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Infantile Spasms: Opportunities to Improve Care

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Abstract

Infantile spasm (IS) is a distinct epilepsy syndrome characterized by epileptic spasms (the clinical seizure type) and hypsarrhythmia (the electrographic abnormality). IS is frequently accompanied by impaired neurodevelopment and is often associated with structural, genetic, or metabolic etiologies. Prompt treatment of this severe epileptic encephalopathy improves long-term outcomes but remains elusive in many situations. Despite common misconceptions, even patients with identified etiologies or preexisting developmental delay benefit from proven standard therapies, including adrenocorticotropic hormone (ACTH), oral corticosteroids, or vigabatrin. Treatment efficacy should be assessed with electroencephalography at 2 weeks, and an alternative therapy is indicated if epileptic spasms or hypsarrhythmia have not resolved. Collaboration with primary care providers is critical to mitigate the potentially serious adverse effects of standard treatments and also to provide developmental interventions. Although new approaches are on the horizon, addressing current challenges and opportunities now can dramatically improve patient outcomes.

Keywords
- infantile spasms
- West syndrome
- adrenocorticotropic hormone
- prednisolone
- vigabatrin

Infantile spasm (IS) is a severe epileptic encephalopathy of early childhood that was first described in 1841.[1] Historically, the classic triad of West syndrome included clinical seizures (epileptic spasm, ES), an abnormal interictal electroencephalogram (EEG) pattern (hypsarrhythmia), and developmental issues. However, developmental delay and hypsarrhythmia are not always present at onset, which the International League Against Epilepsy (ILAE) seizure classification and West Delphi Consensus Statement recognized with broader definitions of IS, West syndrome, ES, and hypsarrhythmia (►**Table 1**).[2,3] The diagnosis of IS requires both a high index of suspicion and a prolonged EEG, and many resources are available to educate the public and providers about this unusual seizure type (►**Fig. 1**). Perhaps more than any other epilepsy syndrome, short- and long-term outcomes are influenced by time to treatment and choice of treatment. This review will highlight several opportunities for improvements in the care of children with IS (►**Table 2**).

Though one of the most common epilepsies of early childhood, IS has an incidence of only 0.01 to 0.58/1,000 live births.[4–7] IS predominately affects children less than 2 years of age, with a peak onset of 3 to 7 months and only rare reports of age of onset up to 4 years of age.[8–12] The epidemiology of IS has been evaluated in several different populations, and a recent meta-analysis suggests that latitude may impact the incidence, but importantly, data from lower latitudes are scarce.[5] Gender differences have also been debated, though most studies suggest a slight preponderance in boys compared with girls.

Seizure Description

Like other seizure types, ESs are paroxysmal, involuntary, repetitive, abnormal movements. The semiology is unique, with sudden contraction of the trunk and extremities lasting less than 1 second, but often occurring in clusters (►**Table 3**). ESs are frequently associated with sleep–wake transitions. Consciousness is not impaired, but the child may briefly cry or appear distressed after each spasm. Mimickers of ES include normal baby movements, exaggerated startle reflex, Sandifer syndrome (abnormal movements provoked by gastroesophageal reflux), benign sleep myoclonus, myoclonic seizures, focal seizures, and tonic seizures.[13,14]

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Table 1 Proposed definitions of terms, modified from West Delphi Consensus and ILAE[3,92]

Term	Definition	Additional information
Infantile spasm (IS)	The epilepsy syndrome—children younger than 2 y with epileptic spasms, with or without hypsarrhythmia	Within the ILAE 2017 epilepsy classification, IS is an epileptic encephalopathy caused by various etiologies
West syndrome (WS)	The constellation of epileptic spasms and hypsarrhythmia, with or without developmental issues	Historically, developmental issues were a defining feature of WS, named after the first person to recognize the constellation of symptoms which were affecting his own child
Epileptic spasm (ES)	The seizure type	The term "ES" is preferable to the term IS when referring to the clinical seizures. ES can have focal motor onset, generalized motor onset, or unknown motor onset, but do not require a specified awareness
Hypsarrhythmia ("hyps")	The abnormal interictal EEG pattern	This random, high-voltage pattern was first described by Gibbs and Gibbs in 1952

Abbreviations: EEG, electroencephalogram; ILAE, International League Against Epilepsy.

Electroencephalogram Findings

Prolonged EEG is required for the diagnosis of IS and helps differentiate between IS mimics. The characteristic EEG background pattern is hypsarrhythmia (►**Fig. 2**)—chaotic, asynchronous, and high-amplitude activity (often greater than 200 microvolts) with intermixed multifocal spikes.[15] Although hypsarrhythmia is considered a biomarker of IS, disagreement about the defining characteristics continues,[3,16] despite standardized grading tools focusing on quantifiable features such as the Burden of Amplitudes and Epileptiform Discharges (BASED) score (►**Table 4**).[17] The BASED score creates an objective scale to determine the features of hypsarrhythmia and has been shown to improve inter-rater reliability. Hypsarrhythmia is most likely to be seen during non-REM sleep. Most, but not all, children with ES have hypsarrhythmia; studies report 52%[18] to 100%.[8,19–21] This variation is primarily due to inclusion of variants of hypsarrhythmia.[22] When hypsarrhythmia is not present, the EEG pattern is still markedly abnormal. If spells are not captured on the EEG, repeat EEG may be warranted if concerning spells continue to occur. Parental video of the spells may also help clarify the diagnosis.

During the seizure, the ictal EEG has a distinctive, diffuse high-amplitude slow wave with superimposed fast activity, followed by electrodecrement (diffuse attenuation), which may appear to be more normal activity (►**Fig. 3**). This "pseudo-normalization" can lasts for several seconds, even minutes. In addition to IS, other epilepsy syndromes, such as Ohtahara syndrome or early infantile myoclonic epilepsy, may have ES as

Fig. 1 Pneumonic developed by the Infantile Spasms Action Network to improve awareness of infantile spasms.

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Table 2 Key opportunities and goals for improving the care of patients with IS

Opportunity	Goal
1. Make the diagnosis early[a,b,c,d]	Evaluate with prolonged EEG within 1–2 wk of symptom onset
2. Initiate treatment early[a,b,c,d,e]	Initiate treatment within 1 wk of diagnosis
3. Investigate the etiology[a,c,d]	Perform brain MRI within 4 wk of diagnosis; consider tiered genetic/metabolic testing
4. Choose a standard first-line treatment[a,b,c,d,e,f,g]	Treat with ACTH, oral corticosteroids, or vigabatrin (see ►**Table 5**)
5. Mitigate adverse side effects of treatments[a,c,e,g]	Monitor for hypertension and infection at least weekly (ACTH, OCS); obtain ophthalmologic evaluation every 3 mo (vigabatrin); see ►**Table 6**
6. Assess treatment efficacy[a,b,c,d,e,g]	Confirm that both clinical spasms *and* hypsarrhythmia have resolved with follow-up EEG at 2–3 wk
7. Change treatments if response is incomplete[a,c,d]	Switch to an alternative standard treatment. For IS refractory to two standard treatments, consider surgery and/or additional treatments (pyridoxine, ketogenic diet, typical antiseizure mediations)
8. Monitor developmental outcomes[c,d,e,g]	Refer to early intervention services; assess every 6 mo

Abbreviations: ACTH, adrenocorticotropic hormone; EEG, electroencephalogram; ILAE, International League Against Epilepsy; IS, infantile spasm.
Sources for opportunities:
[a]U.S. Consensus Report.[29]
[b]AAN/CNS Guideline.[37]
[c]Quality of Care Indicators.[27]
[d]ILAE Recommendations.[30]
[e]AAN Quality Measures.[28]
[f]Cochrane Review.[38]
[g]AAN/CNS Practice Parameter MacKay.[36]

Table 3 Distinguishing features of various types of clinical spasms

Clinical spasm type	Distinguishing features
Flexor spasms (“Jackknife seizures”)	The child may appear to do an abdominal “crunch”—the neck and trunk suddenly flex, the knees are pulled up, and the arms either come in toward the chest or, more commonly, stiffen and are flung outward
Extensor spasms	The child may throw the head back, arch the back, and stiffen and extend the arms and legs
Mixed extensor–flexor spasms	The child may show features of both types
Hemi-spasms	Only one side of the body is affected
Asymmetric spasms	These may mimic the asymmetric tonic posture reflex or otherwise affect the two sides of the body differently
Subtle spasms	The child may demonstrate isolated forceful head bobs, facial grimace, eye rolling, eye deviation, or brief staring

a seizure type, but these disorders have other EEG features, as well as a more concerning prognosis.

Early Diagnosis and Treatment Impact Developmental Outcomes—Opportunities 1 and 2

Onset of ES is frequently preceded by developmental delays, plateau, or regression. A recent study found 90% of infants with IS had developmental delay at the time of presentation.[23] More than half had impaired social responsiveness, such as absent social smile, as well as auditory impairments, including poor response to voice. In addition, 44% displayed visual inattention, which caregivers may notice as a decrease in eye contact or tracking. Over time, the developmental impact becomes more pronounced, and the child may lose head control, stop sitting, and become less interactive.

Fortunately, timely treatment, particularly within 7 to 30 days of ES onset, is associated with improved response to treatment and neurodevelopmental outcomes.[13,24–26] Thus, consensus quality improvement guidelines strongly recommend evaluation with prolonged EEG and treatment initiation as soon as possible, certainly within 1 to 2 weeks of presentation.[27–30]

Take a Step-Wise Approach to the Etiologic Investigation—Opportunity 3

After the diagnosis of IS has been established, the etiology should be investigated, particularly since some causes may

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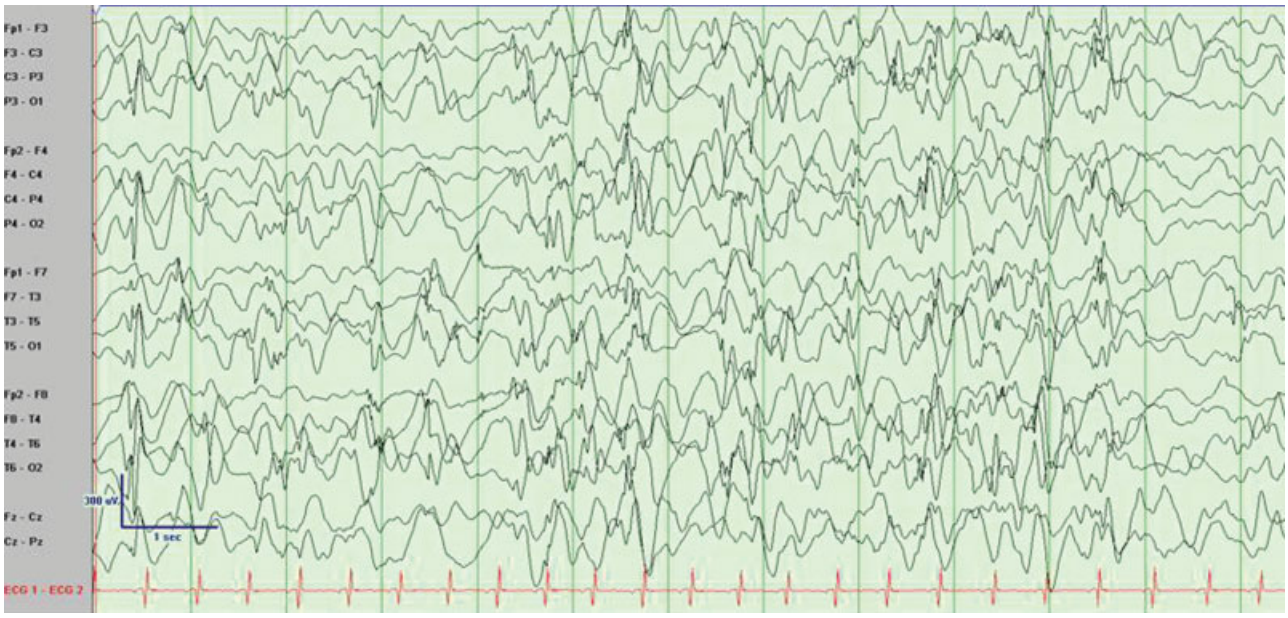

Fig. 2 Example of hypsarrhythmia.

Table 4 BASED score[17]

BASED score	Description
0	Normal
1	Any definite nonepileptiform abnormality
2	<3 spike foci *and* no common background slow waves ≥200 μv[a,b]
3	MFS <50% of one second bins[c] *and* no common background slow waves ≥200 μv,[a,b] *or* no MFS but common background slow waves ≥200 μv[a,b]
4 (Hyps[d])	MFS <50% of one second bins[c] *and* common background slow waves ≥200 μv[a,b]
5 (Hyps[d])	MFS ≥50% of one second bins,[c] *or* Common background slow waves ≥300 μv[a,e] in two or more bilateral head regions

Abbreviations: BASED, Burden of Amplitudes and Epileptiform Discharges; MFS, multifocal spikes—at least three different foci; μv, microvolts.
[a]Peak-to-peak amplitude on a longitudinal bipolar montage, refers to background slow waves and excludes (1) the slow wave associated with a preceding spike, (2) hypnagogic patterns, and (3) arousal rhythms.
[b]May be one or more head regions, must be a common finding, may be regional (e.g., left posterior), and may exist in the presence of other lower amplitude background activities.
[c]The percentage of one second bins that include one or more spikes in the most severely abnormal 5-minute epoch (i.e., the epoch that gives the highest BASED score).
[d]To determine the presence or absence of hypsarrhythmia, findings should be representative of the most severely abnormal 5-minute epoch of the study (i.e., the epoch that gives the highest BASED score); a score of 4 or 5 suggests electrographic evidence of hypsarrhythmia.
[e]Must be two of the following: bilateral frontal, bilateral temporal, bilateral parietal, and bilateral occipital; must be a common finding.

benefit from specialized treatment (►**Table 5**).[27,29–31] Many speculate that brain dysfunction from essentially any cause early in life may converge into a "final common pathway" that ultimately results in the development of IS. Indeed, more than 200 conditions are known to be associated with IS.

The combination of history, physical exam, and early imaging yields a diagnosis in 40 to 55% of cases.[32,33] Patients with disorders such as tuberous sclerosis complex, Trisomy 21, and Menkes disease have high rates of IS, and may have notable physical exam findings, such as ash leaf spots (identified most easily with a Wood's lamp), syndromic facies, or unusually brittle hair. Structural causes, such as brain malformations, traumatic brain injury, hypoxic–ischemic encephalopathy, and congenital cytomegalovirus account for roughly 40% of cases, including 20% with acquired brain injury.[32–34] Thus, brain MRI is strongly recommended for the initial diagnostic evaluation of patients with IS, and additional testing can be deferred, unless syndromic features, concerning symptoms, or metabolic derangements are also present.

If imaging is uninformative, chromosomal microarray/comparative genomic hybridization, followed by an epilepsy gene panel if needed, as well as serum lactate, serum amino acids, and urine organic acids are recommended. Genetic testing demonstrates an etiology in 23% of those without imaging findings.[32] Various inborn errors of metabolism, including GLUT1 deficiency, pyridoxine-dependent seizures, phenylketonuria, nonketotic hyperglycinemia, and methylmalonic aciduria continue to be reported as rare but potentially treatable

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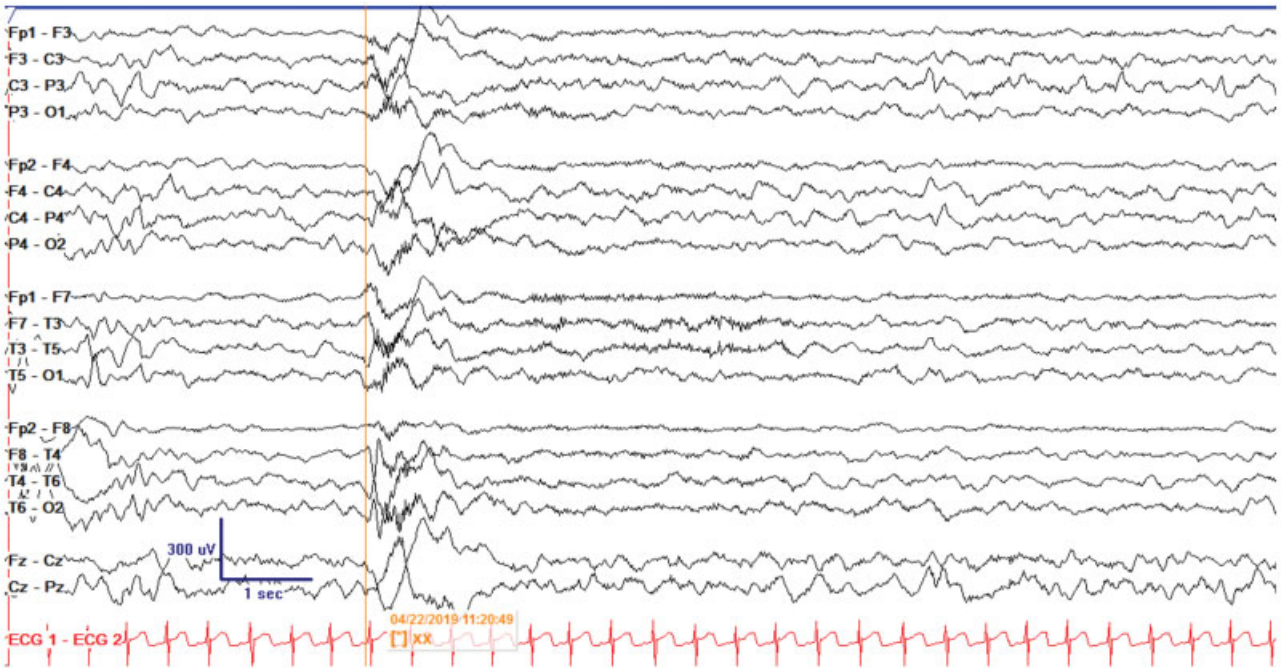

Fig. 3 Example of electroencephalogram findings during an epileptic spasm.

Table 5 Comparison of standard first-line IS treatments

Treatment	Efficacy	Logistics	Side effects (see ►Table 6)
ACTH	*ILAE*: "preferred treatment" *Short-term response*: 76–87% *3-mo response*: 55% *Risk of relapse*: likely less	*Cost*: $$$ + admission *Dosing*: intramuscular injections, 150 units/m^2/d for 2 wk, 2-wk taper *Other*: specialty pharmacy	*Mild-moderate*: irritability, increased appetite, weight gain, poor sleep, stomach ulcers, hypertension, hyperglycemia *Severe*: infection, cardiomyopathy, adrenal crisis
Oral corticosteroids (prednisolone)	*ILAE*: "probably effective" *Short-term response*: 63-80% *3-mo response*: 39% *Risk of relapse*: possibly higher than ACTH	*Cost*: $, no admission *Dosing*: oral liquid, 4–8 mg/kg/d (max 60 mg) for 2 wk, 2-wk taper *Other*: any retail pharmacy	
Vigabatrin	*ILAE*: "possibly effective, especially for TSC" *Short-term response*: 35–54% *3-mo response*: 36% *Risk of relapse*: higher than ACTH	*Cost*: $$ +/− admission *Dosing*: powder mixed into oral liquid, increased from 50 to 150 mg/kg/d over 7 14 d, then 3–12 mo *Other*: specialty pharmacy and REMS enrollment	*Mild-moderate*: poor sleep, drowsiness, hypotonia, behavioral changes, reversible MRI changes *Severe*: irreversible peripheral vision loss

Abbreviations: ACTH, adrenocorticotropic hormone; ILAE, International League Against Epilepsy; REMS, Risk Evaluation and Mitigation Service; TSC, tuberous sclerosis.

causes of IS, although patients with the newly recognized "IS-associated gene" disruptions, such as ARX (Aristaless-related homeobox) and CDKL5 (cyclin-dependent kinase-like 5), and STXBP1 (syntaxin-binding protein 1), may be much more likely to develop IS.[31,35] Third/fourth tier testing could include novel gene testing or repeat brain MRI, since advances in genetic technology occur rapidly, and ongoing myelination may permit visualization of small abnormalities. Despite exhaustive evaluations, a definitive etiology is not found in 30 to 50% of children.

Offer an Effective Standard Treatment—Opportunity 4

Unlike other epilepsy types, the efficacy of IS treatment is determined with an "all-or-none" approach that requires both cessation of ES and resolution of hypsarrhythmia, thus requiring a repeat EEG within 2 to 3 weeks of treatment initiation.[3,27,36] Partial reduction of ES frequency or cessation of ES with persistence of hypsarrhythmia is considered treatment failure.

IS responds poorly to typical antiseizure medications. Currently, adrenocorticotropic hormone (ACTH), oral corticosteroids (OCS), and vigabatrin are the only identified "possibly" or "probably effective" therapies for IS (►**Table 5**).[28,30,37] Importantly, comparing treatment efficacy has been confounded by evolving dosing regimens and outcome measures, and most guidelines were published prior to several recent clinical studies. Although the 2012 American Academy of Neurology/Child Neurology Society guidelines found insufficient evidence to support short-term efficacy of OCS, they agreed with the ILAE

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consensus and Cochrane review that hormonal treatment with either ACTH or OCS improved long-term outcomes compared with vigabatrin, particularly for children with an unknown etiology.[30,37,38] Furthermore, increasing the percentage of children with IS who receive ACTH, OCS, or vigabatrin as a first-line agent was identified as a key quality improvement metric by the 2018 Child Neurology Quality Measurement Set Workgroup.[28] The 2016 National Infantile Spasms Consortium (NISC) observational study of more than 230 patients found that the most important determinant of response to treatment was utilizing any one of these three treatments as the first-line agent, regardless of etiology, prior developmental delay, or presence of hypsarrhythmia.[20,39]

Steroid/Hormonal Treatments (ACTH and OCS)

Steroid/hormonal medications, including ACTH and OCS, have been used since the 1950s.[40,41] Some speculate that the hypothalamic–pituitary–adrenal axis is dysregulated in the pathophysiology of IS, possibly due to stress, and that ACTH may have additional neuromodulatory properties compared with OCS.[42,43] Synthetic and naturally derived ACTH have similar efficacy, with 2-week response rates of 76 to 87% in controlled trials, though a direct comparison has not occurred.[44,45] The high cost and poor availability of ACTH have fueled the pursuit of alternative hormonal treatments, including OCS, though the comparative efficacy between ACTH and OCS is debated. Early studies using low-dose OCS (1–2 mg/kg/day) demonstrated inferior efficacy compared with ACTH,[45,46] whereas recent studies of high-dose OCS (4–8 mg/kg/day) have found response rates of 63 to 80%, similar to ACTH.[44,47–49]

Vigabatrin

Vigabatrin is a specific inhibitor of gamma-aminobutyric acid transaminase (GABA-T), the enzyme responsible for metabolizing GABA at the synapse. Short-term response rates to vigabatrin range from 35 to 54%, significantly lower than hormonal treatments; however, the 14-day assessment point of most studies may not sufficiently account for the longer titration period of vigabatrin.[44,50–53] Although long-term outcomes were similar between vigabatrin and hormonal treatments across all etiologies, hormonal therapies were associated with improved development in children with unknown etiologies.[54] Interestingly, in patients with tuberous sclerosis complex, vigabatrin is more efficacious than steroids and is, therefore, the treatment of choice.[51,55]

Alternative Treatments

Although other IS treatments have been investigated, in general, these studies have small sample sizes, inadequate primary outcome measures, or lack of randomization. Some therapies show promise as first-line treatment when standard treatment options are not possible. A small prospective study of the ketogenic diet as initial treatment for IS demonstrated a 2-week clinical response rate of 56%, all of whom had normal EEGs at 6 months.[56] The efficacy of pyridoxine as a first-line agent has not been clearly established, despite frequent use at some centers. Early studies with topiramate showed a 28 to 45% response rate at 3 months; however, a newer study found only a 9.7% response rate, and all relapsed.[57–59] Interestingly, a recent randomized controlled study of zonisamide found a 20% clinical and electrographic response rate at 2 weeks.[60] Other typical antiseizure medications have been trialed throughout the years. Two small prospective studies found levetiracetam was effective in 14 to 40% of patients.[61,62] A retrospective study of sodium valproate with or without a benzodiazepine demonstrated ES cessation in 45.8%,[63] though use of valproate acid is often avoided in young children due to concern for POLG pathogenic variants. Overall, the NISC study grouped all nonstandard treatments, including the ketogenic diet, topiramate, zonisamide, clobazam, clonazepam, valproic acid, phenobarbital, oxcarbazepine, and levetiracetam, into a single "other" category, and found response rates of 22% at 2 weeks and only 9% (3/32) at 3 months.[39]

Mitigate the Side Effects of Treatments—Opportunity 5

All three standard treatments carry significant risk of serious side effects (►**Table 5**).[36] The Children's Hospital Colorado clinical pathway outlines one institution's approach to recommended surveillance and treatment (►**Table 6**). In some studies, more than half of patients with IS treated with steroid/hormonal medications experienced adverse effects, such as irritability, hypertension, and infection, which may require medical intervention.[48,64] Although 34 to 52% of all patients treated with vigabatrin were found to have permanent visual field loss, the incidence of clinically significant visual impairment may be less than 4% in the IS population.[65–67] Nonetheless, in the United States, vigabatrin initiation requires enrollment in a Risk Evaluation and Mitigation Service (REMS) program, and frequent ophthalmologic evaluations are recommended. Some concerns remain about the clinical significance of vigabatrin-associated reversible MRI changes, though these have not been definitively associated with any symptom, including movement disorders.[64,68,69]

Assess Treatment Efficacy and, if Needed, Switch to an Alternative Treatment—Opportunities 6 and 7

Prolonged repeat EEG 2 to 3 weeks after treatment initiation is strongly recommended.[27,29] If ES or hypsarrhythmia persists, then the first medication should be weaned while a second medication is started.[27] The NISC study found that children who failed an initial standard treatment had a 55% response rate when given another standard treatment with a different mechanism of action.[26] A similar approach is likely warranted for IS recurrence, defined as recurrence of ES, which occurs in 30 to 50% of patients.

The best approach after two standard medications have failed is not clear, but in general, additional therapy trials and ongoing reassessment of efficacy are recommended.[30,70] The ketogenic diet is another important consideration, with one study demonstrating a 37% clinical response rate at 6 months, most of who had failed standard treatments.[56] Typical

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Table 6 Strategies for mitigating side effects of hormonal treatments and vigabatrin

Hormonal treatments	
Irritability, increased appetite, and poor sleep	Provide anticipatory guidance and coping strategies
Complex treatment plan and high risk of side effects	Neurology nurse phone call within 1 wk Primary care provider monitors weight, blood/urine glucose, and hypertension (defined as SBP > 95th% × 3 d) twice a week
Stomach irritation/ulcer	Prescribe histamine blockers (such as ranitidine) or proton pump inhibitors (such as omeprazole) for duration of treatment
Infection—Part 1: Pretreatment screening	Assess for any signs/symptoms of infection. If the patient has tuberculosis risk factors, place purified protein derivative skin test (Quantiferon gold is not accurate in infants)
Infection: Part 2—During treatment and for 2–3 mo after	Avoid live vaccines; defer other vaccines if possible. Prescribe antibiotic prophylaxis (sulfamethoxazole/trimethoprim) × 8 wk. Counsel caregivers to avoid sick contacts and monitor for thrush. Evaluate child immediately for any sick symptoms
Adrenal suppression	Consider stress dose steroids for any illness, surgery, or other physical stressor. Provide caregivers with a letter explaining possible need for stress dose steroids during treatment and for 2–3 mo after
Hypertension management—Part 1: Electrolyte disturbances	Obtain electrolyte levels within 24 h of HTN diagnosis. If hypokalemia, alkalosis, or hypernatremia is found, obtaining endocrinology input, evaluation for cardiac arrhythmia, and initiation of a diuretic (rather than propanolol) may be needed
Hypertension management—Part 2: Risk of cardiomyopathy	Initiate propranolol within 24 h of diagnosis of HTN and refer patient to nephrology for further HTN management. Obtain ECHO within 1 wk. If ECHO is abnormal, urgent cardiology evaluation is warranted. Weaning steroids is typically not recommended
Hyperglycemia management	Refer to endocrinology for possible initiation of insulin
Vigabatrin	
Irritability, poor sleep	Provide anticipatory guidance and coping strategies
Sedation, lethargy, hypotonia	Evaluate child immediately if feeding is impacted or caregivers are concerned. Consider increasing the vigabatrin dose more slowly
Risk of permanent vision loss	Enroll child in the REMS program. Obtain ophthalmology evaluation within 4 wk of treatment initiation, every 3 mo during treatment, and 3 mo after completing treatment. Monitor for signs of worsening vision, such as being easily startled
Reversible MRI abnormalities	Counsel caregivers about the potential risk; report possible associated symptoms to REMS

Abbreviations: ECHO, echocardiography; HTN, hypertension; MRI, magnetic resonance imaging; REMS, Risk Evaluation and Mitigation Service; SBP, spontaneous bacterial peritonitis.

anticonvulsants, such as topiramate, zonisamide, or clobazam, are often utilized as third- and fourth-line agents. One study evaluated whether topiramate or zonisamide could prevent IS recurrence when given for several months after initial treatment with standard therapies, but found that neither was effective.[71] Epilepsy surgery has been used with great success in appropriately chosen children with focal etiologies for seizures, but is not recommended as first-line therapy due to the lengthy surgical evaluation process and risks associated with surgical intervention.[72,73] Children with focal findings on imaging, EEG, and/or asymmetric clinical spasms might be considered as a candidate for surgical evaluation. Corpus callosotomy maybe an option in children without focal imaging abnormalities.[74] Careful evaluation should occur urgently in an appropriate epilepsy center, as outcome may be improved with earlier treatment.

Improving Long-Term Outcomes—Opportunity 8

Although short-term efficacy focuses on resolution of ES and hypsarrhythmia, ultimately, the goal of therapy is to improve long-term outcomes, such as neurodevelopment and subsequent epilepsy. Several studies indicate that 11 to 60% of patients experience other seizure types later in life,[19,75–80] with almost one-third presenting by the age of 1 year. Evolution into Lennox–Gastaut syndrome has been reported in approximately 25% of infants with IS; identifying any etiology and children of older age at diagnosis both are known risk factors.[10,81,82]

Intellectual impairment is often the primary concern for both parents and providers. Fewer than 10% of children with prenatal and perinatal etiologies have normal intellectual outcomes,[83] compared with 41 to 57% of those without prior developmental delay and unknown etiologies.[19,82,84] One long-term study evaluated specific developmental domains, and found 30% with visual impairment and severe cerebral palsy in 45%, though 42% of children were able to ambulate.[19] Psychiatric disorders and autism as long-term outcomes have not been well studied, but one study found psychiatric disorders in 28% of children.[19] Autism has been reported in 13 to 33%.[85,86] All children with IS should be referred for early intervention evaluation, and many children may benefit from multidisciplinary care from rehabilitation providers, neuropsychologists,

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social work, and developmental pediatricians.[87] Ongoing improvements in supportive care have already impacted mortality rates in children with IS, which historically reached 15% by 11 years, but more recent cohorts have reported 5 to 8%.[4]

Recent Updates and Future Directions

Ongoing research focuses on several aspects of the disease, including identification of IS risk factors, determining best treatment paradigms with current medications, evaluating new treatments, understanding risk factors for poor outcomes, and determining the full spectrum of long-term outcomes. An exciting recent study evaluated the efficacy of combination treatment with hormonal therapy (ACTH or OCS) and vigabatrin, finding that short-term outcomes were improved in those receiving combination therapy.[64] A second study investigating combination treatment is currently enrolling in the United States (NCT03347526), though some centers have already adopted dual treatment approaches.[88] A team science approach to developing new animal models for IS was recently an initiative of Citizens United for Research in Epilepsy (CURE; https://www.cureepilepsy.org), leading to several new animal models. Ongoing studies seek to determine if transcranial direct stimulation,[89] cannabidiol (CBD; NCT034211496), AQB-565 (a novel fusion peptide derived from ACTH),[90] or CPP-115 (a vigabatrin analogue)[91] could be effective. Future research may also address treatment of subpopulations, such as those without hypsarrhythmia, or hypsarrhythmia without clinical spasms, and also to determine the appropriate duration of treatment. A consistent theme in the research to date is that the most important opportunity to improve outcomes is rapid treatment with appropriate medication.

Conflict of Interest
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