AMERICAN EPILEPSY SOCIETY

Management of Infantile Epilepsy

An educational slide set — American Epilepsy Society Clinical Practice Guideline (2026)

Evidence-based recommendations for infants 1 month to <36 months of age

American Epilepsy Society Clinical Practice Guideline: Infantile Epilepsy

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Scope

- Evidence-based recommendations for pharmacological, dietary, and surgical therapy of epilepsy in infants and children 1 month to <36 months of age.
- **West syndrome and infantile spasms are excluded,** a separate treatment guidance already exists for infantile epileptic spasms.
- Multidisciplinary panel including epileptologists, neurosurgeons, pharmacists, dietitians, and parent/caregiver representatives.
- Updated a PCORI-funded AHRQ/ECRI systematic review using GRADE methodology; added studies through September 2025.

How were these guidelines developed?

Evidence base

- Updated systematic review synthesizing 45 prior studies with new evidence identified through September 2025 (6248 records screened).
- 55 studies included: 18 pharmacotherapy, 13 dietary, 24 surgical.

PICO questions

- Each question specifies Population, Intervention, Comparator, and patient-important Outcomes (e.g., seizure freedom, adverse events).

GRADE approach

- Certainty of evidence rated from high to very low based on risk of bias, consistency, directness, precision, and publication bias.
- Recommendations balance benefits, harms, patient values, feasibility, equity, and cost.

How to interpret the recommendations

Strong recommendation: "the panel recommends"

- Most individuals would want the recommended course of action; only a small proportion would not.
- Clinicians: most patients should follow this course; formal decision aids usually not needed.

Conditional recommendation: "the panel suggests"

- The majority would want the suggested course, but many would not.
- Clinicians: different choices will be appropriate for different patients; shared decision-making and decision aids are valuable.

Note: Most recommendations in this guideline are conditional and based on low or very low certainty of evidence. Only two recommendations, both surgical, are strong.

Objectives

By the end of this session, you should be able to:

- Describe recommended first- and second-line antiseizure medications for infants with new-onset epilepsy.
- Apply guidance on drug choice by seizure type and etiology, including agents to avoid.
- Outline pharmacologic options for drug-resistant infantile epilepsy.
- Recognize the role and timing of dietary therapy, particularly the ketogenic diet.
- Identify surgical candidates and understand the two strong recommendations for epilepsy surgery.

Case 1

New-onset infantile epilepsy: first-line therapy

Case 1: New-onset infantile epilepsy

Clinical vignette

- 14-month-old, previously developing normally, presents with new-onset focal seizures with impaired awareness.
- MRI brain: unremarkable. EEG: focal epileptiform discharges. Genetic testing pending.
- No prior antiseizure medication (ASM) exposure. No history of severe behavioral disorder.

This is new-onset epilepsy in an infant 1 month to <36 months of age.

- The guideline addresses first-line pharmacologic choices and agents to avoid in this setting.

Case 1: What would you do?

Which initial antiseizure medication approach is best supported for this infant with new-onset epilepsy?

A. Start levetiracetam
B. Start valproate
C. Start phenobarbital
D. Start levetiracetam plus valproate combination therapy

Consider seizure type, etiology, and the balance of benefits and harms as you decide.

Case 1: Recommendations for new-onset epilepsy

I-A-1 Levetiracetam

- The panel **suggests levetiracetam rather than no levetiracetam**. Widely available, inexpensive, no routine lab monitoring. *(Conditional, Very Low CoE)*
  - Consider an alternative ASM in infants with a history of severe behavioral disorders.

I-A-4 Levetiracetam over phenobarbital

- The panel **suggests levetiracetam rather than phenobarbital**. *(Conditional, Low CoE)*
  - Prolonged phenobarbital use is associated with potential neurotoxicity and adverse cognitive effects.

I-A-2 Avoid valproate when etiology is uncertain

- The panel **suggests against valproate** in new-onset epilepsy of uncertain etiology. *(Conditional, Very Low CoE)*
  - Genetic testing to exclude POLG variants should precede valproate; hepatotoxicity risk is increased in children <2 years.

Case 1: Evidence and rationale

Levetiracetam (I-A-1)

- May increase seizure freedom vs no levetiracetam (RR 0.34, 95% CI 0.20–0.45); NNT 1.51. Desirable effects moderate, undesirable effects small.

Levetiracetam vs phenobarbital (I-A-4)

- Seizure freedom at 6 months 40.2% with levetiracetam vs 15.8% with phenobarbital (OR 4.2, 95% CI 1.3–14); NNT 4.1.

Valproate in uncertain etiology (I-A-2)

- Desirable effects small in new-onset disease; hepatotoxicity risk, especially in POLG and mitochondrial disorders, drives the recommendation against use.

Combination levetiracetam + valproate: no recommendation was made — the panel prioritized comparison of combination vs levetiracetam alone (as opposed to valproate alone) as a future research question.

Case 1: Summary

- **Levetiracetam is a reasonable first-line ASM** for infants with new-onset epilepsy and is preferred over phenobarbital.
- **Avoid valproate when the epilepsy etiology is uncertain**; obtain genetic testing to exclude POLG before considering it.
- Etiology and seizure type matter: see Case 2 for focal epilepsy, where oxcarbazepine is preferred over levetiracetam.
- Most recommendations rest on very low certainty evidence; individualize using shared decision-making.

Back to the question: Answer A: Start levetiracetam.

Case 2

New-onset focal epilepsy: choosing an agent

Case 2: New-onset focal epilepsy — choosing an agent

Clinical vignette

- 10-month-old with new-onset focal epilepsy; MRI shows a focal structural lesion. Generalized epilepsy and Dravet syndrome are not suspected.

Beyond levetiracetam, how should first-line therapy be tailored for focal epilepsy?

A. Oxcarbazepine may be preferred over levetiracetam for focal epilepsy
B. Lacosamide is a reasonable option
C. Either topiramate or carbamazepine is acceptable
D. All of the above are supported, depending on the clinical context

Case 2: Focal epilepsy — oxcarbazepine and lacosamide

I-A-3 Oxcarbazepine over levetiracetam (focal)

– For new-onset **focal** epilepsy, the panel **suggests oxcarbazepine rather than levetiracetam**. *(Conditional, Very Low CoE)*

- Seizure freedom 74% with oxcarbazepine vs 41% with levetiracetam (RR 1.79, 95% CI 1.33–2.41); NNT 3.08.
- **Contraindicated** in generalized epilepsy and Dravet syndrome; use caution with sodium-channel disorders and in patients with hypersensitivity reactions (SJS, HLA predisposition).

I-A-6 Lacosamide

– The panel **suggests lacosamide rather than no lacosamide**. *(Conditional, Very Low CoE)*

- May increase seizure freedom (RR 0.54, 95% CI 0.45–0.65); NNT 2.86. Consider ECG monitoring where arrhythmia risk exists.

Case 2: Topiramate or carbamazepine (I-A-5)

Either agent is acceptable

- The panel **suggests treatment with either topiramate or carbamazepine**. *(Conditional, Very Low CoE)*
- No clinically meaningful difference in seizure freedom (RR 1.06, 95% CI 0.78–1.44); undesirable effects small.

Prefer topiramate when…

- Carbamazepine is contraindicated; risk of hypersensitivity reactions (SJS, HLA predisposition); SCN1A disorders.

Prefer carbamazepine when…

- Focal epilepsy or certain channelopathies (KCNQ2, KCNQ3, SCN2A).
- **Carbamazepine is contraindicated in Dravet syndrome**; topiramate is FDA-approved only from age 2 years and warrants caution with the ketogenic diet.

Case 2: Summary

- **Match the drug to the seizure type and etiology.** For new-onset focal epilepsy, oxcarbazepine may be preferred over levetiracetam.
- Lacosamide is a reasonable additional option; monitor for cardiac conduction effects in at-risk infants.
- Topiramate and carbamazepine are interchangeable first-line choices, guided by contraindications and hypersensitivity risk.
- **Beware sodium-channel agents (oxcarbazepine, carbamazepine, phenytoin) in Dravet syndrome and certain channelopathies.**

Back to the question: Answer D: all are supported, depending on context.

Case 3

Drug-resistant epilepsy: pharmacologic options

Case 3: Drug-resistant infantile epilepsy

Clinical vignette

- 20-month-old with focal epilepsy of unknown etiology. Seizures persist despite two appropriately chosen and dosed ASMs.
- **This meets the definition of drug-resistant epilepsy (DRE)** — an estimated 35–65% of infants with epilepsy.

Which pharmacologic options does the guideline support in DRE?

A. Valproate (with POLG testing) or topiramate
B. Lamotrigine or rufinamide
C. Brivaracetam; stiripentol if drug-resistant Dravet syndrome
D. All of the above are conditionally suggested options

Case 3: DRE pharmacology — valproate, topiramate, lamotrigine

I-B-1 Valproate

- Panel **suggests valproate rather than no valproate** in DRE. *(Conditional, Very Low CoE)*
  - Exclude POLG variants first; monitor for hepatotoxicity; with the ketogenic diet, monitor carnitine and vitamin D.

I-B-2 Topiramate

- Panel **suggests topiramate rather than no topiramate**. *(Conditional, Low CoE)* NNT 5.21.
  - On the ketogenic diet, increased risk of metabolic acidosis and kidney stones.

I-B-3 Lamotrigine

- Panel **suggests lamotrigine rather than no lamotrigine**. *(Conditional, Very Low CoE)*
  - Requires slow titration; SJS risk rises with concomitant valproate; contraindicated in Dravet syndrome.

Case 3: DRE pharmacology — rufinamide, stiripentol, brivaracetam

I-B-4 Rufinamide

– Panel **suggests rufinamide rather than no rufinamide**. *(Conditional, Very Low CoE)*

- May increase seizure freedom (RR 0.81) and reduce seizure frequency; greatest reductions in LGS, atonic, and tonic seizures. FDA-approved from 12 months.

I-B-5 Stiripentol (drug-resistant Dravet syndrome)

– Panel **suggests stiripentol** for drug-resistant Dravet syndrome, **with concomitant clobazam**. *(Conditional, Very Low CoE)*

- A second-line agent in the international Dravet consensus; dispensed via specialty pharmacy.

I-B-6 Brivaracetam

– Panel **suggests brivaracetam rather than no brivaracetam**. *(Conditional, Very Low CoE)*

- May increase seizure freedom (RR 0.86); FDA-approved from 1 month for partial-onset seizures.

Case 3: Summary

- **DRE = persistent seizures despite two appropriate ASMs.** Confirm the diagnosis and re-evaluate etiology.
- Conditionally supported options include valproate, topiramate, lamotrigine, rufinamide, and brivaracetam; stiripentol (with clobazam) for drug-resistant Dravet syndrome.
- All are conditional recommendations on low or very low certainty evidence — choice is individualized by seizure type, etiology, tolerability, and access.
- **Critically, DRE should prompt timely referral** to a pediatric epilepsy center to evaluate dietary and surgical therapy (Cases 4 and 5).

Back to the question: Answer D: all are conditionally suggested options.

Case 4

Dietary therapy for drug-resistant epilepsy

Case 4: Dietary therapy for drug-resistant epilepsy

Clinical vignette

- 18-month-old with drug-resistant epilepsy after multiple ASMs. Family asks about non-drug options; the child is not yet a surgical candidate.
- Dietary therapy is considered after failure of two appropriate ASMs, or earlier/first-line in GLUT1 deficiency or PDH.

Which dietary approach does the guideline support for a child <24 months?

A. Classic ketogenic diet
B. Modified Atkins diet
C. Low glycemic index treatment
D. Any of the three is equally preferred

Case 4: Dietary recommendations

II-A Ketogenic diet

- Panel **suggests a ketogenic diet rather than no ketogenic diet** in DRE. *(Conditional, Low CoE)* NNT 5.65 at 12 months.
  - **Classic ketogenic diet is preferred for children <24 months**; better response with genetic etiologies; may be first-line in GLUT1 or PDH.

II-C Ketogenic diet over modified Atkins diet

- Panel **suggests the ketogenic diet rather than the modified Atkins diet**. *(Conditional, Low CoE)*

II-B Modified Atkins diet — suggested against

- Panel **suggests against the modified Atkins diet** in children <24 months; it may be a reasonable alternative only if the ketogenic diet cannot be accessed or tolerated. *(Conditional, Low CoE)*

II-D Age 24 to <36 months

- Panel **suggests either modified Atkins diet or low glycemic index treatment**; above 24 months, any diet can be used. *(Conditional, Low CoE)*

Case 4: Summary

- **The classic ketogenic diet is the preferred dietary therapy for infants <24 months** with drug-resistant epilepsy.
- Preferred due to higher efficacy and the more exact nutritional calculations needed during rapid growth at this age
- Consider dietary therapy early, even first-line, in GLUT1 deficiency and PDH.
- Dietary therapy is a complex, multidisciplinary intervention (dietitian, neurologist, nursing, social work) with meaningful cost, equity, and feasibility considerations.
- Screen for contraindications (e.g., fatty-acid oxidation defects, carnitine and pyruvate carboxylase deficiencies, porphyria) before initiation.

Back to the question: Answer A: classic ketogenic diet for a child <24 months.

Case 5

Epilepsy surgery in infancy

Case 5: Epilepsy surgery in infancy

Clinical vignette

- 8-month-old with drug-resistant epilepsy and MRI showing hemimegalencephaly (holohemispheric structural pathology).
- Uncontrolled seizures in this critical developmental window carry risk to cognition and a risk of SUDEP.

What is the guideline's position on surgery for this infant?

A. Continue adding antiseizure medications before considering surgery
B. Strong recommendation for hemispherectomy / hemispherotomy
C. Surgery is not appropriate under 12 months of age
D. Vagus nerve stimulation is first-line

Case 5: Surgical recommendations

III-A Hemispherectomy / hemispherotomy: STRONG

– For holohemispheric DRE from select pathologies (hemimegalencephaly, Rasmussen's encephalitis, Sturge-Weber, perinatal stroke, hemispheric cortical dysplasia), the panel **recommends** surgery. *(Strong, Low CoE)*

- Decreases failure to achieve seizure freedom (RR 0.32, 95% CI 0.19–0.55); NNT 1.42; seizure freedom in up to 70–90% of selected cases.

III-B Focal / multilobar resection or disconnection: STRONG

– For drug-resistant focal or lesional epilepsy, the panel **recommends** intralobar, multilobar, or focal resection or posterior disconnection. *(Strong, Very Low CoE)*

- Decreases failure to achieve seizure freedom (RR 0.42, 95% CI 0.34–0.53); NNT 1.59.

III-C Supratentorial tumor resection

– For tumor-related epilepsy, the panel **suggests** supratentorial tumor resection. *(Conditional, Very Low CoE)*

Case 5: Summary

- **These are the guideline's only two strong recommendations** — hemispherectomy/hemispherotomy (III-A) and focal/multilobar resection or disconnection (III-B).
- Strength reflects the life-threatening nature of DRE from select pathologies and the high morbidity and mortality when left untreated, despite low certainty of evidence.
- Surgery requires an experienced multidisciplinary team; ILAE Level 2 centers for extensive procedures or infants <12 weeks. Communicate compassionately with families.
- **Do not delay referral:** Early surgery offers the best chance of seizure freedom and improved developmental outcomes.

Back to the question: **Answer B: Strong recommendation for hemispherectomy/hemispherotomy.**

Where the panel made no recommendation

Some interventions had insufficient in-scope evidence to support a recommendation (knowledge gaps):

Phenytoin

- Uncommonly used in infants (poor oral absorption, chronic adverse effects); primary use is IV fosphenytoin for status epilepticus, outside this scope.

Vigabatrin

- Available evidence was in epileptic spasms, which are excluded from this guideline.

Levetiracetam + valproate combination

- No recommendation; the more useful comparison (combination vs levetiracetam alone) is a future research priority.

Vagus nerve stimulation (VNS)

- Insufficient data in this age group; no evidence that VNS should not be pursued as palliative therapy in selected non-surgical candidates.

In summary: back to our objectives

New-onset epilepsy

- Levetiracetam is a reasonable first-line agent (preferred over phenobarbital); oxcarbazepine may be preferred for focal epilepsy; avoid valproate when etiology is uncertain.

Drug-resistant epilepsy: pharmacology

- Valproate, topiramate, lamotrigine, rufinamide, and brivaracetam are conditionally suggested; stiripentol with clobazam for drug-resistant Dravet syndrome.

Dietary therapy

- Classic ketogenic diet is preferred for infants <24 months; consider early in GLUT1 deficiency and PDH.

Surgery

- Two strong recommendations: hemispherectomy/hemispherotomy for select holohemispheric pathologies, and focal/multilobar resection or disconnection for focal or lesional DRE.

Refer drug-resistant infants to a specialized pediatric epilepsy center early.

Acknowledgements & resources

Guideline

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Work Group

- A multidisciplinary panel of epileptologists, neurosurgeons, pharmacists, and dietitians, together with parent and caregiver advocate representatives.
- Methodologic support provided by the Evidence Foundation; evidence base derived from the PCORI-funded AHRQ/ECRI systematic review.

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