICO question, with guidance from methodologists. The evidence profiles that supported the GRADE evidence-to-decision process and documentation of the related Work Group discussion served as the basis for each PICO section leader to draft the corresponding guideline section.

Recommendations are informed by data presented in the EPs, certainty of evidence ratings, the balance of benefits and harms of the intervention and comparator, and patient values and preferences.

Table 1. Interpretation of certainty of evidence.[23,26,30-32]

Certainty	Interpretation
High	The Work Group is very confident that the true effect is similar to the estimate of the effect.
Moderate	The Work Group is moderately confident that the true effect is similar to the estimate of the effect, but there is a possibility that it is substantially different.
Low	The Work Group's confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low	The Work Group has very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

Interpretation of Strong and Conditional Recommendations

Recommendations are classified as either “strong” or “conditional.” The phrase “the guideline Work Group recommends” indicates a strong recommendation; the phrase “the guideline Work Group suggests” indicates a conditional recommendation. The interpretation and implication of strong and conditional recommendations for patients, clinicians, researchers, and policy makers are presented in Table 2.

Table 2. Interpretation of strong and conditional recommendations[23,26,32]

Implication for:	Strong	Conditional
Patients	Most of the people in this situation would want the recommended course of action and only a small proportion would not.	The majority of people in this situation would want the suggested course of action, but some would not. Decision aids may be useful in helping patients make decisions consistent with their personal risks, values, and preferences.
Clinicians	Most people should follow the recommended course of action. Formal decision aids are not likely to be needed to help patients make decisions consistent with their values and preferences.	Different choices will be appropriate for specific patients, and clinicians must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping patients make decisions consistent with their personal values and preferences.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendation.	This recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on whether an appropriate decision-making process is duly documented.

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Supplemental Materials 3. Systematic Review Update: New studies Included Since PCORI/AHRQ/ECRI Systematic Review

Pharmacotherapy

First Author's Last Name	Publication Year	Title	Study Design (RCT, Pre/Post, etc.)	Geographic Location (Country)	Funding Source	Clinical Trial Registration Number (RCTs)	Total Sample size	Sex (% F)	Mean/Median age at intervention	SD/IQR	Seizure Types	Seizure Etiology	Baseline number of seizures	Prior and concurrent treatments	Intervention/Comparison	Outcomes reported
Zhao	2022	Effectiveness and Safety of Oxcarbazepine vs. Levetiracetam as Monotherapy for Infantile Focal Epilepsy: A Longitudinal Cohort Study	Cohort	China	Clinical Research Program CEpiDB(lcjy2015-10) from CHCMU	ChiCTR1900028463	161	57.8	6 months	4.3-9.0 months	Only focal seizure = 51.6%; Focal to bilateral tonic-clonic = 48.5%	Genetic = 34.2%; Structural = 9.3%; Infectious = 3.15; Metabolic = 1.2%; Unknown = 52.2%	NR	NR	Oxcarbazepine (OXC)/Levetiracetam (LEV)	Seizure freedom, Adverse events
Muthaffar	2021	Valproic acid for children below 2 years of age with epilepsy	Pre/Post (Retrospective chart review)	Saudi Arabia	None listed	N/A	50	50	16 months	4.87 months	All types	Symptomatic (including genetic, structural etiologies, and asphyxia) identified in 88% of patients	NR	At least one prior treatment in participants	Valproic acid (VPA)	50% or more seizure reduction, Seizure freedom, Adverse events

Dietary Interventions

First Author's Last Name	Publication Year	Title	Study Design (RCT, Pre/Post, etc.)	Geographic Location (Country)	Funding Source	Clinical Trial Registration Number (RCTs)	Total Sample Size	Sex (% F)	Mean/Median age at intervention	SD/(IQR)	Seizure Types	Seizure Etiology	Baseline number of seizures	Prior and concurrent treatments	Intervention/Comparison	Outcomes Reported
Gupta	2021	Modified Atkins Diet vs Low Glycemic Index Treatment for Drug-Resistant Epilepsy in Children: An Open Label, Randomized Controlled Trial	RCT	India	None	CTRI/2017/12/010898	60	21.7	Modified Atkins = 30 months Low glycemic index = 24 months	Modified Atkins = (12,60) Low glycemic index = (23.5,51)	Modified Atkins = Tonic clonic: 14(46.7%); Epileptic spasms: 13(43.3%); Myoclonic: 0; Focal: 2(6.7%). Low glycemic index = Tonic clonic: 19(63.3%); Epileptic spasms: 9(30%); Myoclonic: 2(6.7%); Focal: 0.	NR	NR	NR	Modified Atkins Diet (mAD)/ Low Glycemic Index treatment (LGIT)	Seizure freedom, 50-90% seizure reduction, > 90% seizure reduction, Adverse events

Armeno	2021	Long-term effectiveness and adverse effects of ketogenic diet therapy in infants with drug-resistant epilepsy treated at a single center in Argentina	Pre/Post	Argentina	Not reported	N/A	56	42.9	12.23 months	(1.73, 25.87)	West syndrome: 30 (53.6%) Focal seizures: 7 (12.5%) Dravet syndrome: 4 (7.1%) Ohtahara syndrome: 2 (3.6%) Myoclonic epilepsy: 1 (1.8%) Infantile spasms without hypsarrhythmia: 1 (1.8%)	Genetic: 12 (21.4%) Structural: 16 (28.6%) Metabolic: 3 (5.4%) Unknown: 25 (44.7%)	Not reported	Number of AEDs at KD onset (median/range): 4.05 ± 1.3 (0-7)	Classic ketogenic diet	Seizure freedom, >50% seizure reduction, Adverse events
Tong	2022	Clinical implementation of ketogenic diet in children with drug-resistant epilepsy: Advantages, disadvantages, and difficulties	Cohort	China	e National Natural Science Foundation of China under Grants No. 82101523, the Regional Innovation Cooperation Project of Sichuan Provincial Science and Technology Department under Grant No. 2020YFQ0021, and the Horizontal Scientific Research Project of Sichuan University under Grant No. 20H0072	NA	157	42	2.9 years	NR	NR	NR	Daily 104 (66.2%); weekly 24 (15.3%); monthly 25 (15.9%); yearly 4 (2.5%)	3.6+/-1.3 (range 2-8) prior ASMs; 2.7 +/-0.9 (range 0-4) concurrent ASMs	Ketogenic diet	Seizure freedom, Seizure reduction rate, Adverse events
Dou	2022	Efficacy and tolerability of ketogenic diet therapy in 55 Chinese children with drug-resistant epilepsy in Northwest China	Cohort	Northwest China	Shanxi Science and Technology Support program	20210058	55	27.2	28.97 months		1 seizure type or 2> seizure types	Genetic 21.8%, Structural 47.3% Unknown 30.9%	< 5/day 30.9%, > 5/day 38,69.1%	< 2 ASMs = 27.3%, >2 ASMs = 72.7%	Ketogenic diet	Seisure freedom, Seizure reduction rate, Adverse events

Surgical Interventions

First Author's Last Name	Publication Year	Title	Study Design (RCT, Pre/Post, etc.)	Geographic Location (Country)	Funding Source	Clinical Trial Registration Number (RCTs)	Total Sample Size	Sex (% F)	Number of patients < 36 months at surgery (%)	Mean/Median age at Surgery	SD/IQR	Seizure Types	Seizure Etiology	Baseline number of seizures	Prior and concurrent treatments	Surgery/Comparison	Outcomes Reported	Complications reported
Iwasaki	2021	Epilepsy surgery in children under 3 years of age: Surgical and developmental outcomes	Cohort	Japan	NR	NA	75	52	NA	11.9 months	10.8 months	NR	Hemimegalencephaly in 22 patients, other malformations of cortical development in 33, low-grade developmental tumors in 10, tuberous sclerosis complex in 6, Sturge-Weber syndrome in 3, and perinatal ischemia in 1	Daily = 68; Weekly = 6	NR	Hemispherotomy/Multilobar Surgery/ Unilobar Surgery	ILAE classification	Cyst formation, hydrocephalus, subdural hygroma
Pepper	2022	Functional hemispherotomy for epilepsy in the very young	Prospective database	UK	NR	NA	12	33.3	12	15 months	9 months	Infantile spasm, eyelid flickering w/ desturation Eye fluttering, right arm and leg jerking evolving into bilat convulsive sz multifocal motor sz cyanosis eppisodes convulsive bilat s/ more rt0sided involvemnt rt focal heipheric status Focal stwwitcing fo rt arm and leg	Hemidysplagia 2, Hemimeg+poplymicrogyria 3 Hemimeg+TS 1 Hemimeg2 SWS 1 Nonaccidental injury/traumatic brain injury/extensive rit encephaloclastic changes 1 Hemispheric structural focal epiklptic encephalophaty, west syndrome 1 Prenatal intracerebral hemorrhage w/ hypoxic ischemic encephalopathy, west syndrome 1	NR	Mean ASMs: 2.67	Functional hemispherotomy	Engel classification, VABS, COM, DLS, SOC, ABC, MOT	Pseudomeningocele, Hygroma/postop subdural effusion Blood transfusion Staging surgeries
Abdelmoity	2021	The efficacy and tolerability of auto-stimulation-VNS in children with Lennox-Gastaut syndrome	Retrospective Cohort	USA	NR	NA	71	33.8	NR	20.82 months	NR	Tonic clonic 47, Clonic seizures 21 atonic seizure 41 Myoclonic seizures 56 Absence 25 Epileptic spasm 27 Focal seiures with impaired awareness 47 Tonic seiuzres 56	NA	NR	Older VNS models (9 patients), Average number of AEDs preop 3.4 (median 3, range 0-7); postop 3.7 (median 4, range 0-8) Ketogenic diet preop 7; postop 9	VNS placement	Seizure freedom, Seizure frequency, Cognitive function	Surgical site infection, Pain Magnet use side effects Breathing problems Voice change Autostimualtion side effects

Ko	2022	Prognostic Value of Preoperative and Postoperative Electroencephalography Findings in Pediatric Patients Undergoing Hemispheric Epilepsy Surgery	Retrospective cohort	USA	NR	NA	22	50	11	54 months	14-108 months	Ipsilateral only 4, Ipsilateral with spread 1 Contralateral only 3 Generalized 1 Interictal ipsilateral discharges 22 Interictal contralaterl discharges 9	Congenital malformation (focal cortical dysplasia and/or hemimegalencephaly) in 11, Acquired brain lesion (stroek or encephalitis) in 10, Rasmussen's encephalitis in 1, HME5 FCD3 Gliosis 6 PMG4 Oligo 1 Cystic infarct 1 Rassmusen 1 Chronic infarct 1	NR	NR	Functional hemispherectomy	Engel Class, Preop EEG (Engel Class IA vs IB or worse) Postop EEG (Engel Class IA vs IB or worse) Preop Neuropsychological eval Postop Neuropsychological eval , VABS(ABC) Wechsler intelligence scale (FSIQ)	NA
Wang	2022	Characteristics, surgical outcomes, and influential factors of epilepsy in Sturge-Weber syndrome	Cohort	China	National Key Research and Development Program of China and the National Natural Science Foundation of China	NA	132	48.5	NR	13.3 months	28.56 months	focal motor, focal to GTC, GTC, SE	Sturge Weber Syndrome	Medically refractory epilepsy	NR	Hemispherectomy/Focal Resection	Engel Class, Cognitive function, Seizure freedom	Postoperative complications, Superficial infection, intracranial infection, hemorrhage, stroke
Puka	2021	Functional cognitive and language outcomes after cerebral hemispherectomy for hemimegalencephaly	Cohort	USA	National Center for Advancing Translational Sciences, Grant/Award Number: UL1 TR000445	NA	45	60	NA	10.8 months	12.7 months	NR	Hemimegalencephally 100% (cortical dyspalsia 20%, polymicrogyria 16%, pachygyria 9%, heterotopia 4%, TSC 2%, other 2%	Several seizures/hour = 61%, Several seizures/ day = 32%, Several/month = 7%	NR	Hemispherectomy/hemispherotomy	Seizure freedom	NA
Stomberg	2021	Epilepsy associated with tuberous sclerosis complex in childhood:	Case Control	Germany	German Research Council, Bonn,	NA	85	48	NR	Surgical cohort - 2.6 years, Non-surgical	1.6 - 6.2 years, 1.9 - 7.5 years	Unspecified	Tuberous sclerosis 100%	Surgical cohort - daily seizures - 30 of 34 (88.2%),	Surgical cohort - Mean ASM: 2.21 Non-surgical	Unilobar resection/ Multilobar resection	Seizure freedom, Mean number of ASMs, General	NA

		Long-term outcome in children after epilepsy surgery and children non-eligible for epilepsy surgery			Germany					cohort - 3.3 years				less than daily seizures - 4/34 (11.8%) Non-surgical cohort - daily seizures - 30 of 51 (58.8%), less than daily - 14/51 (27.5%), Sz free - 7/51 (13.7%)	cohort - Mean ASM: 2.12		developmental level (VABS II), Quality of life (DISABKIDS), Social adaption (SDQ-D), Concerns about Seizures (GEOS subscale), Impact on family (IOFS)	
Honda	2021	Developmental outcome after corpus callosotomy for infants and young children with drug-resistant epilepsy	Cohort	Japan		NA	106	48	NR	30.3 months	21.2 months	spasms 84%; Tonic 33%; GTC 6.5%; foal 14.2%; Atypical absence 11.3; myoclonic 10.4; atonic 6.6, 10.4% EME or EIEE, 73.6%West syndrome,12.3 %LGS,0.9% CSWS	26% structural ; 16% genetic; 6% infectious	NR	Mean ASM: 4.6 (SD 1.7)	Corpus Callosotomy	Seizure freedom, EEG, Developmental Age, Developmental Quotient	Death, subdural effusiom hydrocepahallus infection

Supplemental Materials 4. Systematic Review Update Studies Excluded at Full Text Review

Author Last Name & Year	Title	Reasons for Exclusion
Varesio 2023	GLUT1-DS Italian registry: past, present, and future: a useful tool for rare disorders	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Meng 2023	Multivariate analysis of seizure outcomes after resective surgery for focal epilepsy: a single-center study on 833 patients	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Sugano 2023	Proper Therapy Selection Improves Epilepsy Outcomes in Patients With Multilobar Sturge-Weber Syndrome	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Yu 2023	The ketogenic diet for Dravet syndrome: A multicenter retrospective study	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Caraballo 2023	Cannabidiol in children with treatment-resistant epilepsy with myoclonic-atonic seizures	Age greater than 36 months
Liu 2023	Clinical characteristics and surgical outcomes in children with mild malformation of cortical development and oligodendroglial hyperplasia in epilepsy (MOGHE)	Insufficient sample size
Muthiah 2023	Investigation of the effectiveness of vagus nerve stimulation for pediatric drug-resistant epilepsies secondary to nonaccidental trauma	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Ramantani 2023	Not surgical technique, but etiology, contralateral MRI, prior surgery, and side of surgery determine seizure outcome after pediatric hemispherotomy	Pediatric population
Yamamoto 2023	Clinical value of therapeutic drug monitoring for levetiracetam in pediatric patients with epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Zhao 2023	Twelve-Month Efficacy of Lacosamide Monotherapy at Maximal Dose and Tolerability for Epilepsy Treatment in Pediatric Patients: Real-World Clinical Experience	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Oshino 2023	Clinical Factors Related to Outcomes in Pediatric Epilepsy Surgery: Insight into Predictors of Poor Surgical Outcome	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Matarrese 2023	Spike propagation mapping reveals effective connectivity and predicts surgical outcome in epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Nissenkorn 2023	Perampanel as precision therapy in rare genetic epilepsies	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Maleknia 2023	Postoperative seizure freedom after vagus nerve stimulator placement in children 6 years of age and younger	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Lu 2023	The natural history of postoperative hydrocephalus after pediatric hemispherectomy for medically refractory epilepsy: an institutional experience	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Yadav 2023	Genetic Expression of CYP2B6 Gene in Phenobarbitone Responder and Non- responder Neonates	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Gogou 2023	Antiseizure medication reduction and withdrawal in children with drug-resistant epilepsy after starting the ketogenic diet	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Szaflarski 2023	Long-term efficacy and safety of cannabidiol in patients with treatment-resistant epilepsies: Four-year results from the expanded access program	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Harford 2023	Functional outcomes of pediatric hemispherotomy: Impairment, activity, and medical service utilization	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Xie 2023	Efficacy of vagus nerve stimulation in 95 children of drug-resistant epilepsy with structural etiology	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Sullivan 2023	Phase 2, placebo-controlled clinical study of oral ganaxolone in PCDH19-clustering epilepsy	Wrong drug/pharmacological intervention
Lu 2023	Impact of ketogenic diet therapy on growth in children with epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Ravindra 2023	Epilepsy Surgery in Young Children With Tuberous Sclerosis Complex: A Novel Hybrid Multimodal Surgical Approach	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)

Phillips 2023	Preliminary Experience Suggests the Addition of Choroid Plexus Cauterization to Functional Hemispherectomy May Reduce Posthemispherectomy Hydrocephalus	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Doddamani 2023	Minimally invasive hemispherotomy for refractory epilepsy in infants and young adults'	Wrong study design (i.e., narrative reviews, editorials etc)
Fronda 2023	Oral Loading of Phenobarbital to Achieve Therapeutic Effects in Pediatric Patients with Acute Repetitive Seizures	Insufficient follow-up period (< 12 weeks for seizure effectiveness outcomes)
Smiałek 2023	Safety of Sirolimus in Patients with Tuberous Sclerosis Complex under Two Years of Age. Bicenter Retrospective Study	Wrong drug/pharmacological intervention
Liu 2023	Retrospective Clinical Analysis of Epilepsy Treatment for Children with Drug-Resistant Epilepsy (A Single-Center Experience)	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Kühne 2023	Real-world data on cannabidiol treatment of various epilepsy subtypes: A retrospective, multicenter study	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Bishop 2023	Fenfluramine treatment is associated with improvement in everyday executive function in preschool-aged children (<5 years) with Dravet syndrome	Included in previous AHRQ report
Lee 2023	PRRT2-positive self-limited infantile epilepsy: Initial seizure characteristics and response to sodium channel blockers	Insufficient sample size
Driessen 2023	Effectiveness and tolerability of lacosamide in children with drug resistant epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
El-Shafie 2023	Impact of two ketogenic diet types in refractory childhood epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Vasquez 2023	Stiripentol for the treatment of seizures associated with Dravet syndrome in patients 6 months and older and taking clobazam	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Smiałek 2023	Effect of mTOR Inhibitors in Epilepsy Treatment in Children with Tuberous Sclerosis Complex Under 2 Years of Age	Wrong intervention
Damante 2023	Impact of Etiology on Seizure and Quantitative Functional Outcomes in Children with Cerebral Palsy and Medically Intractable Epilepsy Undergoing Hemispherotomy/Hemispherectomy	Age greater than 36 months
Schneider 2023	Large Vertex Encephaloceles: Management and Outcomes	Wrong condition (e.g., provoked seizures, infantile spasms, status epilepticus etc)
Yu 2022	Surgical treatment of pediatric intractable frontal lobe epilepsy due to malformation of cortical development	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Bjurulf 2022	Caregiver reported seizure precipitants and measures to prevent seizures in children with Dravet syndrome	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Shan 2022	Vagus Nerve Stimulation for Drug Resistant Epilepsy: Clinical Outcome, Adverse Events, and Potential Prognostic Factors in a Single Center Experience	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Archna 2022	Modified Atkins diet versus levetiracetam for non-surgical drug-resistant epilepsy in children: A randomized open-label study	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Alcala-Zermeno 2022	Invasive neuromodulation for epilepsy: Comparison of multiple approaches from a single center	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Wiegand 2022	EEG-Findings during long-term treatment with everolimus in TSC-associated and therapy-resistant epilepsies in children	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Serrano-Tabares 2022	Tolerance and response to ketogenic therapy in neonates and infants younger than 4 months. Case series in a hospital center in Medellin, Colombia	Not in English.
Tzadok 2022	The Long-Term Effectiveness and Safety of Cannabidiol-Enriched Oil in Children With Drug-Resistant Epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Ch´avez L´opez 2022	Pre-surgical evaluation challenges and long-term outcome in children operated on for Low Grade Epilepsy Associated brain Tumors	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Romão 2022	Use of lacosamide in children: experience of a tertiary medical care center in Brazil	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Doring 2022	Efficacy, Tolerability, and Retention of Antiseizure Medications in PRRT2 -Associated Infantile Epilepsy	Insufficient sample size

Yu 2022	A Mixed-Lipid Diet (Medium-Chain and Long-Chain Triglycerides) for Better Tolerability and Efficiency in Pediatric Epilepsy Patients	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Takayama 2022	Is Hippocampal Resection Necessary for Low-Grade Epilepsy-Associated Tumors in the Temporal Lobe?	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Alzahrany 2022	Epileptiform abnormalities in the disconnected hemisphere are common in seizure-free patients after hemispherectomy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Rahman 2022	Stereoelectroencephalography before 2 years of age	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Remick 2022	Subdural electrodes versus stereoelectroencephalography for pediatric epileptogenic zone localization: a retrospective cohort study	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Larrew 2022	Comparison of outcomes after stereoelectroencephalography and subdural grid monitoring in pediatric tuberous sclerosis complex	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Kandregula 2022	Racial and socioeconomic disparities in the advanced treatment of medically intractable pediatric epilepsy	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Balestrini 2022	Efficacy and Safety of Long-Term Treatment with Stiripentol in Children and Adults with Drug-Resistant Epilepsies: A Retrospective Cohort Study of 196 Patients	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Bölsterli 2022	Ketogenic Diet Treatment of Defects in the Mitochondrial Malate Aspartate Shuttle and Pyruvate Carrier	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Xie 2022	Vagus nerve stimulation in children with drug-resistant epilepsy of monogenic etiology	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Jensen 2022	Fenfluramine treatment for dravet syndrome: Real-world benefits on quality of life from the caregiver perspective	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Zimmerman 2022	Community-engaged research: a powerful tool to reduce health disparities and improve outcomes in pediatric neurosurgery	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Rangarajan 2022	Efficacy of pulse intravenous methylprednisolone in epileptic encephalopathy: a randomised controlled trial	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Rehman 2022	Efficacy and Safety of Levetiracetam in Refractory Seizures in Children	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Teng 2022	Glycemic biomarkers in children with drug-resistant epilepsy on various types of ketogenic diet therapies: A cross-sectional study	Insufficient sample size
Stödberg 2022	Outcome at age 7 of epilepsy presenting in the first 2 years of life. A population-based study	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Fory´s-Basiejko 2022	Epilepsy and Language Development in 8‚Äì36-Month-Old Toddlers with Tuberous Sclerosis Complex	Wrong drug/pharmacological intervention
Fujimoto 2022	Replacement of Valproic Acid with New Anti-Seizure Medications in Idiopathic Generalized Epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Qu 2022	Use of perampanel in children with refractory epilepsy of genetic aetiology	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Kamasak 2022	The effectiveness and tolerability of clobazam in the pediatric population: Adjunctive therapy and monotherapy in a large-cohort multicenter study	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Li 2022	Efficacy and adverse reactions of perampanel in the treatment of epilepsy in children	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Warren 2022	The Optimal Target and Connectivity for Deep Brain Stimulation in Lennox‚ÄìGastaut Syndrome	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Susnerwala 2022	Levetiracetam or Phenobarbitone as a First-Line Anticonvulsant in Asphyxiated Term Newborns? An Open-Label, Single-Center, Randomized, Controlled, Pragmatic Trial	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Handoko 2022	Comparison of Surgical Outcomes in Individuals With Hypothalamic Hamartoma Alone or With Other Potentially Epileptogenic Focal Lesions	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Candela-Cantó 2022	Robot-assisted, real-time, MRI-guided laser interstitial thermal therapy for pediatric patients with hypothalamic hamartoma: surgical technique, pitfalls, and initial results	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)

Fang 2022	Ketogenic Diet Therapy for Drug-Resistant Epilepsy and Cognitive Impairment in Children With Tuberous Sclerosis Complex	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Lowe 2022	Ketonuria and Seizure Control in the Medium Chain Triglyceride and Classic Ketogenic Diets	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Aslan 2022	Effectiveness of zonisamide in childhood refractory epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Perna 2022	Effects of Classic Ketogenic Diet in Children with Refractory Epilepsy: A Retrospective Cohort Study in Kingdom of Bahrain	Insufficient sample size
Asadi-Pooya 2022	Rational therapy with lamotrigine or levetiracetam: Which one to select?	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Lee 2022	Structural connectivity in children after total corpus callosotomy	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Patil 2022	Clinical profile and outcomes of epilepsy surgery in children from a tertiary epilepsy care center in India	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Agrawal 2022	Feasibility of Tailored Unilateral Disconnection vs Callosotomy for Refractory Epilepsy in Patients with Bilateral Parieto-Occipital Gliosis Following Perinatal Insult	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Sadowski 2022	Antiepileptic Effect and Safety Profile of Rapamycin in Pediatric Patients With Tuberous Sclerosis Complex	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Farkas 2022	Pharmacokinetics, safety, and tolerability of intravenous brivaracetam in pediatric patients with epilepsy: An open-label trial	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Lin 2022	Focal Epilepsy in Children With Tuberous Sclerosis Complex: Does Vigabatrin Control Focal Seizures?	Unable to access
Na 2022	Effective application of corpus callosotomy in pediatric intractable epilepsy patients with mitochondrial dysfunction	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Aparicio 2022	Presurgical evaluation of drug-resistant paediatric focal epilepsy with PISCOM compared to SISCOM and FDG-PET	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Kacker 2022	Efficacy and tolerability of the modified Atkins diet in children with drug-resistant genetic generalized epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
PrakashRaju 2022	A study of rationale use of sodium valproate and levetiracetam as monotherapy in pediatric patients with epilepsy at tertiary care hospital	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Legido 2022	Study of paediatric patients with the clinical and biochemical phenotype of glucose transporter type 1 deficiency syndrome	Not in English
Sewell 2022	Association between anti-seizure medication and outcomes in infants	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Segal 2022	PROVE-Phase IV Study of Perampanel in Real-World Clinical Care of Patients with Epilepsy: Interim Analysis in Pediatric Patients	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Alameen Ali 2022	The efficacy of non-fasting ketogenic diet protocol in the management of intractable epilepsy in pediatric patients: a single center study from Saudi Arabia	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
	Perampanel (fycompa) in partialonset or generalised epilepsy in certain children	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Türkdoğan 2022	CLB add-on treatment in patients with epileptic encephalopathy: a single center experience with long-term follow-up	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Kostov 2022	Norwegian population-based study of long-term effects, safety, and predictors of response of vagus nerve stimulation treatment in drug-resistant epilepsy: The NORPulse study	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Hu 2022	Phenotypic and genetic spectrum in Chinese children with SCN8A-related disorders	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Caraballo 2022	Long-term use of cannabidiol-enriched medical cannabis in a prospective cohort of children with drug-resistant developmental and epileptic encephalopathy	Age greater than 36 months
Wang 2022	Efficacy of levetiracetam in STXBP1 encephalopathy with different phenotypic and genetic spectra	Insufficient sample size
Kaur 2022	Cognitive outcomes following pediatric epilepsy surgery	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)

Ostendorf 2022	United States Epilepsy Center Characteristics A Data Analysis From the National Association of Epilepsy Centers	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Lin 2021	Efficacy of Anti-seizure Medications, Quinidine, and Ketogenic Diet Therapy for KCNT1-Related Epilepsy and Genotype-Efficacy Correlation Analysis	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Sullivan 2022	Fenfluramine significantly reduces day-to-day seizure burden by increasing number of seizure-free days and time between seizures in patients with Dravet syndrome: A time-to-event analysis	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Ko 2022	Efficacy of the Ketogenic Diet for Pediatric Epilepsy According to the Presence of Detectable Somatic mTOR Pathway Mutations in the Brain	Does not meet PICO criteria
Yang 2022	Improving the effects of ketogenic diet therapy in children with drug-resistant epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Dou 2022	Evaluation of the seizure control and the tolerability of ketogenic diet in Chinese children with structural drug-resistant epilepsy	Insufficient sample size
Muthiah 2022	Comparison of traditional and closed loop vagus nerve stimulation for treatment of pediatric drug-resistant epilepsy: A propensity-matched retrospective cohort study	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Tong 2022	Vagus nerve stimulation for drug-resistant epilepsy induced by tuberous sclerosis complex	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Iwasaki 2022	Predictors of Seizure Outcome after Repeat Pediatric Epilepsy Surgery: Reasons for Failure, Sex, Electrophysiology, and Temporal Lobe Surgery	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Feng 2022	Prospective control study of efficacy and influencing factors of a ketogenic diet on refractory epilepsy in children	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Yillmaz 2022	The effectiveness of the ketogenic diet in drug-resistant childhood epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
	Fenfluramine (fintepla) in Dravet syndrome	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Na 2022	Treatment strategies for Lennox-Gastaut syndrome: outcomes of multimodal treatment approaches	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Abramov 2022	PERSONALIZED SURGERY IN CHILDREN WITH TEMPORAL LOBE EPILEPSY	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Guo 2022	Effectiveness of vagus nerve stimulation therapy in refractory hypoxic-ischemic encephalopathy-induced epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Treves 2021	Efficacy and safety of medical cannabinoids in children: a systematic review and meta-analysis	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Yilmaz 2021	The effect of ketogenic diet on thyroid functions in children with drug-resistant epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Marefi 2021	The epilepsy-movement disorder phenotypic spectrum and phenytoin-induced dyskinesia associated with GABRB3 pathogenic variants	Wrong condition (e.g., provoked seizures, infantile spasms, status epilepticus etc)
Wiegand 2021	Long-term treatment with everolimus in TSC-associated therapy-resistant epilepsies	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Samia 2021	Qualitative exploration of feasibility and acceptability of the modified ketogenic dietary therapy for children with drug-resistant epilepsy in Kenya	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Cross 2021	Impact of fenfluramine on the expected SUDEP mortality rates in patients with Dravet syndrome	Age greater than 36 months
Breu 2021	The relation of etiology based on the 2017 ILAE classification to the effectiveness of the ketogenic diet in drug-resistant epilepsy in childhood	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Fallah 2021	Comparison of the real-world effectiveness of vertical versus lateral functional hemispherotomy techniques for pediatric drug-resistant epilepsy: A post hoc analysis of the HOPS study	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Klotz 2021	Effect of Cannabidiol on Interictal Epileptiform Activity and Sleep Architecture in Children with Intractable Epilepsy: A Prospective Open-Label Study	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)

Liu 2021	Postoperative seizure and developmental outcomes of children with hemimegalencephaly and drug-resistant epilepsy	Insufficient sample size
Ruiz-Herrero 2021	Efficacy and safety of ketogenic dietary theraphies in infancy. A single-center experience in 42 infants less than two years of age	Included in previous AHRQ report
Arzimanoglou 2021	Safety and efficacy of rufinamide in children and adults with Lennox-Gastaut syndrome: A post hoc analysis from Study 022	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Ferragut Ferretjans 2021	Efficacy of Brivaracetam in children with epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Anderson 2021	Seizure frequency, quality of life, behavior, cognition, and sleep in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Castagno 2021	Seizure outcomes of large volume temporo-parieto-occipital and frontal surgery in children with drug-resistant epilepsy	Age greater than 36 months
Numoto 2021	Sodium channel blockers are effective for benign infantile epilepsy	Insufficient sample size
Kadam 2021	Posterior Quadrant Disconnection for Childhood Onset Sub-Hemispheric Posterior Head Region Epilepsy: Indications in an Indian Cohort and Outcome	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Liu 2021	Severity Grading, Risk Factors, and Prediction Model of Complications After Epilepsy Surgery: A Large-Scale and Retrospective Study	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Tsai 2021	Vagus nerve stimulation in pediatric patients with failed epilepsy surgery	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Suo 2021	Effects of levetiracetam and oxcarbazepine monotherapy on intellectual and cognitive development in children with benign epilepsy with centrotemporal spikes	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Gautham 2021	Magnetic source imaging in presurgical evaluation of paediatric focal drug-resistant epilepsy and its predictive value of surgical outcome in lesional cases: A single-centre experience from South India	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Wheeler 2021	Efficacy and tolerability of a whey-based, medium-chain triglyceride-enhanced ketogenic formula in children with refractory epilepsy: A retrospective study	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Yilmaz 2021	The effect of ketogenic diet on serum lipid concentrations in children with medication resistant epilepsy	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Liu 2021	Two-trajectory laser amygdalohippocampotomy: Anatomic modeling and initial seizure outcomes	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Strzelczyk 2021	Efficacy, tolerability, and retention of fenfluramine for the treatment of seizures in patients with Dravet syndrome: Compassionate use program in Germany	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Abdelmesih 2021	Initial levetiracetam versus valproate monotherapy in antiseizure medicine (ASM)-navØve pediatric patients with idiopathic generalized epilepsy with tonic-clonic seizures	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Scheffer 2021	Add-on cannabidiol in patients with Dravet syndrome: Results of a long-term open-label extension trial	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Zhao 2021	PRRT2 variants and effectiveness of various antiepileptic drugs in self-limited familial infantile epilepsy	Insufficient sample size
Mangunatmadja 2021	Risk factors predicting intractability in focal epilepsy in children under 3years of age: A cohort study	Wrong drug/pharmacological intervention
Pristas 2021	An observational report of swallowing outcomes following corpus callosotomy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Madan Cohen 2021	Time to onset of cannabidiol treatment effects in Dravet syndrome: Analysis from two randomized controlled trials	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Patel 2021	Long-term safety and efficacy of add-on cannabidiol in patients with Lennox,ÄìGastaut syndrome: Results of a long-term open-label extension trial	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Gambardella 2021	Selection of antiseizure medications for first add-on use: A consensus paper	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Kurwale 2021	Surgical outcomes for medically refractory epilepsy secondary to posterior cortex ulegyria as sequelae of perinatal insults	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)

Grayson 2021	Longitudinal impact of cannabidiol on EEG measures in subjects with treatment-resistant epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Okumura 2021	Effects of L-carnitine supplementation in patients with childhood-onset epilepsy prescribed valproate	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Russo 2021	Brivaracetam in treating epileptic encephalopathy and refractory focal epilepsies in patients under 14 years of age	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Sun 2021	Vagus Nerve Stimulation Therapy for the Treatment of Seizures in Refractory Postencephalitic Epilepsy: A Retrospective Study	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Roth 2021	Epilepsy surgery in infants up to 3 months of age: Safety, feasibility, and outcomes: A multicenter, multinational study	Included in previous AHRQ report
Zhu 2021	Comparison of efficiency between VNS and ANT-DBS therapy in drug-resistant epilepsy: A one year follow up study	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Chari 2021	The UK experience of stereoelectroencephalography in children: An analysis of factors predicting the identification of a seizure-onset zone and subsequent seizure freedom	Age greater than 36 months
Lukka 2021	Use of Real-World Data and Pharmacometric Modeling in Support of Lacosamide Dosing in Pediatric Patients Under 4 Years of Age	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Patel 2021	The long-term efficacy of cannabidiol in the treatment of refractory epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Zhao 2021	Long-term safety, efficacy, and tolerability of levetiracetam in pediatric patients with epilepsy in Uygur, China: A retrospective analysis	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Ricci 2021	Source imaging of seizure onset predicts surgical outcome in pediatric epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Munro 2021	Neutropenia in Children Treated With Ketogenic Diet Therapy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Sathe 2021	Early Exposure of Fosphenytoin, Levetiracetam, and Valproic Acid After High-Dose Intravenous Administration in Young Children With Benzodiazepine-Refractory Status Epilepticus	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Liguori 2021	Is sulthiame effective and tolerated as add-on therapy for infants with epilepsy? A Cochrane Review summary with commentary	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Johnson 2021	Analyses of seizure responses supportive of a novel trial design to assess efficacy of antiepileptic drugs in infants and young children with epilepsy: Post hoc analyses of pediatric levetiracetam and lacosamide trials	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Franco 2021	Pediatric adverse reactions to antiseizure medications: An analysis of data from the Italian spontaneous reporting system (2001,Äì2019)	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Sarat Chandra 2021	Robotic thermocoagulative hemispherotomy: Concept, feasibility, outcomes, and safety of a new "bloodless" technique	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Iannone 2021	Results From an Italian Expanded Access Program on Cannabidiol Treatment in Highly Refractory Dravet Syndrome and Lennox,ÄìGastaut Syndrome	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Kessi 2021	Treatment for the Benign Childhood Epilepsy With Centrotemporal Spikes: A Monocentric Study	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Weil 2021	Hemispherectomy Outcome Prediction Scale: Development and validation of a seizure freedom prediction tool	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Baumer 2021	Treatment Practices and Outcomes in Continuous Spike and Wave during Slow Wave Sleep: A Multicenter Collaboration	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Aledo-Serrano 2021	Sodium channel blockers for the treatment of epilepsy in CDKL5 deficiency disorder: Findings from a multicenter cohort	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Fernández-Concepción 2021	Safety and effectiveness of surgery for epilepsy in children. Experience of a tertiary hospital in Ecuador	Not in English
Gong 2021	Genetic Etiologies in Developmental and/or Epileptic Encephalopathy With Electrical Status Epilepticus During Sleep: Cohort Study	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)

Alotaibi 2021	Medication choices for paediatric epilepsy	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Zhao 2021	Safety, efficacy, and tolerability of lacosamide for the treatment of epilepsy in pediatric patients in Uygur, China	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Orduña 2021	Cognitive and behavioral profiles of pediatric surgical candidates with frontal and temporal lobe epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Caruso 2021	Retrospective analysis of open surgical versus laser interstitial thermal therapy callosotomy in pediatric patients with refractory epilepsy	Age greater than 36 months
Wang 2021	Surgical treatment of children with drug-resistant epilepsy involving the Rolandic area	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Lin 2021	Genetic factors and the risk of drug-resistant epilepsy in young children with epilepsy and neurodevelopment disability: A prospective study and updated meta-analysis	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Herrero 2021	Classic ketogenic diet and modified Atkins diet in slc2a1 positive and negative patients with suspected glut1 deficiency syndrome: A single center analysis of 18 cases	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Abdelmoity 2021	Combined use of the ketogenic diet and vagus nerve stimulation in pediatric drug-resistant epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Devinsky 2021	Ataluren for drug-resistant epilepsy in nonsense variant-mediated Dravet syndrome and CDKL5 deficiency disorder	Age greater than 36 months
Yildirim 2021	Levetiracetam monotherapy in children with epilepsy: Experience from a tertiary pediatric neurology center	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Sullivan 2021	Fenfluramine responder analyses and numbers needed to treat: Translating epilepsy trial data into clinical practice	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Frigeri 2021	Control of drop attacks with selective posterior callosotomy: Anatomical and prognostic data	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Lakshminarayanan 2021	Efficacy of low glycemic index diet therapy (LGIT) in children aged 2,Äì8 years with drug-resistant epilepsy: A randomized controlled trial	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Stephenson 2021	Resection of tuber centers only for seizure control in tuberous sclerosis complex	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Knyazeva 2021	Pharmacoepidemiology of antiepileptic drugs in children	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Gunning 2021	Cannabidiol in conjunction with clobazam: analysis of four randomized controlled trials	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Kotulska 2021	Prevention of Epilepsy in Infants with Tuberous Sclerosis Complex in the EPISTOP Trial	Wrong condition (e.g., provoked seizures, infantile spasms, status epilepticus etc)
Shiraki 2021	Initial treatment of seizures in children in an emergency department in rural Japan	Wrong condition (e.g., provoked seizures, infantile spasms, status epilepticus etc)
Kurwale 2021	Failed Hemispherotomy: Insights from Our Early Experience in 40 Patients	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Yamada 2021	Long-term safety and effectiveness of stiripentol in patients with Dravet syndrome: Interim report of a post-marketing surveillance study in Japan	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Knorr 2021	Subgroup analysis of seizure and cognitive outcome after vagal nerve stimulator implantation in children	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Lim 2021	The early response to dietary therapy can predict the late outcome in children with intractable epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Al-Baradie 2021	The role of ketogenic diet in controlling epileptic seizures	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Wagner 2021	Levetiracetam compared to phenobarbital as a first line therapy for neonatal seizures: An unexpected influence of benzodiazepines on seizure response	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Song 2021	Gamma-knife radiosurgery for hypothalamic hamartoma-related epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Villanueva 2021	Initiating antiepilepsy treatment: An update of expert consensus in Spain	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)

Ricci 2021	Measuring the effects of first antiepileptic medication in Temporal Lobe Epilepsy: Predictive value of quantitative-EEG analysis	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Roland 2021	Corpus callosotomy performed with laser interstitial thermal therapy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Pan 2021	The effectiveness of medical and surgical treatment for children with refractory epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Qiu 2021	Valproic acid therapy decreases serum 25-hydroxyvitamin D level in female infants and toddlers with epilepsy - a pilot longitudinal study	Insufficient sample size
Pan 2021	Effect of levetiracetam in combination with topiramate on immune function, cognitive function, and neuronal nutritional status of children with intractable epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Marson 2021	Lamotrigine versus levetiracetam or zonisamide for focal epilepsy and valproate versus levetiracetam for generalised and unclassified epilepsy: Two SANAD II non-inferiority RCTs	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Fayyazi 2021	Evaluation of the Levetiracetam treatment on reduction of epileptic discharges in electroencephalogram in children with epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Liu 2021	Ketogenic diet and growth in Chinese infants with refractory epilepsy	Insufficient sample size
Fearn 2023	Peri-ictal EEG in infants with PRRT2-related self-limited infantile epilepsy	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Jain 2021	Surgical outcomes in children with bottom-of-sulcus dysplasia and drug-resistant epilepsy: a retrospective cohort study	Wrong study design (i.e., narrative review, editorial, letter, textbook, etc)
Liu 2023	Clinical characteristics and surgical outcomes in children with mild malformation of cortical development and oligodendroglial hyperplasia in epilepsy	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Mir 2023	Outcomes of resective surgery in pediatric patients with drug-resistant epilepsy: a single center study from the Eastern Mediterranean Region	Wrong population (i.e., age < 1 month, age > 36 months, or < 80% of patients meeting the relevant criteria)
Schoeler 2024	Randomised, open-label phase 4 trial of classical ketogenic diet versus further anti-seizure medicine in 2 infants with epilepsy (KIWE)	Insufficient follow-up period (< 12 weeks for seizure effectiveness outcomes)
Makridis 2023	Epilepsy surgery in early infancy: A retrospective, multicenter study	Insufficient sample size
Nam 2022	Effects of the ketogenic diet therapy in patients with STXBP1-related encephalopathy	Insufficient sample size
Tanritanir 2021	Efficacy and Tolerability of Rufinamide in Epileptic Children Younger Than 4 Years	Included in previous AHRQ report
Ueda 2021	Improvement of brain function after surgery in infants with posterior quadrant cortical dysplasia	Wrong condition (e.g., provoked seizures, infantile spasms, status epilepticus etc)

Supplemental Materials 5: Evidence Profiles for each Recommendation

Recommendation I-A-1. Evidence Profile, PICO: Levetiracetam compared to no Levetiracetam for epilepsy in infants (1 - < 36 months) diagnosed with epilepsy

In infants and children less than 36 months of age diagnosed with new onset epilepsy, the AES guideline panel **suggests for** the use of Levetiracetam rather than no Levetiracetam. (**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levetiracetam	No Levetiracetam	Relative (95% CI)	Absolute (95% CI)		
Failure to achieve Seizure Freedom (follow-up: median 12 months)												
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	31/92 (33.7%)	(100.0%)	**RR 0.34** (0.26 to 0.45)	**660 fewer per 1,000** (from 740 fewer to 550 fewer)	⊕◯◯◯ Very low	CRITICAL
Seizure Frequency - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Adverse Events Leading to Discontinuation (respiratory disorder, respiratory distress, infantile spasms, irritability, lower respiratory tract infection, psychomotor retardation and respiratory failure)												
2[1,2]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	One study, (Arzimanoglou 2016) reported that 7/101 (7%) patients discontinued treatment due to adverse events. While a second study (Arican 2018) reported that no patient discontinued due adverse events in the 92 included patients (0%).				⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Study does not meet optimal information size (OIS) requirement (small sample size).

References

1. Arican P, Gencpinar P, Cavusoglu D, Olgac Dundar N. Levetiracetam monotherapy for the treatment of infants with epilepsy. Seizure. 2018;56:73-77. doi:10.1016/j.seizure.2018.02.006

2. Arzimanoglou A, Lösch C, Garate P, Bentz J. Safety of levetiracetam among infants younger than 12 months--Results from a European multicenter observational study. Eur J Paediatr Neurol. 2016;20(3):368-375. doi:10.1016/j.ejpn.2016.01.006

Recommendations I-A-2 and I-B-1. Evidence Profile for PICO: Valproate compared to no Valproate in infants (1 - < 36 months) diagnosed with epilepsy

I-A-2. In infants and children less than 36 months of age newly diagnosed with epilepsy, the AES guideline panel **suggests against** the use of valproate. (**Conditional** Recommendation, **Very Low** Certainty of Evidence).

I-B-1. In infants and children less than 36 months of age diagnosed with drug-resistant epilepsy, the AES guideline panel **suggests** treatment with valproate rather than no valproate. (**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproate	No Valproate	Relative (95% CI)	Absolute (95% CI)		
Failure to achieve seizure freedom (follow-up: mean 14.86 months)												
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	39/50 (78.0%)	(100.0%)	**RR 0.78** (0.67 to 0.91)	**220 fewer per 1,000** (from 330 fewer to 90 fewer)	⨁◯◯◯ Very low	CRITICAL
Seizure Frequency (follow-up: mean 14.86 months; assessed with: ≥50% reduction)												
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	One study showed 32/50 patients (64%) experienced a 50% reduction in seizure frequency at the final clinic visit.				⨁◯◯◯ Very low	CRITICAL
Adverse Events (follow-up: mean 14.86 months)												
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	Adverse events reported by the study include: • Encephalopathy (sleepiness and hypoactivity: 2/50 patients • Elevated liver function test: AST: pretreatment (18/50), posttreatment (20/50) ALT: pretreatment (2/50), posttreatment (2/50) GGT: pretreatment (4/50), posttreatment (9/50) Alkaline phosphate: pretreatment (3/50), posttreatment (2/50) Bilirubin: pretreatment (0/50), posttreatment (0/50).				⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Study does not meet optimal information size (OIS) requirement (small sample size).

References

1. Muthaffar OY, Almahmudi SM, Alrabghi MO, Bin Mahfouz MM, Alfawaz NS. Valproic acid for children below 2 years of age with epilepsy. Neurosciences (Riyadh). 2021;26(4):357-365. doi:10.17712/nsj.2021.4.20210075

Recommendation I-A-3. Evidence Profile for PICO: Oxcarbazepine compared to Levetiracetam in infants (1- <36 months) diagnosed with epilepsy

In infants and children less than 36 months of age diagnosed with new onset focal epilepsy, the AES guideline panel suggests treatment with oxcarbazepine rather than levetiracetam. (**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxcarbazepine	Levetiracetam	Relative (95% CI)	Absolute (95% CI)		
Seizure Freedom (follow-up: median 2 years)												
1[1]	non-randomised studies	serious[a]	not serious	not serious	very serious[b]	none	61/83 (73.5%)	32/78 (41.0%)	**RR 1.79** (1.33 to 2.41)	**324 more per 1,000** (from 135 more to 578 more)	⊕◯◯◯ Very low	CRITICAL
Seizure Frequency - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse Events (Rash, DIHS, Somnolence, Excitement, Irritation, Vomiting) (follow-up: median 2 years)												
1[1]	non-randomised studies	serious[a]	not serious	not serious	very serious[b,c]	none	8/83 (9.6%) [d]	3/78 (3.8%)	**RR 2.51** (0.69 to 9.11)	**58 more per 1,000** (from 12 fewer to 312 more)	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Some concerns with confounding control.

b. Study does not meet optimal information size (OIS) requirement (small sample size).

c. Fragility estimate. Confidence intervals crossing thresholds of benefit and harm.

d. These adverse events include: With the use of Oxcarbazepine: Rash: 3/83 patients Drug-Induced Hypersensitivity Syndrome (DIHS): 1/83 patients Somnolence: 2/83 patients Excitement: 0/83 patients Irritation: 1/83 patients Vomit: 1/83 patients With the use of Levetiracetam: Rash: 0/78 patients Drug-Induced Hypersensitivity Syndrome (DIHS): 0/78 patients Somnolence: 1/78 patients Excitement: 1/78 patients Irritation: 1/78 patients Vomit: 0/78 patients

References

1. Zhao B, Liao S, Zhong X, Luo Y, Hong S, Cheng M, Zhang J, Li T, Jiang L. Effectiveness and Safety of Oxcarbazepine vs. Levetiracetam as Monotherapy for Infantile Focal Epilepsy: A Longitudinal Cohort Study. Front Neurol. 2022;13:909191. doi:10.3389/fneur.2022.909191

Recommendation I-A-4. Evidence Profile for PICO: Levetiracetam compared to Phenobarbital for epilepsy in Infants (1 to < 36 months) diagnosed with epilepsy

For infants and children 1 month to less than 36 months of age diagnosed **with new-onset epilepsy**, the AES guideline panel **suggests for** the use of levetiracetam rather than phenobarbital. (**Conditional** Recommendation, **Low** Certainty of Evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levetiracetam	Phenobarbital	Relative (95% CI)	Absolute (95% CI)		
Seizure freedom (follow-up: 6 months; assessed with: Freedom from monotherapy failure defined as no second prescribed antiepileptic medication and freedom from seizures beginning within 3 months of initiation of treatment.)												
1[1]	non-randomised studies	serious[a]	not serious	not serious	serious[b]	none	47/117 (40.2%)	6/38 (15.8%)	**OR 4.2** (1.3 to 14.0)[c]	**283 more per 1,000** (from 38 more to 566 more)	⨁⨁◯◯ Low	CRITICAL
Seizure frequency - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Some concern with the risk of unknown confounding factors which may influence the outcomes.
b. Sample size does not meet optimal information size (OIS).
c. Unadjusted OR 3.6 (95% CI 1.5 to 10). Authors performed several additional analyses of these data, and all yielded the same conclusion that LEV was superior to PB. 1. Unadjusted analysis using generalized estimating equations OR 3.6 (95% CI 1.7 to 7.8). 2. Multivariable analysis with adjustment for age at onset, developmental delay, and time from seizure onset to first drug 3.1 (95% CI 1.3 to 7.4). 3. Propensity analysis, no adjustment for covariates, OR 4.2 (95% CI 1.1 to 16). 4. Propensity analysis, with adjustment for age at onset, developmental delay, and time from seizure onset to first drug, OR 4.2 (95% CI 1.3 to 14). 5. A variant of #3 above that excluded early failures, OR 4.8, (95% CI 1.3 to 18), and 6. a variant of #3 above that excluded those who failed monotherapy for reasons other than efficacy, OR=3.6 95% CI 1.2 to 11.

References

1. Grinspan ZM, Shellhaas RA, Coryell J, Sullivan JE, Wirrell EC, Mytinger JR, Gaillard WD, Kossoff EH, Valencia I, Knupp KG, Wusthoff C, Keator C, Ryan N, Loddenkemper T, Chu CJ, Novotny EJ Jr, Millichap J, Berg AT. Comparative Effectiveness of Levetiracetam vs Phenobarbital for Infantile Epilepsy. JAMA Pediatr. 2018;172(4):352-360. doi:10.1001/jamapediatrics.2017.5211

Recommendation I-A-5. Evidence Profile for PICO: Topiramate compared to Carbamazepine for epilepsy in infants (1- <36 months) diagnosed with epilepsy

In infants and children less than 36 months of age diagnosed with epilepsy, the American Epilepsy Society (AES) guideline panel **suggests treatment with either** topiramate or carbamazepine. (**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Carbamazepine	Relative (95% CI)	Absolute (95% CI)		
Seizure Freedom												
1[1]	non-randomised studies	serious[a]	not serious	not serious	very serious[b,c]	none	24/41 (58.5%)	58/105 (55.2%)	**RR 1.06** (0.78 to 1.44)	**33 more per 1,000** (from 122 fewer to 243 more)	⊕◯◯◯ Very low	CRITICAL
Seizure Frequency - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse Events leading to discontinuation												
1[1]	non-randomised studies	serious[a]	not serious	not serious	very serious[b,c]	none	1/41 (2.4%)	7/105 (6.7%)	**RR 0.37** (0.05 to 2.88)	**42 fewer per 1,000** (from 63 fewer to 125 more)	⊕◯◯◯ Very low	CRITICAL
Adverse Events (Anhidrosis, Hyperactivity, Nausea/vomiting, poor oral intake, sleepiness, psychomotor retardation, hair loss, skin rash, liver enzymes, skin rash)												
1[1]	non-randomised studies	serious[a]	not serious	not serious	very serious[b,c]	none	10/41 (24.4%)	18/105 (17.1%)	**RR 1.42** (0.72 to 2.82)	**72 more per 1,000** (from 48 fewer to 312 more)	⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Concerns with the control of critical confounders
b. Study does not meet optimal information size (OIS) requirement (small sample size).
c. Fragile estimate. Confidence intervals cross thresholds of benefit and harm.

References

1. Kim JM, Kwon S, Seo HE, Choe BH, Cho MH, Park SP. Long-term effectiveness and tolerability of topiramate in children with epilepsy under the age of 2 years: 4-year follow-up. J Korean Med Sci. 2009;24(6):1078-1082. doi:10.3346/jkms.2009.24.6.1078

Recommendation I-B-1. See evidence profile 1-A-2.

Recommendation I-B-2. Evidence Profile for PICO: Topiramate compared to no topiramate for epilepsy in infants (1- <36 months) diagnosed with drug-resistant epilepsy

In infants and children less than 36 months of age diagnosed with drug-resistant epilepsy, the AES guideline panel **suggests** treatment with topiramate rather than no topiramate. (**Conditional** Recommendation, **Low** Certainty of Evidence).

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	No topiramate	Relative (95% CI)	Absolute (95% CI)		
Failure to achieve Seizure Freedom												
2[1,2]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	257/318 (80.8%)	(100.0%)	**RR 0.81** (0.77 to 0.85)	**190 fewer per 1,000** (from 230 fewer to 150 fewer)	⊕◯◯◯ Very low	CRITICAL
Seizure Frequency - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Adverse events leading to discontinuation (viral infection, maculo-papular rash, aggravated convulsions, and somnolence).												
2[3,4]	randomised trials	not serious	not serious	not serious	very serious[a,b]	none	4/112 (3.6%) [c]	2/37 (5.4%)	**RR 0.66** (0.13 to 3.46)	**18 fewer per 1,000** (from 47 fewer to 133 more)	⊕⊕◯◯ Low	CRITICAL
Weight Decrease												
2[3,4]	randomised trials	not serious	very serious[d]	not serious	very serious[a]	none	One study (Manitpisitkul 2019) reported 2/50 infants with weight loss due to treatment. Another study (Novotny 2010) found a dose-related association in weight loss observed in patients (3% placebo, 0% for 5 mg/kg/day, 5% for 15 mg/kg/day, and 14% for 25 mg/kg/day).				⊕◯◯◯ Very low	CRITICAL

Vomiting									
2[3,4]	randomised trials	not serious	very serious[d]	not serious	very serious[a]	none	One study (Manitpisitkul 2019) reported that incidence of vomiting increased with dose of topiramate (1/14 (7%) with 3 mg/kg/day, 1/13 (8%) with 5 mg/kg/day, 2/13 (15%) with 15 mg/kg/day, and 3/15 (20%) with 25 mg/kg/day). Another study (Novotny 2010) found no dose response association (5% placebo, 18% for 5 mg/kg/day, 8% for 15 mg/kg/day, and 16% for 25 mg/kg/day)	⊕◯◯◯ Very low	CRITICAL
Upper respiratory tract infection									
2[3,4]	randomised trials	not serious	not serious	not serious	very serious[a]	none	Two studies found a dose related increase in incidence of upper respiratory tract infection. **Novotny 2010**: 5/37 (14%) placebo, 8/38 (21%) with 5 mg/kg/day, and 8/37 (22%) with 15&25 mg/kg/day each. **Manitpisitkul 2019**: 0/14 (0%) with 3 mg/kg/day, 1/13 (8%) with 5 mg/kg/day, 2/13 (15%) with 15 mg/kg/day, and 5/15 (33%) with 25 mg/kg/day.	⊕⊕◯◯ Low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Study does not meet optimal information size (OIS) requirement (small sample size).

b. Wide confidence interval crossing thresholds suggesting appreciable benefit and harm

c. Manitpisitkul et al noted that 3 out of 55 patients discontinued topiramate due to adverse events.

d. inconsistent on dose-response association

References

1. Grosso S, Galimberti D, Farnetani MA, Cioni M, Mostardini R, Vivarelli R, Di Bartolo RM, Bernardoni E, Berardi R, Morgese G, Balestri P. Efficacy and safety of topiramate in infants according to epilepsy syndromes. Seizure. 2005;14(3):183-189. doi:10.1016/j.seizure.2005.01.006

2.Kholin AA, Zavadenko NN, Il'ina ES, Fedonyuk ID, Kolpakchi LM, Khalilov VS, Kosyakova ES. Relationship between the efficacy and safety of topiramate and patients' ages and types of epilepsy. Neurosci Behav Physiol. 2014 Sep, 014-9981-7, 44(7):765-771. doi.org/10.1007/s11055-014-9981-7

3.Novotny E, Renfroe B, Yardi N, Nordii D, Ness S, Wang S, Weber T, Kurland CL, Yuen E, Eerdekens M, Venkatraman L, Nye JS, Ford L. Randomized trial of adjunctive topiramate therapy in infants with drug resistant partial seizures. *Neurology*. 2010;74(9):714-720. doi:10.1212/WNL.0b013e3181d1cd4c

4. Manitpisitkul P, Shalayda K, Todd M, Wang SS, Ness S, Ford L. Pharmacokinetics and safety of adjunctive topiramate in infants (1-24 months) with drug resistant partial-onset seizures: a randomized,multicenter,open-label phase 1 study. Epilepsia. 2013;54(1):156-164. doi:10.1111/epi.12019

Recommendation I-B-3. Evidence Profile for PICO: Lamotrigine compared to no lamotrigine for epilepsy in infants (1- <36 months) diagnosed with drug-resistant epilepsy

In infants and children less than 36 months of age diagnosed with drug-resistant epilepsy, the AES guideline panel **suggests** treatment with lamotrigine rather than no lamotrigine (**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamotrigine	No lamotrigine	Relative (95% CI)	Absolute (95% CI)		
Failure to achieve seizure freedom (follow-up: 48 weeks)												
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	178/204 (87.3%)	(100.0%)	**RR 0.87** (0.83 to 0.92)	**130 fewer per 1,000** (from 170 fewer to 80 fewer)	⊕◯◯◯ Very low	CRITICAL
Seizure Frequency (follow-up: 48 weeks; assessed with: ≥50% seizure frequency reduction)												
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	One study reported a ≥50% seizure frequency reduction from baseline in 62% of patients in a sample of patients (n = 204) consisting of naive and experienced patients. ● Lamotrigine-naïve subgroup(n = 79): 60% ● Lamotrigine-experienced subgroup(n = 125): 63%				⊕◯◯◯ Very low	CRITICAL
Discontinuation due to adverse events (Pneumonia, status epilepticus, rash, pyrexia, death) (follow-up: 48 weeks)												
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	One study reported 9% (18/204) discontinuation during the long-term open-label phase. This includes 7 deaths.				⊕◯◯◯ Very low	CRITICAL

Serious or severe adverse events (Serious bronchitis and status epilepticus) (follow-up: 8 weeks)												
1[2]	randomised trials	not serious	not serious	not serious	very serious[a]	none	2/19 (10.5%)	0/19 (0.0%)	**RR 4.00** (0.19 to 83.04)	**780 more per 1,000** (from 190 more to 830 more)[b]	⊕⊕◯◯ Low	CRITICAL
Serious or severe adverse events (follow-up: 48 weeks)												
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	One study reported the following during the long- term open-label phase: ● Pneumonia: 8% (16/204), ● Status epilepticus: 6% (12/204), ● Complex partial seizures: 6% (12/204), ● Fever: 4% (12/204), ● Convulsion: 3% (6/204), ● Dehydration: 3% (6/204), and ● Gastroenteritis: 3% (12/204)				⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Study does not meet optimal information size (OIS) requirement (small sample size). Fragile estimate

b. Manually calculated

References

1. Piña-Garza JE, Elterman RD, Ayala R, Corral M, Mikati MA, Piña-Garza MJ, Warnock CR, Conklin HS, Messenheimer JA. Long-term tolerability and efficacy of lamotrigine in infants 1 to 24 months old. J Child Neurol. 2008;23(8):853-861. doi:10.1177/0883073808317348

2. Piña-Garza JE, Levisohn P, Gucuyener K, Mikati MA, Warnock CR, Conklin HS, Messenheimer J. Adjunctive lamotrigine for partial seizures in patients aged 1 to 24 months. *Neurology*. 2008;70(22 Pt 2):2099-2108. doi:10.1212/01.wnl.0000285493.08622.35

Recommendation I-B-4. Evidence Profile for PICO: Rufinamide compared to no rufinamide for epilepsy in infants (1- <36 months) diagnosed with drug-resistant epilepsy

In infants and children less than 36 months of age diagnosed with drug-resistant epilepsy, the AES guideline panel suggests the use of rufinamide rather than no rufinamide. (**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rufinamide	No Rufinamide	Relative (95% CI)	Absolute (95% CI)		
Failure to achieve seizure freedom												
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	83/103 (80.6%)	100.0%	**RR 0.81** (0.73 to 0.89)	**190 fewer per 1,000** (from 270 fewer to 110 fewer)	⨁◯◯◯ Very low	CRITICAL
Seizure Frequency per 30 days												
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	103	-[b]	-	MD **360 seizures fewer** (389.65 fewer to 330.35 fewer)	⨁◯◯◯ Very low	CRITICAL
Adverse events leading to treatment discontinuation												
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	One pre/post study reported that 15% (15/103) discontinued due to AEs.				⨁◯◯◯ Very low	CRITICAL
Adverse Events (Somnolence and Irritability)												
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	One pre/post study reported somnolence in 12% (12/103), and irritability in 10% (10/103) of patients.				⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Study does not meet optimal information size (OIS) requirement (small sample size).
b. Baseline seizure frequency was 450 (IQR 150-900) per 30 days

References

1. Tanritanir A, Wang X, Loddenkemper T. Efficacy and Tolerability of Rufinamide in Epileptic Children Younger Than 4 Years. J Child Neurol. 2021;36(4):281-287. doi:10.1177/0883073820967159

Recommendation I-B-5. Evidence Profile for PICO: Stiripentol compared to no stiripentol for epilepsy in infants (1- <36 months) diagnosed with drug-resistant epilepsy

In infants and children less than 36 months of age with drug-resistant epilepsy and Dravet syndrome, the AES guideline panel **suggests** treatment with stiripentol rather than no stiripentol. (**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stiripentol	No Stiripentol	Relative (95% CI)	Absolute (95% CI)		
Seizure Freedom - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Seizure Frequency (follow-up: 104 weeks; assessed with: Physician assessment using 5-point scale)												
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	One study reported that 50/92 (54.4%) showed marked or moderate improvement of seizures on physician assessment. [b]				⨁◯◯◯ Very low	CRITICAL
Any adverse events (Somnolence, ataxia/vertigo, loss of appetite, and weight reduction) (follow-up: 104 weeks)												
1[1]	non-randomised studies	not serious	not serious	not serious[c]	very serious[a]	none	One study reported that 58 out of 95 patients (61%) had at least one adverse drug reaction.				⨁◯◯◯ Very low	CRITICAL

CI: confidence interval

Explanations

a. Study does not meet optimal information size (OIS) requirement (small sample size).

b. The physician in charge comprehensively compared the patient's condition, including the frequency of seizures after the start of STP administration, the duration and the intensity of seizures, and ability to undertake activities of daily living, with those before the start of STP administration, and rated the overall improvement on a 5-point scale (marked, moderate, mild, unchanged, or worsened) or as undetermined according to the impression of each attending physician.

c. Majority of adverse events in the full study cohort (n= 410; Ages 0-19 years) were somnolence, ataxia/vertigo, loss of appetite, and weight reduction.

References

1. Yamada M, Suzuki K, Matsui D, Inoue Y, Ohtsuka Y. Long-term safety and effectiveness of stiripentol in patients with Dravet syndrome: Interim report of a post-marketing surveillance study in Japan. Epilepsy Res. 2021;170:106535. doi:10.1016/j.eplepsyres.2020.106535

Evidence Profiles for PICO questions focused Pharmacological Treatments for infants 1 month to less than 36 months diagnosed with focal or unknown epilepsy for which no recommendation is made

Evidence Profile, PICO: Levetiracetam + Valproate compared to Valproate for epilepsy in infants (1 - < 36 months) diagnosed w/ epilepsy

For infants and children 1 month to less than 36 months of age diagnosed with epilepsy, the AES guideline panel makes no recommendation on the use of levetiracetam plus valproate rather than levetiracetam alone.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levetiracetam + Valproate	Valproate	Relative (95% CI)	Absolute (95% CI)		
Seizure Freedom												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	16/50 (32.0%)	11/50 (22.0%)	**RR 1.45** (0.75 to 2.81)	**99 more per 1,000** (from 55 fewer to 398 more)	⨁⨁◯◯ Low	CRITICAL
Seizure Frequency - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Quality of Life (follow-up: 12 weeks; assessed with: Barthel Index Higher = better)												
1[1]	randomised trials	not serious	not serious	not serious	very serious[b]	none	One study (n = 100) reported QOL scores of scores 84 in patients who received Levetiracetam plus valproate vs 60 in patients who received valproate alone.				⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. 95% CI (0.75 to 2.81) for absolute effect is crossing thresholds of benefit and harm. Also, effect estimate is fragile estimate due to small sample not meeting OIS.

b. Study does not meet optimal information size (OIS) requirement (small sample size).

References

1. Liu Z, Li J, Yang F, Hu Y, Liu J, Hu H, Su W. Sodium valproate combined with levetiracetam in pediatric epilepsy and its influence on NSE, IL-6, hs-CRP and electroencephalogram improvement. Exp Ther Med. 2020;20(3):2043-2048. doi:10.3892/etm.2020.8916

Recommendation II-A. Evidence Profile for PICO: Ketogenic Diet compared to no Ketogenic Diet in infants (1- <36 months) diagnosed with epilepsy

For infants and children 1 month to less than 36 months of age diagnosed with drug-resistant epilepsy, the AES guideline panel **suggests** a ketogenic diet rather than no ketogenic diet. (**Conditional** Recommendation, **Low** Certainty of Evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketogenic Diet	No Ketogenic Diet	Relative (95% CI)	Absolute (95% CI)		
Failure to achieve seizure freedom (follow-up: 3 months)												
5[1,2,3,4,5]	non-randomised studies	not serious	not serious	not serious	not serious	none	281/369 (76.2%)	100.0%	**RR 0.77** (0.72 to 0.82)	**230 fewer per 1,000** (from 280 fewer to 180 fewer)	⊕⊕◯◯ Low	CRITICAL
Failure to achieve seizure freedom (follow-up: 6 months)												
4[1,2,3,5]	non-randomised studies	not serious	not serious	not serious	not serious	none	190/260 (73.1%)	100.0%	**RR 0.74** (0.66 to 0.82)	**260 fewer per 1,000** (from 340 fewer to 180 fewer)	⊕⊕◯◯ Low	CRITICAL
Failure to achieve seizure freedom (follow-up: 12 months)												
4[1,2,5,6]	non-randomised studies	not serious	not serious	not serious	not serious	none	302/367 (82.3%)	100.0%	**RR 0.82** (0.74 to 0.91)	**180 fewer per 1,000** (from 260 fewer to 90 fewer)	⊕⊕◯◯ Low	CRITICAL

Failure to achieve seizure freedom after diet discontinuation (follow-up: 6 months)												
1[2]	non-randomised studies	not serious	not serious	not serious	serious[a]	none	79/100 (79.0%)	100.0%	**RR 0.79** (0.71 to 0.88)	**210 fewer per 1,000** (from 290 fewer to 120 fewer)	⊕◯◯◯ Very low	CRITICAL
> 90% Seizure Reduction (follow-up: 3 months)												
4[2,3,4,7]	non-randomised studies	not serious	not serious	not serious	serious[a]	none	Four pre/post studies reported number of patients with ≥90% seizure reduction rates: ● **Liu 2021**: 7/41 (17%) ● **Dressler 2015**: 9/115 (8%) ● **Wu 2016**: 3/40 (7.5%) ● **Kim 2019**: 3/109 (3%)				⊕◯◯◯ Very low	CRITICAL
> 90% Seizure Reduction (follow-up: 6 months)												
3[2,3,7]	non-randomised studies	not serious	not serious	not serious	serious[a]	none	Three pre/post studies reported number of patients with ≥90% seizure reduction rates at 6 months: ● **Liu 2021**: 8/41 (17%) ● **Dressler 2015**: 11/115 (8%) ● **Wu 2016**: 2/40 (7.5%)				⊕◯◯◯ Very low	CRITICAL
> 90% Seizure Reduction (follow-up: 12 months)												
2[2,7]	non-randomised studies	not serious	not serious	not serious	serious[a]	none	Two pre/post studies reported number of patients with ≥90% seizure reduction rates at 12 months: ● **Liu 2021**: 9/41 (17%) ● **Dressler 2015**: 6/115 (8%)				⊕◯◯◯ Very low	CRITICAL
> 90% Seizure Reduction After Ketogenic Diet Withdrawal (follow-up: 6 months)												
1[2]	non-randomised studies	not serious	not serious	not serious	serious[a]	none	One pre/post study (**Dressler 2015**) reported (n = 14/100) 14% of patients maintained > 90% seizure frequency reduction months after diet was withdrawn.				⊕◯◯◯ Very low	CRITICAL

> 50% Seizure Reduction (follow-up: 3 months)									
6[1,2,3,4,5,7]	non-randomised studies	not serious	not serious	not serious	serious[a]	none	Six pre/post studies reported number of patients with ≥50% seizure reduction rates at 3 months: ● **Liu 2021**: 21/41 (17%) ● **Dressler 2015**: 31/115 (8%) ● **Hoon 2005**: 12/49 ● **Wu 2016**: 6/40 (7.5%) ● **Kim 2019**: 19/109 (3%) ● **Armeno 2021**: 35/56 (53%)	⊕◯◯◯ Very low	CRITICAL
> 50% Seizure Reduction (follow-up: 6 months)									
5[1,2,3,5,7]	non-randomised studies	not serious	not serious	not serious	serious[a]	none	Five pre/post studies reported number of patients with ≥50% seizure reduction rates at 6 months: ● **Liu 2021**: 24/41 (17%) ● **Dressler 2015**: 23/115 (8%) ● **Hoon 2005**: 9/49 (18%) ● **Wu 2016**: 6/40 (7.5%) ● **Armeno 2021**: 34/56 (60%)	⊕◯◯◯ Very low	CRITICAL
> 50% Seizure Reduction (follow-up: 12 months)									
4[1,2,5,7]	non-randomised studies	not serious	not serious	not serious	serious[a]	none	Four pre/post studies reported number of patients with ≥50% seizure reduction rates at 12 months: ● **Liu 2021**: 25/41 (17%) ● **Dressler 2015**: 20/115 (8%) ● **Hoon 2005**: 3/49 (6%) ● **Armeno 2021**: 14/56 (25%)	⊕◯◯◯ Very low	CRITICAL
> 50% Seizure Reduction After Ketogenic Diet Withdrawal (follow-up: 6 months)									
1[2]	non-randomised studies	not serious	not serious	not serious	serious[a]	none	One pre/post study (**Dressler 2015**) reported (n = 7/100) 7% of patients maintained > 50% seizure frequency reduction months after diet was withdrawn.	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Study does not meet optimal information size (OIS) requirement (small sample size).

References

1. Dou, X., Wang, Z., Li, X, Wang Y, Jia S, Song X, Wang D. Efficacy and tolerability of ketogenic diet therapy in 55 Chinese children with drug-resistant epilepsy in Northwest China. Acta Epileptologica 4, 10 (2022). https://doi.org/10.1186/s42494-021-00076-8

2. Armeno M, Verini A, Caballero E, Cresta A, Valenzuela GR, Caraballo R. Long-term effectiveness and adverse effects of ketogenic diet therapy in infants with drug-resistant epilepsy treated at a single center in Argentina. Epilepsy Res. 2021;178:106793. doi:10.1016/j.eplepsyres.2021.106793

3. Tong X, Deng Y, Liu L, Tang X, Yu T, Gan J, Cai Q, Luo R, Xiao N. Clinical implementation of ketogenic diet in children with drug-resistant epilepsy: Advantages, disadvantages, and difficulties. Seizure. 2022;99:75-81. doi:10.1016/j.seizure.2022.04.015

4. Dressler A, Trimmel-Schwahofer P, Reithofer E, Gröppel G, Mühlebner A, Samueli S, Grabner V, Abraham K, Benninger F, Feucht M. The ketogenic diet in infants--Advantages of early use. Epilepsy Res. 2015;116:53-58. doi:10.1016/j.eplepsyres.2015.06.015

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6. Kim SH, Shaw A, Blackford R, Lowman W, Laux LC, Millichap JJ, Nordli DR Jr. The ketogenic diet in children 3 years of age or younger: a 10-year single-center experience. Sci Rep. 2019;9(1):8736. Published 2019 Jun 19. doi:10.1038/s41598-019-45147-6

7. Kang HC, Kim YJ, Kim DW, Kim HD. Efficacy and safety of the ketogenic diet for intractable childhood epilepsy: Korean multicentric experience. Epilepsia. 2005;46(2):272-279. doi:10.1111/j.0013-9580.2005.48504.x

8. Suo C, Liao J, Lu X, Fang K, Hu Y, Chen L, Cao D, Huang T, Li B, Li C. Efficacy and safety of the ketogenic diet in Chinese children. Seizure. 2013;22(3):174-178. doi:10.1016/j.seizure.2012.11.014

9. Liu Y, Wan J, Gao Z, Xu L, Kong L. Ketogenic diet and growth in Chinese infants with refractory epilepsy. Asia Pac J Clin Nutr. 2021;30(1):113-121. doi:10.6133/apjcn.202103_30(1).0014

Figure II-A-1. Forest Plot for Failure to achieve seizure freedom at 3 months for PICO: Ketogenic Diet compared to No Ketogenic Diet in infants (1- <36 months) diagnosed with epilepsy

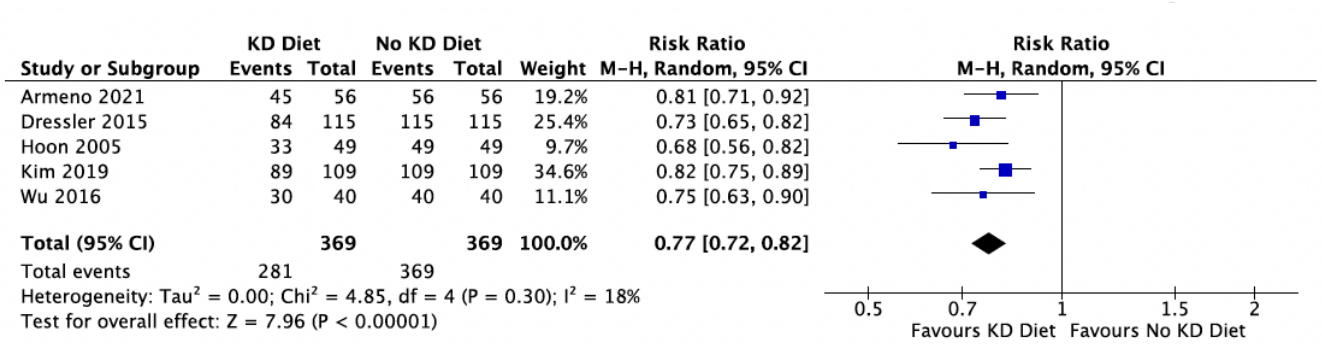


Figure II-A-2. Forest Plots for Failure to achieve seizure freedom at 6 months for PICO: Ketogenic Diet compared to No Ketogenic Diet in infants (1- <36 months) diagnosed with epilepsy

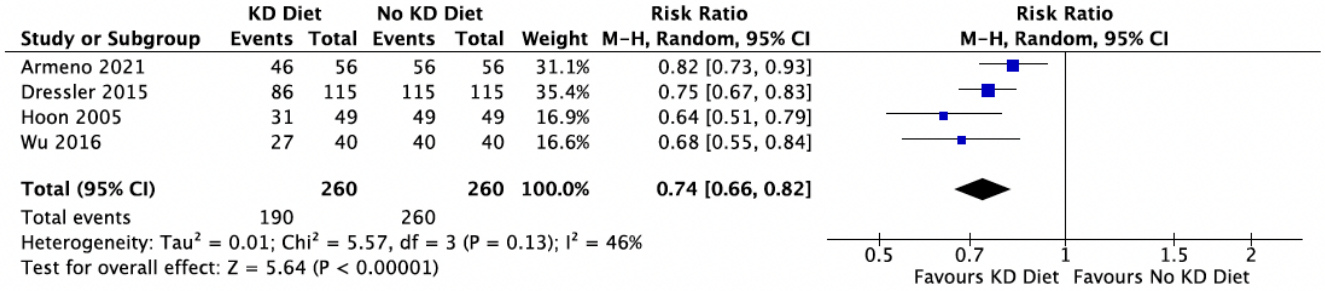
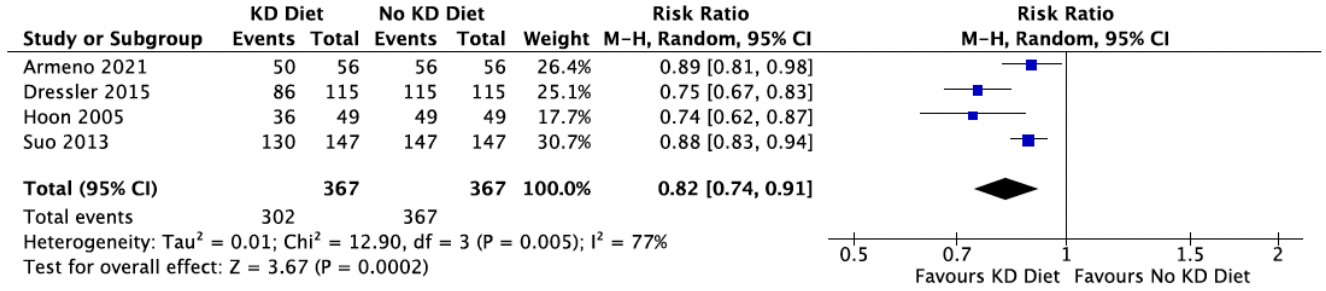


Figure II-A-3. Forest Plots for Failure to achieve seizure freedom at 12 months for PICO: Ketogenic Diet compared to No Ketogenic Diet in infants (1- <36 months) diagnosed with epilepsy



Recommendation II-B. Evidence Profile for PICO: Ketogenic Diet compared to Modified Atkins Diet in infants (1- <36 months) diagnosed with drug-resistant epilepsy

For infants and children 1 month to less than 36 months of age diagnosed with drug-resistant epilepsy, the AES guideline panel **suggests** against the use of a modified Atkins diet. (**Conditional** Recommendation, **Low** Certainty of Evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketogenic Diet	Modified Atkins Diet	Relative (95% CI)	Absolute (95% CI)		
Seizure Freedom (follow-up: 3 months)												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	9/17 (52.9%)	4/20 (20.0%)	**RR 2.65** (0.99 to 7.08)	**330 more per 1,000** (from 2 fewer to 1,000 more)	⊕⊕◯◯ Low	CRITICAL
Seizure Freedom (follow-up: 6 months)												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	9/17 (52.9%)	5/20 (25.0%)	**RR 2.12** (0.88 to 5.11)	**280 more per 1,000** (from 30 fewer to 1,000 more)	⊕⊕◯◯ Low	CRITICAL
> 90% Seizure Reduction or Seizure Freedom (follow-up: 3 months)												
1[1]	randomised trials	not serious	not serious	not serious[b]	very serious[a]	none	9/17 (52.9%)	5/20 (25.0%)	**RR 2.12** (0.88 to 5.11)	**280 more per 1,000** (from 30 fewer to 1,000 more)	⊕⊕◯◯ Low	CRITICAL

> 90% Seizure Reduction or Seizure Freedom (follow-up: 6 months)												
1[1]	randomised trials	not serious	not serious	not serious[b]	very serious[a]	none	10/17 (58.8%)	7/20 (35.0%)	**RR 1.68** (0.82 to 3.44)	**238 more per 1,000** (from 63 fewer to 854 more)	⊕⊕◯◯ Low	CRITICAL
> 50% Seizure Reduction or Seizure Freedom (follow-up: 3 months)												
1[1]	randomised trials	not serious	not serious	not serious[b]	very serious[a]	none	10/17 (58.8%)	8/20 (40.0%)	**RR 1.47** (0.75 to 2.87)	**188 more per 1,000** (from 100 fewer to 748 more)	⊕⊕◯◯ Low	CRITICAL
> 50% Seizure Reduction or Seizure Freedom (follow-up: 6 months)												
1[1]	randomised trials	not serious	not serious	not serious[b]	very serious[a]	none	10/17 (58.8%)	9/20 (45.0%)	**RR 1.31** (0.70 to 2.45)	**140 more per 1,000** (from 135 fewer to 653 more)	⊕⊕◯◯ Low	CRITICAL
Adverse Events Leading to Diet Discontinuation												
2[1,2]	randomised trials	not serious	not serious	not serious[c]	very serious[ae]	none	21/61 (34.4%)	24/68 (35.3%)	**RR 0.94** (0.59 to 1.49)	**21 fewer per 1,000** (from 145 fewer to 173 more)	⊕⊕◯◯ Low	CRITICAL

Adverse Events Reported									
1[2]	randomised trials	not serious	not serious	not serious	very serious[a]	none	The MAD group (n = 15) showed vomiting in 30.8%, constipation in 15.4%, diarrhea in 15.4%, and dysphagia in 23.1% of patients when compared with 0%, 25%, 12.5%, and 12.5% in the classic 4:1 KD group (n = 10). [d,e]	⊕⊕◯◯ Low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Study does not meet optimal information size (OIS) requirement (small sample size).

b. includes children who reported seizure freedom

c. Kim (2016) events are from age 1-18 years

d. QUESTION FOR CHAIRS - Which of these need to be presented quantitatively?

e. Kim (2016) also reports these outcomes (age range 0-18)

References

1. Kim JA, Yoon JR, Lee EJ, Lee JS, Kim JT, Kim HD, Kang HC. Efficacy of the classic ketogenic and the modified Atkins diets in refractory childhood epilepsy. Epilepsia. 2016;57(1):51-58. doi:10.1111/epi.13256

2. El-Rashidy OF, Nassar MF, Abdel-Hamid IA, Shatla RH, Abdel-Hamid MH, Gabr SS, Mohamed SG, El-Sayed WS, Shaaban SY. Modified Atkins diet vs classic ketogenic formula in intractable epilepsy. Acta Neurol Scand. 2013;128(6):402-408. doi:10.1111/ane.12137

Recommendation II-C. Evidence Profile for PICO: Modified Atkins Diet compared to Low glycemic index treatment in infants (1-36 months) diagnosed with epilepsy

For infants and children 1 month to less than 36 months of age diagnosed with drug-resistant epilepsy, the AES guideline panel **suggests** a ketogenic diet rather than a modified Atkins diet. (**Conditional** recommendation, **Low** certainty of evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modified Atkins Diet	Low glycemic index treatment	Relative (95% CI)	Absolute (95% CI)		
Seizure freedom (follow-up: 12 weeks)												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	5/30 (16.7%)	2/30 (6.7%)	**RR 2.50** (0.53 to 11.89)	**100 more per 1,000** (from 31 fewer to 726 more)	⨁⨁◯◯ Low	CRITICAL
> 90% Seizure reduction (follow-up: 12 weeks)												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	9/30 (30.0%)	4/30 (13.3%)	**RR 2.25** (0.78 to 6.52)	**167 more per 1,000** (from 29 fewer to 736 more)	⨁⨁◯◯ Low	CRITICAL
50-90% Seizure reduction (follow-up: 12 weeks)												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	13/30 (43.3%)	22/30 (73.3%)	**RR 0.59** (0.37 to 0.94)	**301 fewer per 1,000** (from 462 fewer to 44 fewer)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modified Atkins Diet	Low glycemic index treatment	Relative (95% CI)	Absolute (95% CI)		
Serious adverse effects (Significant weight loss, severe respiratory tract infection requiring hospitalization)												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	2/30 (6.7%)	2/30 (6.7%)	**RR 1.00** (0.15 to 6.64)	**0 fewer per 1,000** (from 57 fewer to 376 more)	⊕⊕◯◯ Low	CRITICAL
Lethargy												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	16/30 (53.3%)	20/30 (66.7%)	**RR 0.80** (0.53 to 1.22)	**133 fewer per 1,000** (from 313 fewer to 147 more)	⊕⊕◯◯ Low	CRITICAL
Constipation												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	15/30 (50.0%)	9/30 (30.0%)	**RR 1.67** (0.87 to 3.20)	**201 more per 1,000** (from 39 fewer to 660 more)	⊕⊕◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modified Atkins Diet	Low glycemic index treatment	Relative (95% CI)	Absolute (95% CI)		
Vomiting												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	5/30 (16.7%)	3/30 (10.0%)	**RR 1.67** (0.44 to 6.36)	**67 more per 1,000** (from 56 fewer to 536 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Fragile estimate due to sample not meeting the optimal information size (OIS) (n=60).

References

1. Gupta S, Dabla S, Kaushik JS. Modified Atkins Diet vs Low Glycemic Index Treatment for Drug-Resistant Epilepsy in Children: An Open Label, Randomized Controlled Trial. Indian Pediatr. 2021;58(9):815-819.

Recommendation II-D. Evidence Profile for PICO: Modified Atkins Diet compared to Low glycemic index treatment in infants (1-36 months) diagnosed with epilepsy

For infants and children 24 months to less than 36 months of age diagnosed with **drug-resistant epilepsy**, the AES guideline panel **suggests** a ketogenic diet rather than a modified Atkins diet. (**Conditional** recommendation, **Low** certainty of evidence)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modified Atkins Diet	Low glycemic index treatment	Relative (95% CI)	Absolute (95% CI)		
Seizure freedom (follow-up: 12 weeks)												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	5/30 (16.7%)	2/30 (6.7%)	**RR 2.50** (0.53 to 11.89)	**100 more per 1,000** (from 31 fewer to 726 more)	⊕⊕◯◯ Low	CRITICAL
> 90% Seizure reduction (follow-up: 12 weeks)												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	9/30 (30.0%)	4/30 (13.3%)	**RR 2.25** (0.78 to 6.52)	**167 more per 1,000** (from 29 fewer to 736 more)	⊕⊕◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modified Atkins Diet	Low glycemic index treatment	Relative (95% CI)	Absolute (95% CI)		
50-90% Seizure reduction (follow-up: 12 weeks)												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	13/30 (43.3%)	22/30 (73.3%)	**RR 0.59** (0.37 to 0.94)	**301 fewer per 1,000** (from 462 fewer to 44 fewer)	⊕⊕◯◯ Low	CRITICAL
Serious adverse effects (Significant weight loss, severe respiratory tract infection requiring hospitalization)												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	2/30 (6.7%)	2/30 (6.7%)	**RR 1.00** (0.15 to 6.64)	**0 fewer per 1,000** (from 57 fewer to 376 more)	⊕⊕◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modified Atkins Diet	Low glycemic index treatment	Relative (95% CI)	Absolute (95% CI)		
Lethargy												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	16/30 (53.3%)	20/30 (66.7%)	**RR 0.80** (0.53 to 1.22)	**133 fewer per 1,000** (from 313 fewer to 147 more)	⊕⊕◯◯ Low	CRITICAL
Constipation												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	15/30 (50.0%)	9/30 (30.0%)	**RR 1.67** (0.87 to 3.20)	**201 more per 1,000** (from 39 fewer to 660 more)	⊕⊕◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modified Atkins Diet	Low glycemic index treatment	Relative (95% CI)	Absolute (95% CI)		
Vomiting												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	5/30 (16.7%)	3/30 (10.0%)	**RR 1.67** (0.44 to 6.36)	**67 more per 1,000** (from 56 fewer to 536 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Fragile estimate due to sample not meeting the optimal information size (OIS) (n=60).

References

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Recommendation III-A. Evidence Profile, PICO: Hemispherectomy/Hemispherotomy compared to No hemispherectomy/ hemispherotomy in Infants (1 to <36 months) diagnosed with unilateral drug-resistant epilepsy

For infants 1 month to less than 36 months of age diagnosed with lateralizing drug-resistant epilepsy, secondary to select pathologies, the AES guideline panel makes a **strong recommendation for** hemispherectomy/hemispherotomy surgery. (**Strong** recommendation, **Low** certainty of evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hemispherectomy /Hemispherotomy	No hemispherectomy/ hemispherotomy	Relative (95% CI)	Absolute (95% CI)		
Failure to achieve seizure freedom (follow-up: range 6 months to 5 years; assessed with: Engel 1a/ILAE I)												
13[1,2,3,4,5,6,7,8,9,10,11,12,13,14]	non-randomised studies	not serious	not serious[a]	not serious	not serious[b]	strong association	90/306 (29.4%)	(100.0%)	**RR 0.32** (0.19 to 0.55)	**680 fewer per 1,000** (from 810 fewer to 450 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
Favorable outcome Engel I or II												
9[1,5,7,8,10,11,14,15,16]	non-randomised studies	not serious	not serious	not serious	serious[b]	none	Nine non-randomized studies reported on Engel class I or II in patients who underwent hemispherectomy or hemispherotomy: • **Iwasaki 2015**: 8/10 (80%) • **Kadish 2019:** 12/22 (54.5%) • **Kumar 2015**: 14/16 (88%) • **Lettori 2007**: 9/10 (90%) • **Pinto 2014**: 8/10 (80%) • **Steinbok 2009**: 35/48 (73%) • **Pepper 2022**: 11/12 (92%) • **Ko 2022**: 22/22 (100%) • **Wang 2022**: 45/46 (98%)				⊕◯◯◯ Very low	CRITICAL
Favorable outcome ILAE I to IV												
3[4,6,9]	non-randomised studies	not serious	not serious	not serious	serious[b]	none	Three studies reported on ILAE I to IV outcome after surgery: • **Otsuki 2013**: 13/18 (72%) • **Roth 2021**: 37/43 (86%) • **Schramm 2012**: 16/21 (76%) - ILAE I				⊕◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hemispherectomy /Hemispherotomy	No hemispherectomy/ hemispherotomy	Relative (95% CI)	Absolute (95% CI)		
Surgical complications												
3[8,10,15]	non-randomised studies	not serious	not serious	not serious	very serious[b]	none	• One study (Iwasaki 2021) reported that 2/27 (7%) patients who underwent hemispherectomy formed cysts and 6/27 (22%) patients developed hydrocephalus as a surgical complication. • Another study (Wang 2022) reported that 3/46 (7%) developed postoperative complications. • The third study (Pepper 2022) reported 1/12 (8%) developed hygroma/postop subdural effusion; 11/12 (92%) need blood transfusions, and 2/12 developed pseudomeningocele.			⊕◯◯◯ Very low	CRITICAL
Surgical Mortality												
2[10,15]	non-randomised studies	not serious	not serious	not serious	very serious	none	Two studies reported mortality: • One study (Kumar 2015) reported 1 death (of 16 procedures); post-operatively the infant had drug resistant seizures and care was withdrawn. • Another study (Cook 2004 and Jonas 2004) reported 1 death (of 55 procedures) postoperatively due to shunt failure many months after surgery.			⊕◯◯◯ Very low	CRITICAL
Developmental assessment												
5[1,3,7,8,13]	non-randomised studies	not serious	not serious	not serious	very serious[b]	none	Five studies reported on developmental outcomes in patients postoperatively: Loddenkemper 2007: (n=14) **Median Developmental age (Using Bayley scale)** • Preop: 3 months (mean 5.83 months) • Postop: 9 months (mean 11.94 months). **Developmental Quotient (DQ)** • Preop: Median: 37 (range 0-92) • Postop: Median: 49 (range 2-92) **Developmental delays** • Preop: 22 infants • Postop: 18 infants Jonas 2004: (n=19) **Vineland DQ** • Difference 6 to 24 months postop: 9.1 (SD=16)			⊕◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hemispherectomy /Hemispherotomy	No hemispherectomy/ hemispherotomy	Relative (95% CI)	Absolute (95% CI)		
							Spoken language rank (SLR)- • Preop: 0.33±0.5 • Postop: 1.4±1.8 Lettori 2007: (n=19) **Functional status**: • Preoperative: Unable to assess at baseline (8/19) Dependent (2/19) • Postoperative: (7.7 years, 2.1 to 11.2) Dependent (6/19) Semi-independent (3/19) Independent (1/19) Pepper 2022 (n=11) **VABS score** • COM Domain - Postop: 49.03 Preop: 70.14 • DLS Domain - Postop: 57.63 Preop: 68.71 • SOC Domain - Postop: 65.55 Preop: 74.71 • ABC Domain - Postop: 57.72 Preop: 71.67 • MOT Domain - Postop: 38.4 Preop: 64.14 Ko 2022: **VABS (ABC) [n=13]** • Preop: Median 65 (IQR: 60-74; Range: 34-81) • Postop: Median 62(IQR:50-70; Range: 39-76) • Change: Median -2 (-6 -7; Range: -21 - 11) **Wechsler intelligence scale (FSIQ) [n=5]** • Preop: Median 62 (IQR: 61-65; Range: 58-71) • Postop: Median 62(IQR:58-67; Range: 50-70) • Change: Median -1 (-4 to 4; Range: -15 to 10)				

CI: confidence interval; **RR:** risk ratio

Explanations

a. Statistical heterogeneity detected (I2=85%). Pinto 2014 appears to be the biggest contributor of heterogeneity.

b. Study does not meet optimal information size (OIS) requirement (small sample size).

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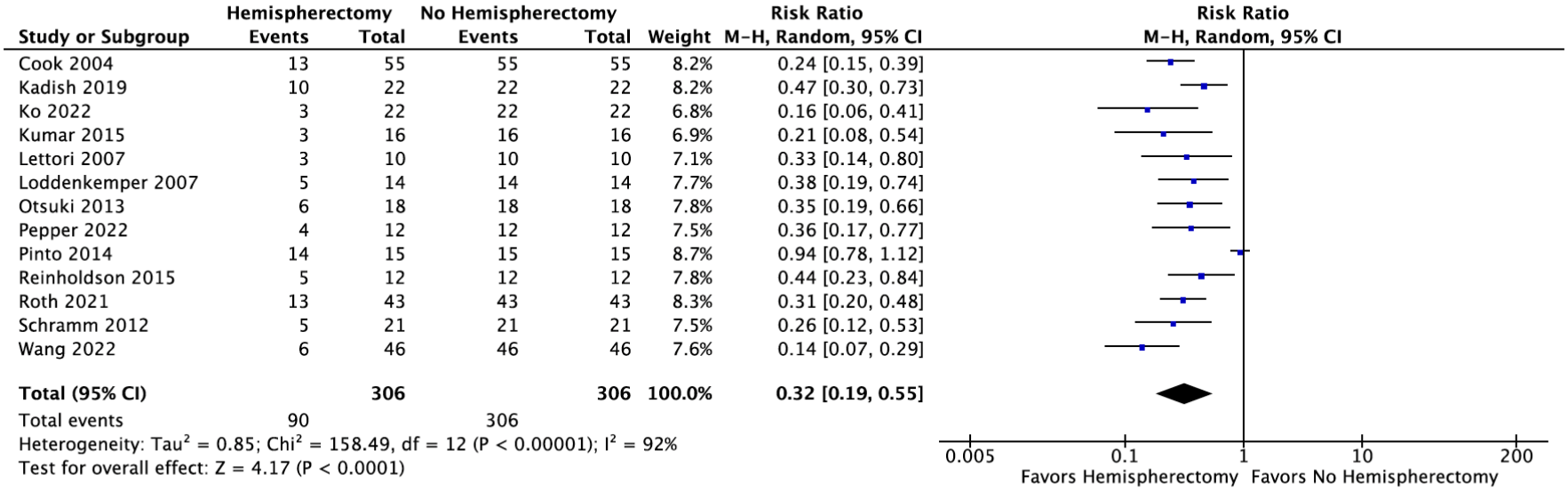
Figure III-A-1. Forest Plot for Failure to Achieve Seizure Freedom for PICO: Hemispherectomy/Hemispherotomy compared to No hemispherectomy/ hemispherotomy in Infants (1 to <36 months) diagnosed with unilateral drug resistant epilepsy

Forest Plot: Failure to Achieve Seizure Freedom



Recommendation III-B. Evidence Profile, PICO: Intralobar, multilobar, posterior disconnections compared to No resections in Infants (1 month to <36 months) diagnosed with epilepsy

For infants and children 1 month to less than 36 months of age diagnosed with **drug-resistant focal or lesional epilepsy**, the AES guideline panel **recommends** intralobar, multilobar, or focal resections or posterior disconnections rather than no intralobar, multilobar, or focal resections or posterior disconnections. (**Strong** recommendation, **Very Low** certainty of evidence).

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intralobar, multilobar, posterior disconnections	No resections	Relative (95% CI)	Absolute (95% CI)		
Failure to achieve seizure freedom (follow-up: range 3 months to 6 years)												
8[1,2,3,4,5,6,7,8]	non-randomised studies	not serious	not serious	not serious	not serious[a]	none	51/164 (37.2%)	100.0%	**RR 0.42** (0.34 to 0.53)	**580 fewer per 1,000** (from 660 fewer to 470 fewer)	⨁⨁◯◯ Low	CRITICAL
Favorable outcome ILAE I to IV (follow-up: mean 2 years)												
1[2]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	One study reported on patients who achieved ILAE I to IV after resection: • **Roth 2021** (focal resection/lobectomy) - 15/16 (94%)				⨁◯◯◯ Very low	CRITICAL
Favorable Engel I or II (follow-up: range 3 months to 6 years)												
5[3,4,9,10]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	Five pre/post studies reported on patients who achieved favorable Engel I or II after resection: • **Kadish 2019** (intralobar or multilobar resection): 16/26 (62%) • **Maton 2007** (temporal lobe resection): 11/ 13 (85%) • **Steinbok 2009** (lesionectomy/cortical resection): 52//58 (90%) • **Sugimoto 1999** (focal cortical resection): 5/10 (50%) • **Wang 2022** (focal resection): 44/44 (100%)				⨁◯◯◯ Very low	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intralobar, multilobar, posterior disconnections	No resections	Relative (95% CI)	Absolute (95% CI)		
Favorable outcome (50% or more seizure frequency reduction) (follow-up: range 6 months to 2 years)												
2[6,7]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	Two studies reported on patients who achieved 50% or greater seizure frequency reduction: • **Loddenkemper 2007** (focal resection) - 10/10 (100%) • **Reinholdson 2015** (temporal/frontal resection) - 20/24 (83%)				⊕◯◯◯ Very low	CRITICAL
Hydrocephalus												
1[5]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	1 study (**Sugimoto 1999**) reported 3/10 (30%) cases of hydrocephalus after cortical resection.				⊕◯◯◯ Very low	CRITICAL
Postoperative complications												
1[3]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	1 study **(Wang 2022**) reported that 2/44 (4.5%) patients who underwent focal resection developed postoperative complications. Khalbern – Include data on 3 strokes				⊕◯◯◯ Very low	CRITICAL
Developmental delay												
2[5,7]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	One study (Loddenkemper 2007) reported developmental measure in patients before and after surgery: **Median Developmental age (Using Bayley scale)** • Preop: 3 months (mean 5.83 months) • Postop: 9 months (mean 11.94 months). **Developmental Quotient (DQ)** • Preop: Median: 37 (range 0-92) • Postop: Median: 49 (range 2-92) **Developmental delays** • Preop: 22 infants • Postop: 18 infants One study (**Sugimoto 1999**) reported the number of patients preop and postop with developmental delays:				⊕◯◯◯ Very low	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intralobar, multilobar, posterior disconnections	No resections	Relative (95% CI)	Absolute (95% CI)		
							Preop: • Delay:8/10 (80%) **Postop**: • Improved: 4/9 (44%) • Good: 2/9 (22%) • Severe delay: 1/9 (11%)					

CI: confidence interval; **RR:** risk ratio

Explanations

a. Study does not meet optimal information size (OIS) requirement (small sample size).

References

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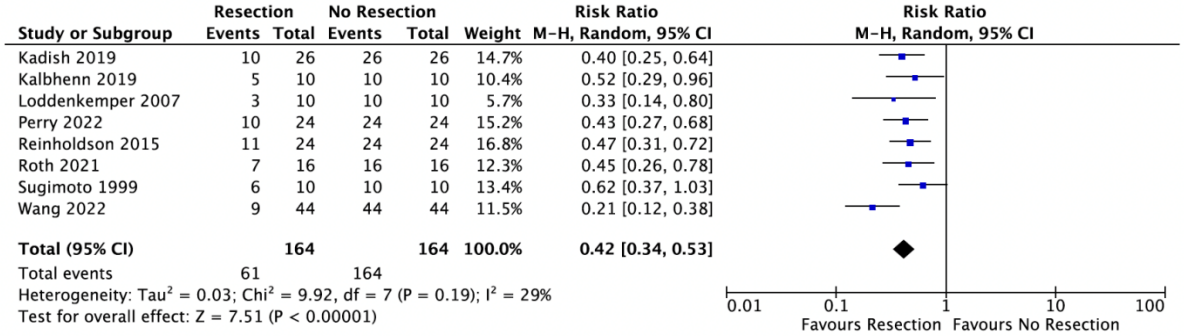
Figure III-B-1. Forest Plot, Failure to Achieve Seizure Freedom for PICO: Intralobar, multilobar, posterior disconnections compared to No resections in Infants (1 month to <36 months) diagnosed with epilepsy



Recommendation III-C. Evidence Profile, PICO: Supratentorial brain tumor resection compared to No resection for Infants (1 month to <36 months) diagnosed with epilepsy

For infants and children 1 month to less than 36 months of age diagnosed with **tumor-related epilepsy**, the AES guideline panel **suggests** for supratentorial brain tumor resection rather than no supratentorial tumor resection. (**Conditional** recommendation, **Very Low** certainty of evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Supratentorial brain tumor resection	No resection	Relative (95% CI)	Absolute (95% CI)		
Seizure Freedom - not reported												
-	-	-	-	-	-	-					-	CRITICAL
Favorable outcome (Engel I or II) (follow-up: range 1 years to 8 years)												
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	One pre/post study (Gaggero 2009) reported the number of patients who achieved Engel I or II at 1, 4, or 8 years after surgery: • 1 year: 16/20 [80%] (9 - Engel I; 7 - Engel II) • 4 years: 16/20 [80%] (11 - Engel I; 5- Engel II) • 8 years: 13/17 [76%] (9 - Engel I; 4 - Engel II)				⊕◯◯◯ Very low	CRITICAL
Mortality (follow-up: range 1 years to 8 years)												
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	One study (Gaggero 2009) reported 3/20 deaths from tumor recurrence[b].				⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval

Explanations

a. Study does not meet optimal information size (OIS) requirement (small sample size).

b. Deaths were due to metastasis of tumors and not as a result of seizures.

References

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Evidence Profiles for PICO questions focused Pharmacological Treatments for infants 1 month to less than 36 months diagnosed with focal or unknown epilepsy for which no recommendation is made

Table III-D. Evidence Profile, PICO: Vagus nerve stimulator (VNS) placement compared to No vagus nerve stimulator (VNS) for infant (1 month to <36 months) diagnosed with epilepsy

For infants and children 1 month to less than 36 months of age diagnosed with **epilepsy**, the AES guideline panel makes **no recommendation for or against** the use of VNS. **(Knowledge Gap)**

Certainty assessment							Impact	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Seizure freedom (follow-up: range 3 months to 24 months)									
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	One study (Abdelmoity 2021) reported the number of patients who achieved seizure freedom after VNS placement at 3,6,12,18 and 24 months: • **3 months**: 3/32 [9%] (90 fewer failures to achieve seizure freedom per 1000 patients; 95% CI: 200 fewer to 30 more) • **6 months**: 5/44 [11%] (110 fewer failures to achieve seizure freedom per 1000 patients; 95% CI: 10 to 210 fewer) • **12 months**: 4/37 [11%] (110 fewer failures to achieve seizure freedom per 1000 patients; 95% CI: 210 fewer to 10 more) • **18 months**: 5/24 [21%] (200 fewer failures to achieve seizure freedom per 1000 patients; 95% CI: 10 to 360 fewer) • **24 months**: 4/23 [17%] (170 fewer failures to achieve seizure freedom per 1000 patients; 95% CI: 320 fewer to 10 more)	⨁◯◯◯ Very low	CRITICAL
Decrease in seizure frequency (follow-up: range 3 months to 24 months)									
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	One study (Abdelmoity 2021) reported the decrease in seizure frequency after VNS placement at 3,6,12, 18and 24 months: • **3 months**: 18/32 [56%] • **6 months**: 32/44 [73%] • **12 months**: 29/37 [78%] • **18 months**: 18/24 [75%]	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							Impact	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
							• **24 months**: 19/23 [83%]		
Increase in seizure frequency (follow-up: range 3 months to 24 months)									
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	One study (Abdelmoity 2021) reported the increase in seizure frequency after VNS placement at 3,6,12,18 and 24 months: • **3 months**: 4/32 [13%] • **6 months**: 3/44 [7%] • **12 months**: 6/37 [16%] • **18 months**: 5/24 [21%] • **24 months**: 3/23 [13%]	⨁◯◯◯ Very low	CRITICAL
Cognitive outcome									
1[1]	non-randomised studies	not serious	not serious	not serious	very serious[a]	none	One study (Abdelmoity 2021) reported the changes in cognitive outcomes at 3 and 24 months: **Attention** • **3 months** (n=32): 8 improved, 2 no improvement, 22 no data available • **24 months** (n=23): 12 improved, 1 no improvement, 10 no data available **Academic performance** • **3 months** (n=32): 4 improved, 1 no improvement, 27 no data available • **24 months** (n=23): 7 improved, 2 no improvement, 14 no data available **Developmental Gains** • **3 months** (n=32): 7 improved, 5 no improvement, 20 no data available • **24 months** (n=23): 11 improved, 4 no improvement, 8 no data available **Sleep** • **3 months** (n=32): 9 improved, 4 no improvement, 19 no data available • **24 months** (n=23): 11 improved, 3 no improvement,	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							Impact	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
							9 no data available **Alertness** • **3 months** (n=32): 8 improved, 2 no improvement, 22 no data available • **24 months** (n=23): 12 improved, 2 no improvement, 9 no data available		

CI: confidence interval

Explanations

a. Study sample size does not meet optimal information size.

References

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