Treatment of infantile spasms

*Shaun A. Hussain

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SUMMARY

The treatment of infantile spasms is challenging, especially in the context of the following: (1) a severe phenotype with high morbidity and mortality; (2) the urgency of diagnosis and successful early response to therapy; and (3) the paucity of effective, safe, and well-tolerated therapies. Even after initially successful treatment, relapse risk is substantial and the most effective therapies pose considerable risk with long-term administration. In evaluating any treatment for infantile spasms, the key short-term outcome measure is freedom from both epileptic spasms and hypsarrhythmia. In contrast, the most important long-term outcomes are enduring seizure-freedom and measures of intellectual performance in later childhood and adulthood. First-line treatment options—namely hormonal therapy and vigabatrin—display moderate to high efficacy but also exhibit substantial side-effect burdens. Data on efficacy and safety of each class of therapy, as well as the combination of these therapies, are reviewed in detail. Specific hormonal therapies (adrenocorticotropic hormone and various corticosteroids) are contrasted. Those etiologies that prompt specific therapies are reviewed briefly, as are an array of second-line therapies supported by less-compelling data. The ketogenic diet is discussed in greater detail, with a focus on the limitations of numerous available studies that generally suggest that it is efficacious. Special discussion is allocated to cannabidiol—the investigational therapy that has received the most attention, and which is already in use in the form of various artisanal cannabis extracts. Finally, a treatment algorithm reflecting the concepts and controversies discussed in this review is presented.

KEY WORDS: Epileptic spasms, Hypsarrhythmia, West syndrome, Epileptic encephalopathy.

Infantile spasms (IS) is an umbrella term that denotes a specific type of seizure—epileptic spasms (ES)—as well as West Syndrome, which refers to infants who present with the triad of ES, hypsarrhythmia, and developmental regression. It is important to note that a significant minority of children with ES do not exhibit hypsarrhythmia, and in many cases, a critical goal of treatment is to prevent the emergence of hypsarrhythmia. In this review, IS is used in the broad syndromic sense to identify infants with ES, but not exclusively those who present with hypsarrhythmia and developmental regression. Although IS is the most common epilepsy syndrome in the first year of life, diagnosis and treatment are often significantly delayed with potentially catastrophic consequences. Too often, IS masquerades as gastroesophageal reflux (Sandifer syndrome), benign sleep myoclonus, and a variety of “normal” infant behaviors. The diagnosis is established with video-electroencephalography (EEG) to confirm the presence of ES and ascertain the presence or absence of hypsarrhythmia. Prognosis is bimodal: Approximately one-fourth of children with IS—those with favorable premorbid development, prompt diagnosis, and successful early treatment—achieve enduring seizure freedom and normal (or near-normal) intellectual outcomes. In contrast, despite the therapies discussed below, the remaining children face substantial risk of intellectual
KEY POINTS

- Hormonal therapy is the most effective single therapy for short-term treatment of infantile spasms
- Although highly effective in the setting of tuberous sclerosis complex (TSC), short-term response to vigabatrin is lower in the setting of other etiologies
- Based on one study, combination therapy (hormonal therapy plus vigabatrin) appears to be more efficacious than hormonal therapy alone; this finding needs replication
- Surgical resection is a favorable option for highly selected patients with well-defined cortical lesions
- An array of second-line therapies exhibit lower efficacy and should be reserved for refractory cases

Outcome Measures of Treatment

There are multiple outcomes of interest in the treatment of IS. The key short-term goals of therapy are the rapid eradication of ES and the elimination of hypsarrhythmia (or prevention of hypsarrhythmia when absent at baseline). In brief, hypsarrhythmia is the most common interictal EEG pattern that accompanies ES in infancy, and usually manifests with disorganized high-voltage slowing with superimposed abundant multifocal epileptiform discharges. There are multiple variations on this theme, collectively termed modified hypsarrhythmia. Hypsarrhythmia (and variants thereof) are of great importance, as they represent the electrographic manifestation of epileptic encephalopathy in the setting of IS. However, it is important to note that although hypsarrhythmia is seemingly obvious in some cases, there are also many instances in which hypsarrhythmia is difficult to identify. The demonstration that interrater reliability for identification of hypsarrhythmia is poor betrays the conventional notion that hypsarrhythmia is an obvious present-or-absent phenomenon and illustrates hypsarrhythmia’s many “shades of gray.” With this limitation in mind, it comes as little surprise that the presence of hypsarrhythmia does not predict response to initial therapy. Despite these limitations, the gold standard measure of short-term response to therapy is freedom from ES and hypsarrhythmia, usually after a treatment interval of not more than 2 weeks, and without relapse of ES or hypsarrhythmia over a prespecified interval such as 1–3 months. This outcome measure requires the implementation of extended video-EEG to verify resolution of spasms and exclude the possibility of persistent or intermittent hypsarrhythmia. Although there is no established standard for the length of follow-up of video-EEG to confirm response, intervals of 4 h (including at least one sleep cycle) to 24 h are typical in clinical practice and research protocols.

The most important long-term outcomes include enduring (years) freedom from ES and hypsarrhythmia, lack of evolution to other forms of epilepsy (e.g., Lennox-Gastaut syndrome), and an array of standardized measures of intellectual and developmental performance in later childhood and adulthood. Although these long-term outcomes are more meaningful than short-term outcomes, they require extended clinical follow-up and pose additional methodologic challenge. Furthermore, inasmuch as these long-term outcomes reflect successful early treatment, they also vary substantially as a function of etiology and other factors. In comparison to clinical trials that simply evaluate short-term outcomes, the rigorous assessment of long-term outcomes requires larger sample sizes and the allocation of much greater resources for follow-up testing. As such, most studies evaluating specific treatments for IS focus on short-term outcomes.

Urgency of Treatment

The expeditious diagnosis and treatment of IS is essential. To the extent that ongoing IS and hypsarrhythmia pose a significant threat to long-term development, the greatest harm is believed to be sustained early in the course. The risk posed by treatment delay was most convincingly established in the United Kingdom Infantile Spasms Study (UKISS). In this prospective study, after statistical adjustment for the impact of etiology, treatment modality, and age of onset, O’Callaghan and colleagues observed an inverse relationship between the length of treatment delay and performance on the Vineland Adaptive Behavior Scales (VABS), when administered at age 4 years. Specifically, in comparison to patients with treatment delay not exceeding 7 days, a 3.9 point reduction in VABS score was associated with each sequential interval of delay as follows: 8–14 days; 2–4 weeks; 4–8 weeks; >8 weeks. For example, a patient with treatment delay of 6 weeks will on average exhibit an 11.7 point reduction in VABS score that is specifically attributable to treatment delay. Although an association between treatment latency and long-term outcome has been observed in multiple studies and recapitulated in a large-scale meta-analysis, the precise mechanism by which delayed treatment mediates adverse developmental outcome is unclear. It is presumed that favorable long-term developmental outcomes are linked to early cessation of ES, and it has been postulated that the duration of hypsarrhythmia is most important.

Although we may hypothesize that long-term seizure-freedom enhances development—above and beyond the benefit of early response to treatment—this has not been conclusively established. In addition, the potential harm of recurrent seizures after initial early response...
likely varies as a function of specific seizure types, as well as the presence or absence of ongoing epileptic encephalopathy.

**Hormonal Therapy**

With the exception of IS in the setting of tuberous sclerosis complex (TSC, discussed below), there is relatively broad consensus that hormonal therapy is the most effective class of initial treatment for IS. However, there is considerable debate as to the best agent, dose, and duration of treatment. The most popular hormonal therapies include natural adrenocorticotropic hormone (ACTH, a 39 amino acid peptide), synthetic ACTH (sACTH, a truncated peptide spanning the first 24 N-terminal residues), prednisolone, and prednisone (the prodrug of prednisolone). Although some investigators have reported favorable response rates using extremely low-dose sACTH, the highest short-term response rates have been observed with ACTH administered at high dose (150 U/m² body surface area/day, divided into 2 daily doses). In a pivotal randomized controlled trial, Baram and colleagues demonstrated that short-term response (freedom from ES and hypsarrhythmia on treatment day 14) was far superior with this regimen of ACTH in comparison to a “traditional” dose of prednisone (2 mg/kg/day). In contrast, a sequence of studies have suggested—but not proven—that higher dose regimens of prednisolone are as effective as ACTH. In the UKISS study, Lux et al. reported no difference in response rate between prednisolone (40–60 mg/day) and a “moderate” dose of sACTH (0.50–0.75 mg on alternate days), although treatment allocation was not randomized. Similarly, in an arguably underpowered retrospective analysis, Kossoff and colleagues reported that efficacy of high-dose prednisolone (40–60 mg/day) was similar to historical experience with high-dose natural ACTH. Similarly, in a relatively small study evaluating short-term efficacy of “very high dose” prednisolone (8 mg/kg/day; max 60 mg/day) followed by high-dose natural ACTH in prednisolone nonresponders, the EEG-confirmed response to prednisolone (63%) was comparable to the reported ACTH response in most contemporary studies. However, among the 10 prednisolone nonresponders, 4 children then responded to ACTH, though 2 subsequently relapsed, and none of the 4 ACTH responders exhibited enduring hypsarrhythmia on day 14 when ACTH was initiated. More recently, in a large-scale prospective observational study conducted by the National (United States) Infantile Spasms Consortium without randomized treatment allocation, Knupp and colleagues reported that response rates to natural ACTH (most with high-dose protocol; 150 U/m²/day) and oral corticosteroids (most with high-dose prednisolone; 40–60 mg/day) were statistically indistinct, although there was a trend favoring ACTH. In a follow-up analysis that carefully adjusted for prescribing bias, response rates for ACTH and corticosteroids were nearly identical. In the only contemporary randomized controlled trial comparing high-dose prednisolone (40–60 mg/day) with moderate-dose sACTH (0.5–0.75 mg on alternate days), Waningasinghe and colleagues found that response to prednisolone was superior, although the response rate to sACTH was inexplicably low (36%). It is critical to note that high-dose ACTH has not been compared to high-dose prednisolone in an adequately powered randomized controlled trial. Perhaps more importantly, all of the aforementioned comparisons have focused on short-term outcomes. Only a handful of studies have evaluated long-term epilepsy and developmental outcomes, and none permits adequate comparison of competing hormonal therapies. In the United States, the choice between ACTH and prednisolone is especially contentious given the enormous disparity in cost between these agents. Whereas the cost of a typical course of ACTH exceeds 100,000 USD, a typical course of prednisolone costs less than 100 USD.

Although the comparative effectiveness of ACTH, sACTH, and prednisolone is subject to ongoing debate, there is general agreement that all hormonal therapies exhibit similar—and substantial—adverse event profiles. The chief risks are immunosuppression, which can be severe and potentially lethal, as well as hypertension, with the potential to yield congestive heart failure. As such, avoidance of infectious contacts and screening for asymptomatic hypertension are key safety measures to be enacted during any course of hormonal therapy. In addition, a subset of clinicians (1) prescribe antibiotic prophylaxis for pneumocystis pneumonia, (2) screen for asymptomatic hyperglycemia, (3) monitor serum potassium given modest risk of hypokalemia, and (4) screen for adrenal or pituitary insufficiency after a course of hormonal therapy.

Whereas it is well established that ACTH stimulates endogenous cortisol production in the adrenal cortex, and that both cortisol and prednisolone (a close structural analog) exert similar corticosteroid effects, the precise mechanisms by which hormonal therapies impact ES and hypsarrhythmia are unknown. It is important to note that the debate surrounding ACTH and prednisolone is in part fueled by the hypothesis that ACTH may act via cortisol production as well as corticosteroid-independent mechanisms mediated by central melanocortin receptors.

**Vigabatrin**

Vigabatrin (VGB) is an irreversible inhibitor of γ-aminobutyric acid (GABA) transaminase, with demonstrated efficacy in the treatment of IS in several randomized, controlled trials. However, in comparison to the hormonal therapies, short-term response rates to VGB are considerably lower. With the respect to long-term outcomes, the superiority of hormonal therapy is not as
clear. In the only controlled trial with rigorous long-term follow-up, patients randomized to VGB or hormonal therapy were statistically indistinct with respect to sustained freedom from ES at 1 year and developmental outcome at age 4 years. Still, among the subgroup of patients with unidentified etiology, developmental outcome was indeed superior among those treated with hormonal therapy. It is notable that the impression that hormonal therapy exhibits superior efficacy does not necessarily generalize to children with TSC. Although a large-scale trial of VGB versus high-dose hormonal therapy has not been undertaken in a TSC cohort, several studies indeed suggest that response to VGB is substantially higher among patients with TSC in comparison to patients with other etiologies. Accordingly, there is broad consensus that patients with IS in the setting of TSC should receive first-line treatment with VGB.

Despite this established efficacy, the use of VGB has been limited by reports of retinopathy manifesting with permanent bilateral concentric peripheral visual field defects in both adults and children. Subsequent to these reports, estimates of the risk and severity of visual field loss have varied considerably. In a large-scale meta-analysis, Maguire and colleagues found that visual field loss among patients treated for focal seizures was high in adults (52%) and somewhat lower in older children (34%). In contrast, 2 small case series describing children with VGB exposure during infancy each reported risk of visual field loss under 7%, as measured by kinetic perimetry performed years later. These disparate risk estimates have fueled speculation that visual field loss may be age-dependent or reversible. However, yet another larger study of children with infantile VGB exposure found a duration-dependent risk of visual field loss, ranging from 9% among children treated less than 12 months to 63% among children treated greater than 2 years, with visual field loss established by perimetry at the age of 9 years. Further complicating the interpretation of these reports is a lack of consensus as to the minimum age or developmental status required of children undergoing kinetic perimetry. False positive results frequently occur with a lack of robust cooperation on the basis of youth and intellectual status. The challenge of visual field testing in young children has prompted many clinicians to employ electrophysiology (ERG) to evaluate the retina in an objective fashion in infants undergoing VGB treatment. In a recent and large-scale cohort study of children treated with VGB for IS, a significant reduction in 30-Hz ERG flicker response amplitude from baseline was observed among 21% of all patients, but just 6% of patients who received VGB for less than 6 months. Still, the adequacy of ERG-derived parameters as a surrogate measure of visual field integrity is controversial. In a study of 39 children who underwent both ERG and kinetic perimetry, Moskowitz and colleagues reported a lack of association between 30-Hz response amplitude and actual visual field defects on perimetry. It is notable that no study has adequately quantified or described how visual field loss affects patient functioning or quality of life after infantile VGB exposure. In a practical retrospective study of 104 patients with IS, the risk of clinically apparent vision loss attributed to VGB (i.e., ascertainable by parents and neurologists) was 0%. With these data in mind, it appears that the risk of meaningful vision loss is low, especially among infants with relatively brief (<1 year) VGB exposure.

Visual field loss is not the only potential adverse effect of VGB. Of arguably greater concern is the emergence of magnetic resonance imaging (MRI) toxicity, namely reversible high T2 signal and restricted diffusion in the thalami, basal ganglia, brainstem tegmentum, and cerebellar dentate nuclei (Fig. 1). Whereas this MRI toxicity has not been reported in older children and adults, the risk of asymptomatic MRI toxicity in infancy is approximately 20–30%. Furthermore, this risk has been linked to high dosage, younger age, and possibly concomitant hormonal therapy. Although the reversibility and largely asymptomatic character of these phenomena may afford some comfort, MRI toxicity has nevertheless been observed in association with hyperkinetic movement disorders including choreoathetosis, myoclonus, and tremor, as well as life-threatening acute encephalopathy and respiratory compromise. Still, the pathophysiology of these phenomena is unknown and a causal relationship between VGB and movement disorders, severe encephalopathy, and respiratory failure has not been established. In the study of Fong and colleagues, attribution of movement disorders to VGB exposure was specifically challenged, as the investigators identified multiple cases in which movement disorders occurred without MRI changes or VGB exposure, as well as patients among whom symptoms persisted despite VGB withdrawal or resolved despite VGB continuation.

Overall, VGB is moderately effective (and highly effective in the setting of TSC) and confers moderate risk. The threat of visual field loss is relatively low and perhaps mitigated by short courses of therapy, and the risk of reversible and usually asymptomatic MRI toxicity is moderately high and dose-dependent.

**Combination Therapy**

Instead of choosing hormonal therapy or VGB as initial therapy, a growing number of clinicians have instead opted to employ both therapies simultaneously from the outset. Given the relatively high rates of treatment failure with either therapy alone, as well as the adverse impact of treatment delay, the hypothesis that combination therapy is superior to either therapy alone is worthy of examination in a clinical trial. This was precisely the aim of the International Collaborative Infantile Spasms Study (ICISS), in which the investigators randomized new-onset patients with IS to receive either hormonal therapy (prednisolone or sACTH)
alone or hormonal therapy in combination with VGB. In contrast to hormonal therapy alone, the combination therapy group exhibited superior response rates with respect to clinical outcome (parent-reported freedom from ES on days 14–42), electroclinical outcome (aforementioned clinical outcome and resolution of hypsarrhythmia on post-treatment EEG), and time to cessation of ES (Fig. 2, panels A–C). Furthermore, combination therapy was relatively well tolerated; as expected, the burden of corticosteroid-associated side effects was similar—and substantial—in both groups. However, in considering the emergence of movement disorders and drowsiness/encephalopathy—2 side effects that could possibly reflect symptomatic VGB-associated MRI toxicity—the prevalence of these side effects was especially high in the combination therapy group. As illustrated in Figure 2 (panels D, E), among those randomized to hormonal therapy and combination therapy, respectively, movement disorders were reported among 1% and 8% ($p = 0.002$), and drowsiness was reported among 2% and 24% ($p < 0.001$). One may speculate that the high prevalence of these particular adverse events reflects not only the effect of VGB, but an elevated risk of symptomatic MRI toxicity, which may accompany combination therapy. Although “high MRI signal in the basal ganglia” was seldom reported in either treatment group, MRI to ascertain VGB toxicity was not a dedicated study procedure, and many of the patients were treated and evaluated prior to the first published accounts of VGB-associated MRI phenomena. Thus, some patients with MRI toxicity may have escaped detection.

It is important to note that although treatment allocation was randomized in the ICISS study, VGB administration was open-label (no placebo). As a result, the quantification of short-term clinical outcome and adverse events may have been influenced by bias. Conversely, short-term electroclinical outcome determined by blinded EEG reviewers was relatively protected from such reporting bias. Overall, it appears that combination therapy yields substantially higher short-term response rates, but there is some concern that combination treatment may impart elevated risk of VGB-associated MRI toxicity. Practitioners shall eagerly await the evaluation of long-term outcomes in the ICISS study as well as the results of a separate ongoing study being conducted by the National Infantile Spasms Consortium, which seeks to compare combination therapy with hormonal therapy alone and VGB alone (ClinicalTrials.gov NCT03 347526).

With only one randomized controlled trial supporting the use of combination therapy as initial treatment for IS, there has been only limited adoption of combination treatment protocols thus far. In addition to the need for a study replicating this finding, several related questions remain. (1) Even if combination therapy is superior to hormonal monotherapy, is it also superior to sequential therapy (e.g., ACTH or prednisolone 14 days followed by optional VGB 14 days) with outcome assessed at day 28? Indeed, limited observational data suggest that substantial response accompanies the use of VGB after hormonal therapy failure, as well as hormonal therapy following VGB failure. Similarly, in the study of Ko and colleagues, initial response to VGB monotherapy was modest, and cumulative response to add-on high-dose prednisolone was excellent. (2) Is there any benefit with respect to meaningful long-term outcomes including enduring seizure-freedom and subsequent intellectual performance? (3) Do these presumptive short- or long-term benefits justify the additional risk—and financial cost—of combination therapy? Until these questions are considered, we shall not reach consensus as to the ideal approach to initial treatment.

Figure 1.
Example of vigabatrin-associated MRI toxicity. These T2-weighted MRI images were acquired in a patient with symptomatic vigabatrin-associated toxicity (encephalopathy, respiratory compromise, and bradycardia) during vigabatrin exposure (panels A, B) and several months following vigabatrin discontinuation and symptomatic recovery (panels C, D). First published in Hussain et al. © ILAE Epilepsia Open 2018
A minority of children with IS are excellent candidates for surgical resection. The etiologies best suited to surgical resection include focal malformations of cortical development (chiefly cortical dysplasia), cortical tubers in association with TSC, and various acquired structural insults such as unifocal stroke or hemorrhage. Like epilepsy surgery evaluation in general, most favorable surgical targets are identified with the use of ictal and interictal video-EEG (scalp and/or intracranial), MRI, and positron-emission tomography (PET). However, the evaluation of IS is distinguished from other forms of epilepsy in that there is less reliance on EEG. ES, especially when hypsarrhythmia is present, are notoriously difficult to localize with EEG alone. Although hypsarrhythmia is sometimes focal (e.g., “hemi-hypsarrhythmia” seen ipsilateral to hemimegalencephaly), it is common to encounter diffuse and symmetric hypsarrhythmia (and similar patterns) in the setting of a focal cortical lesion. Similarly, in evaluating ictal EEG, the onset is typically diffuse, and in those cases in which focality or asymmetry is detected, it tends to be rather subtle. Despite the electrophysiologic challenges in localizing ES, short-term response rates following surgical resection approach 80% among children with complete resection of well-defined lesions. Furthermore, relapse rates are considerably lower among children who have responded to

**Surgery**

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**Figure 2.**

Key results of the International Collaborative Infantile Spasms Study. CT, combination therapy; HT, hormonal therapy. Adapted from O’Callaghan et al.56

*S. A. Hussain*
surgical resection in comparison to those who have responded to hormonal therapy or VGB.60

Although surgical resection is a well-established treatment option for highly selected patients with IS, the ideal sequence of treatment is unknown. For example, if a patient with IS is found to harbor a small temporal focal cortical dysplasia, must the patient try hormonal therapy and VGB before surgery is undertaken? Among patients with larger lesions such as hemimegalencephaly, there tends to be a lower threshold for pursuing surgical intervention. Similarly, comprehensive failure of medical therapy is more often viewed as a prerequisite for surgery among children with acquired structural abnormalities (e.g., stroke) in comparison to patients with focal malformations of cortical development—the latter viewed as exhibiting greater epileptogenicity.

Despite the added challenge of surgical evaluation of IS, functional outcomes following even large resections in infancy tend to be quite favorable, reflecting greater neuroplasticity in this age group. In the effort to refine the identification of the epileptogenic zone—the minimum volume of brain resection required to achieve enduring seizure freedom—advances in neuroimaging such as PET/MRI coregistration61 and the identification of localizing biomarkers such as fast ripples62,63 will hopefully yield higher response rates and superior functional outcomes.

In comparison to surgical resection, the role of nonresective surgical approaches is not well-established in the setting of IS. In particular, treatment of IS with corpus callosotomy (anterior-only, posterior-only, or complete) is controversial. With the hypothesis that bilateral ictal cortical synchrony is required to propagate an epileptic spasm (and that callosal disconnection may arrest this synchronization or otherwise disrupt a pathologic epileptic network which underlies IS) corpus callosotomy has been carried out with variable success in several uncontrolled case series.64,65 To the extent that a suspected focal epileptogenic zone may be obscured by hypsarrhythmia and seemingly generalized ictal electrographic onsets, corpus callosotomy has also been implemented as a means to identify focal onset and facilitate subsequent surgical resection.66 Nevertheless, the utility of corpus callosotomy is unclear, and although targeting a key structural mediator of interhemispheric hypersynchrony may be logical, this hypothesis is seemingly betrayed by the observation that IS often accompanies corpus callosus agenesis or hypoplasia.

With respect to surgical neurostimulation modalities, such as vagus nerve stimulation (VNS), there is speculation that functional modulation of brainstem and thalamic targets may effectively desynchronize the widespread cortical networks that mediate IS and hypsarrhythmia. However, although children with IS have been included in several series evaluating the efficacy of VNS among young children with epilepsy,67–69 IS-specific outcomes have been reported in only one study and were rather modest, without mention of any impact on hypsarrhythmia.67 In my own center’s experience with VNS in the treatment of 19 highly refractory children with IS, we have observed only one case with prompt resolution of both ES and hypsarrhythmia. It is notable that this collective experience has been limited to refractory cases, which are less likely to respond to any effective therapy. The efficacy of VNS may be more favorable in younger and less-refractory children.

**Special Cases**

Beyond TSC, there are rare instances in which a specific metabolic etiology of IS prompts a specific therapeutic intervention, either as an alternative or adjunct to first-line therapy.70 The most notable examples include pyridoxine (vitamin B6) dependency (treated with pyridoxine or levocovarin), pyridoxal-5-phosphate deficiency (treated with pyridoxal-5-phosphate), GLUT1 deficiency (treated with the ketogenic diet), and nonketotic hyperglycinemia (ameliorated to some extent by sodium benzoate and other interventions to promote central glycine clearance). Among these etiology-specific treatments, there is some evidence suggesting that high-dose pyridoxine is effective in the treatment of IS associated with etiologies other than pyridoxine dependency,71,72 although other evidence suggests little or no benefit.73

**Second-Line Therapies**

Aside from hormonal therapy, VGB, and surgery, a cornucopia of other (“second-line”) therapies are each supported by very limited—and often conflicting—reports of efficacy. Such data provide only modest enthusiasm for the use of an array of traditional antiseizure drugs including topiramate,74–77 zonisamide,78–82 valproic acid,83–87 felbamate,88–92 and various benzodiazepines—chiefly clonazepam86,93 and nitrazepam.94–96

Among nonpharmacologic therapies, the greatest attention has been focused on the ketogenic diet. Numerous studies suggest substantial efficacy for treatment of IS,97–111 and several investigators have advocated for implementation of the ketogenic diet as a first-line therapy before hormonal therapy or VGB.112,113 However, most of these studies are retrospective, and none have utilized placebo controls or unbiased outcome assessment. In particular, none have established rapid resolution of hypsarrhythmia with overnight video-EEG. Although several of the studies utilized EEG to bolster the impression of efficacy, EEG was generally implemented in an inconsistent fashion, often without video, and with short-duration studies performed months after ketogenic diet initiation. In contrast to these optimistic reports, in the experience of the author’s center with highly refractory cases of IS, the response rate to ketogenic diet therapy is disappointingly low.114

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Cannabidiol

Among investigational therapies for IS, cannabidiol (CBD) has garnered the most attention and merits special discussion. The hypothesis that CBD may be an effective therapy for IS is relatively new. In considering the use of CBD-enriched artisanal cannabis extracts, initial survey-based reports suggested potential—and seemingly miraculous—effectiveness in the treatment of Dravet syndrome, and were followed by similar reports in the treatment of Lennox-Gastaut syndrome and IS. These reports, in combination with evidence in vitro and in vivo data suggesting favorable efficacy and tolerability across diverse preclinical models, inspired pharmaceutical development of purified and synthetic CBD. However, whereas several controlled trials have now demonstrated substantial benefit of adjunctive purified CBD (Epidiolex, GW Pharmaceuticals) for the treatment of Dravet syndrome and Lennox-Gastaut syndrome, the potential efficacy of CBD for treatment of IS is not yet clear. A small but rigorous phase II study (led by the author and published only in abstract form, without adequate peer-review; Clinicaltrials.gov NCT02551731) evaluating the efficacy of pharmaceutical-grade synthetic CBD (20 mg/kg/day, divided b.i.d., × 14 days) in the treatment of refractory IS (after failure of both ACTH and VGB) reported complete response (freedom from ES and hypsarrhythmia on day 14) in just one of 9 subjects. The lone responder relapsed soon thereafter with return of ES, albeit with lower frequency than at baseline, and without return of hypsarrhythmia. Although this modest response (11%) was not statistically distinct from the estimated rate of spontaneous resolution of ES over 14 days (2%), it nevertheless provided the impetus for an ongoing large-scale randomized controlled trial evaluating CBD as a first-line adjunctive treatment for IS (Clinicaltrials.gov NCT03421496), thus targeting a population with a much higher likelihood of response to any effective therapy.

It is an understatement to point out that the clinical development of CBD has been unusual. Although pharmaceutical-grade CBD continues to be evaluated in clinical trials, a dizzying array of artisanal CBD preparations have been available—though illegal in most jurisdictions—for several years and have been used with little or no physician guidance. The anticipated entry of pharmaceutical CBD into markets in the United States and elsewhere will present patients, caregivers, and practitioners with competing CBD-containing products. Especially in the setting of refractory IS, in which the evidence base for any treatment is quite small, healthcare practitioners and caregivers will be confronted with difficult decisions. In contemplating a trial of CBD, they must weigh very limited (and highly varied) impressions of relative efficacy, safety, tolerability, cost, and even legal risk. Although CBD and a variety of cannabinoids represent an exciting new development in epilepsy therapeutics, myriad scientific questions abound. Among them: Is CBD effective and safe in the treatment of IS? Should CBD be administered with other specific cannabinoids (e.g., tetrahydrocannabinol) with the hypothesis that combination cannabinoid treatment may exert an “entourage effect”? Should CBD be given with other antiseizure drugs (e.g., clobazam) to leverage an advantageous drug–drug interaction and possible synergy? What is the mechanism of action? On this frontier, there are far more questions than answers, and the present use of CBD for treatment of IS should be carried out with great caution and with knowledge that CBD confers many potential risks.

A Proposed Treatment Algorithm

There is no agreement on what constitutes the ideal treatment algorithm for IS. Although there is robust agreement that hormonal therapy and VGB are the most effective therapies, this consensus is undercut by tremendous diversity in practice as it pertains to prescribed agents (e.g., specific forms of hormonal therapy), dosage, and schedule of administration, etc. Even worse, for treatment of refractory IS (i.e., after failure of both hormonal therapy and VGB) there is scarcely any evidence-based guidance at all. Reflecting this author’s impressions that (1) combination therapy is more effective than hormonal therapy or VGB alone, (2) high-dose regimens are more effective than low-dose regimens (for both hormonal therapy and VGB), and (3) VGB exhibits relatively favorable tolerability over the first year of therapy, the following treatment protocol has been enacted at the UCLA Mattel Children’s Hospital and is offered for the reader’s consideration (Fig. 3). The most important aspect of this protocol is the speed with which individual therapies are trialed, with the mandate that any therapeutic strategy be modified if successful response is not yielded within 2 weeks. This concept also holds when initial first-line therapies fail. Although the odds of response to any particular second-line therapy are low, the cumulative likelihood of response to one of many second-line therapies—when trialed consecutively and quickly—is reasonably high and justifies continued aggressive treatment of refractory IS.

The other novel aspect to this protocol is the strategic use of follow-up EEG after successful response to therapy. Based on the reported association of IS relapse with the presence (and often the reemergence) of multifocal epileptiform discharges one month after successful treatment, we routinely obtain repeat video-EEG (including a full wake-sleep-wake cycle) to risk-stratify patients. Among patients with abundant multifocal discharges one month
after response, it is typical (although not evidence-based) for us to titrate VGB dosage in an effort to reduce relapse risk.

**Future Aims**

Despite the identification and continued optimization of moderately effective therapies, there is tremendous demand for safer and more effective options. There is need for both the discovery of novel therapeutic candidates as well as the careful reevaluation of various second-line therapies for which efficacy is uncertain. It is also possible that our current first-line therapies may be reinvented: There is potential that ACTH fragments or analogues may yield a more favorable balance of efficacy and safety, and that a contemporary VGB analogue (CPP-115) may exhibit greater potency and safety than VGB itself. It is important to note that with recognition that the cumulative relapse rate approaches 50% among children followed to age 4 years, our patients require therapies that can be initiated in infancy and safely continued for several years to mitigate the risk of relapse. To a large extent, the relatively slow pace of drug discovery for IS may reflect an inadequate

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**Figure 3.**

A proposed protocol for treatment of infantile spasms. *Prednisolone dosage according to the UKISS/ICISS protocols is a reasonable weight-independent alternative (i.e., 10 mg 4 times daily for 1 week, with further titration to 20 mg 3 times daily among initial nonresponders). If sACTH is used, UKISS/ICISS dosing is suggested (0.5 mg on alternate days for 1 week, with further titration to 0.75 mg on alternate days among initial non-responders). Relapse risk is associated with multifocal epileptiform discharges on follow-up EEG 1 month after successful treatment (Hayashi et al.). An abundance of epileptiform discharges may thus prompt escalation of treatment (especially VGB) to reduce relapse risk. ACTH, adrenocorticotropic hormone; BID, twice-daily administration; CBD, cannabidiol; CLN, clonazepam; ES, epileptic spasms; FBM, felbamate; HYPS, hypsarrhythmia; KETO, ketogenic diet; PRED, prednisolone; sACTH, synthetic adrenocorticotropic hormone; TID, thrice-daily administration; TPM, topiramate; VEEG, video-electroencephalography; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.*

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assortment of preclinical models. None of the proposed models adequately recapitulates the cardinal electroclinical features (i.e., hypsarrhythmia and unprovoked ES) and pharmacologic response profile in humans.\textsuperscript{127,128} Although these challenges are daunting, collective optimism is nevertheless warranted. There is a growing community of physicians and scientists committed to the study of IS, and there are multiple promising drugs in the development pipeline.

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