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### Authors

Pellock, John M  
Hrachovy, Richard  
Shinnar, Shlomo  
et al.

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## SPECIAL REPORT

### Infantile spasms: A U.S. consensus report

\*John M. Pellock, †Richard Hrachovy, ‡Shlomo Shinnar, §Tallie Z. Baram, ¶David Bettis, #Dennis J. Dlugos, \*\*William D. Gaillard, ††Patricia A. Gibson, †††Gregory L. Holmes, §§Douglas R. Nordli, ¶¶Christine O'Dell, ###W. Donald Shields, \*\*\*Edwin Trevathan, and †††James W. Wheless

\*Division of Child Neurology, Department of Neurology, Virginia Commonwealth University School of Medicine, Richmond, Virginia, U.S.A.; †Peter Kellaway Section of Neurophysiology, Department of Neurology, Baylor College of Medicine, Houston, Texas, U.S.A.; ‡Department of Neurology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, U.S.A.; §Department of Neurology, University of California Irvine School of Medicine, Irvine, California, U.S.A.; ¶Pediatric Neurology of Idaho, Boise, Idaho, U.S.A.; #Department of Neurology, The Children's Hospital of Philadelphia/University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, U.S.A.; \*\*Department of Neurology, Children's National Medical Center, Washington, District of Columbia, U.S.A.; ††Director, Epilepsy Information Service, Associate Director, Comprehensive Epilepsy Program, Wake Forest University, Winston-Salem, North Carolina, U.S.A.; †††Department of Neurology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, U.S.A.; §§Epilepsy Center, Children's Memorial Hospital, Chicago, Illinois, U.S.A.; ¶¶The Comprehensive Epilepsy Management Center, Montefiore Medical Center, Bronx, New York, U.S.A.; ###Department of Neurology, Mattel Children's Hospital at University of California, Los Angeles, Los Angeles, California, U.S.A.; \*\*\*National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, U.S.A.; and †††Department of Pediatric Neurology, University of Tennessee Health Science Center, Memphis, Tennessee, U.S.A.

#### SUMMARY

The diagnosis, evaluation, and management of infantile spasms (IS) continue to pose significant challenges to the treating physician. Although an evidence-based practice guideline with full literature review was published in 2004, diversity in IS evaluation and treatment remains and highlights the need for further consensus to optimize outcomes in IS. For this purpose, a working group committed to the diagnosis, treatment, and establishment of a continuum of care for patients with IS and their families—the Infantile Spasms Working Group (ISWG)—was convened. The ISWG participated in a workshop for which the key objectives were to review the state of our understanding of IS, assess the scientific evidence regarding efficacy of currently available therapeutic options, and arrive

at a consensus on protocols for diagnostic workup and management of IS that can serve as a guide to help specialists and general pediatricians optimally manage infants with IS. The overall goal of the workshop was to improve IS outcomes by assisting treating physicians with early recognition and diagnosis of IS, initiation of short duration therapy with a first-line treatment, timely electroencephalography (EEG) evaluation of treatment to evaluate effectiveness, and, if indicated, prompt treatment modification. Differences of opinion among ISWG members occurred in areas where data were lacking; however, this article represents a consensus of the U.S. approach to the diagnostic evaluation and treatment of IS. **KEY WORDS:** West syndrome, Encephalopathic epilepsy, Adrenocorticotrophic hormone, Vigabatrin, Corticosteroids, Infantile spasms, Treatment.

Infantile spasms (IS), or West syndrome, one of the most recognized types of epileptic encephalopathy, constitutes a distinct and often catastrophic form of epilepsy of early infancy (West, 1841). The disorder presents with a unique seizure type, infantile spasms, which may be characterized by flexor, extensor, and mixed flexor–extensor spasms; a

distinct electroencephalography (EEG) pattern of hypsarrhythmia; and psychomotor delay/arrest (Commission on Pediatric Epilepsy of the International League Against Epilepsy, 1992). Typically, the spasms involve brief symmetrical contractions of musculature of the neck, trunk, and extremities, lasting up to 5 s, and frequently occur in clusters (Jeavons & Bower, 1964; Trevathan et al., 1999; Wong & Trevathan, 2001). IS is often associated with many underlying disorders; it is estimated that 60–70% of patients with IS have an associated underlying disorder that is evident (symptomatic IS) (Jellinger, 1987; Riikonen, 2001a). In 10–40% of patients, no underlying cause is detected and patients have a history of normal development prior to onset

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Address correspondence to John M. Pellock, MD, Professor and Chair, Division of Child Neurology, Department of Neurology, Children's Pavilion, 1001 East Marshall Street, Richmond, VA 23298, U.S.A. E-mail: jpellock@mevh-vcu.edu

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(cryptogenic IS). In general, this subset of patients may have a better prognosis.

Although IS was first described more than 160 years ago (West, 1841), its diagnosis, evaluation, and management continue to pose many challenges to the treating physician. The spasms almost always resolve over time, but they are often replaced by other types of refractory seizures. Developmental outcome is poor in a majority of patients with IS, and a majority of children with IS have mental retardation (MR). In one population-based survey, 80% of 10-year-old children with a diagnosis of IS had some form of MR (Trevathan et al., 1999). In this report, 40% of IS patients had cerebral palsy, 94% had active epilepsy at age 10 years, 50% progressed to Lennox–Gastaut syndrome before age 11, and 15% of patients died before age 11 years. In most other series, the rate of progression to Lennox–Gastaut is in the 15–20% range (Hrachovy & Frost, 2003). IS is also associated with a poor neuropsychiatric outcome, in particular the development of autistic spectrum disorders (ASD) in some symptomatic IS patients (Riikonen & Amnell, 1981; Saemundsen et al., 2007). How frequently these patients go on to develop ASD is an area of great interest, particularly with the increased recognition of autism and the focus on the comorbidities of epilepsy syndromes. Most believe that early diagnosis and prompt institution of effective therapy may positively impact outcome, particularly in patients with cryptogenic IS (Darke et al., 2006; Kivity et al., 2004; Riikonen, 1982). Although effective therapeutic options for IS are limited, there is growing agreement among pediatric neurologists regarding selection of therapeutic agents, timing, dosage, and duration of therapy (Wheless et al., 2005, 2007). Robust longitudinal comparative clinical data from well-designed and sufficiently powered prospective clinical trials are needed to build consensus (Mackay et al., 2004).

Recently, a working group committed to the diagnosis, treatment, and establishment of a continuum of care for patients with IS and their families—the Infantile Spasms Working Group (ISWG)—participated in a 2-day workshop. The ISWG included pediatric neurologists with expertise in IS, representatives from federal research agencies, and not-for-profit organizations involved in supporting scientific research and providing resources to families and patients with IS. There were three key goals of the workshop. The first was to review the current state of IS. The second objective was to assess the scientific evidence regarding efficacy of currently available therapeutic options. Currently, adrenocorticotrophic hormone (ACTH) and vigabatrin (VGB; approved for use in the United States in August 2009) are first-line therapies available in the United States (Mackay et al., 2004); however, these agents are not effective in all cases and there is an urgent need for the development of additional therapeutic options for IS. The third objective was to arrive at a consensus on protocols for diagnostic workup and management of IS that

can serve as a guide to help specialists and general pediatricians optimally manage children with IS. Following the workshop, with continued vigorous discussion among all authors, this article was developed to provide an overview of IS and recommend agreed-upon practices for diagnostic evaluation, selection, and implementation of therapy; assessment of treatment efficacy; and follow-up.

## EPIDEMIOLOGY AND ETIOLOGY OF IS

The incidence of IS ranges from 2 to 3.5 per 10,000 live births. Most cases present at peak age of onset between 3 and 7 months, with 90% of patients presenting in the first year; onset after 18 months is rare, although onset up to 4 years of age has been reported (Ludvigsson et al., 1994; Riikonen, 2001a; Trevathan et al., 1999). IS occurs in children from all ethnic groups, and boys are affected slightly more often than girls (ratio 60:40) (Ludvigsson et al., 1994; Riikonen, 2001a; Trevathan et al., 1999). One study reported the lifetime prevalence of IS at 10 years of age as 1.5 to 2 per 10,000 children (Trevathan et al., 1999). Those with IS have an increased risk of mortality due to underlying disease etiology and comorbid conditions; therefore, a lower prevalence rate compared to incidence may be a result of high mortality.

IS can be classified by two etiologies: symptomatic and cryptogenic. Patients with symptomatic IS have a clearly defined underlying cause and/or significant developmental delay prior to onset of spasms. In cryptogenic IS, no underlying cause is identified and normal development is present prior to the onset of spasms (Wong & Trevathan, 2001). The percentage of symptomatic IS cases has increased due to improved diagnostic techniques such as metabolic and genetic testing and neuroimaging. Causes of IS may be prenatal, perinatal, or postnatal. Approximately 50% of cases have a prenatal cause, which includes central nervous system malformations, intrauterine insults, neurocutaneous syndromes such as tuberous sclerosis complex (TSC), metabolic disorders, and genetic syndromes such as Down's syndrome. TSC is an important cause of symptomatic IS (Webb et al., 1996), and the specific mutation appears to influence the risk of IS in TSC (Jansen et al., 2008). Development of IS in children with TSC is closely associated with the development of ASD in later years (Saemundsen et al., 2007, 2008), and 75–80% of individuals with TSC may develop epilepsy. Perinatal causes of IS include hypoxic–ischemic encephalopathy. Postnatal causes include trauma, infection, and tumors. Outcomes may be more favorable in cryptogenic IS than in symptomatic varieties of IS (Ludvigsson et al., 1994), and are mostly dependent on IS etiology. Spasms usually cease by age 3–5 years, but seizures are reported in 60% of IS patients even after cessation of spasms (Riikonen, 1982). Prognosis is better in patients with cryptogenic IS who are treated early (Singer et al., 1980; Riikonen, 1982; Sher & Sheikh, 1993; Kivity et al., 2004).

## PATHOPHYSIOLOGY OF IS

Little is known about the pathophysiology of IS, and the apparent causes of IS in individual children are extremely variable (Jeavons & Bower, 1964). This has led to the consideration that there might be a common mechanism by which all of the different etiologies of IS might converge to lead to these seizures (Baram, 1993). The hypotheses have varied from considerations of immune activation within the brain (Haginoya et al., 2009; Mota et al., 1984) to the possibility that all of the diverse neurologic problems associated with IS might be stressful to the developing brain, activating proconvulsant stress mechanisms (Brunson et al., 2001). Human studies provide some support for these hypotheses (Baram et al., 1992b), but animal models are required to further the understanding of the pathophysiology of IS, to study pathogenic mechanisms, and to develop and test new treatments (Baram, 1993, 2007; Scantlebury et al., 2007; Stafstrom, 2009). Due to its multiple etiologies, there are challenges in the development of a model for IS (Baram, 2007). The great number of etiologies in symptomatic IS suggests that there may be common pathways involved (Baram, 1993; Hrachovy & Frost, 2008). Ideally, the model would closely mimic the disease in humans and would be characterized by onset during early development, occurrence of spasms and their relationship to the sleep–wake cycle, presence of hypsarrhythmia, poor response to conventional antiepileptic drugs (AEDs), cognitive deficits, and, possibly, response to therapeutic agents that are effective in humans (see Table 1).

Current IS models either focus on a specific cause of IS, such as the loss of interneurons (aristaless-related homeobox [ARX] mouse) (Marsh et al., 2009), or propose a final common pathway underlying all causes of IS. When considering common mechanisms or pathways in IS models, there are two potential mechanisms proposed in the pathogenesis of IS—increased excitability and loss of inhibition. The stress/corticotropin-releasing hormone (CRH) hypothesis proposes that the common mechanism in all of the etiologies

of IS causes an increase in the release of stress-activated mediators in the brain, especially the neuropeptide CRH in limbic and brainstem regions in patients with IS (Baram, 2007). CRH causes seizures in developing rodents (Baram et al., 1992a; Baram & Schultz, 1995). ACTH suppresses the synthesis of CRH, which might be a mechanism for the efficacy of this stress hormone in IS (Brunson et al., 2001; Baram, 2007). The *N*-methyl-D-aspartic acid (NMDA) and stress hormones model is an additional model related to the pathway of stress-induced excitability (Velisek et al., 2007). Another animal model is the tetrodotoxin (TTX) model (Lee et al., 2008), which is compatible with the developmental desynchronization hypothesis of IS (Frost & Hrachovy, 2005). Models related to the loss of inhibition common pathway include the ARX-reduced  $\gamma$ -aminobutyric acid (GABA)ergic inhibitory interneurons model currently under development, the triple hit model (Scantlebury et al., 2007), the TTX model, and the Ts65D mouse model (Cortez et al., 2009).

## PATIENT EVALUATION AND DIAGNOSTIC WORKUP

The IS clinical evaluation begins with the history and physical examination of the patient (Hrachovy & Frost, 2003; Shields, 2006). Parental or physician observation of spasms (ictal phenomena) characterized by symmetric or asymmetric (rare) clusters of flexor, extensor, or mixed axial jerks directs the clinical evaluation toward IS (Kellaway et al., 1979; King et al., 1985; Hrachovy & Frost, 1989). The semiology of IS may vary significantly depending on the muscle groups involved, the intensity of the contraction, and position of the patient during the attack—whether supine or sitting. A clinical spasm is represented by three different ictal EEG patterns: a positive-vertex slow wave of medium to high amplitude; a spindle-like activity of medium amplitude; and diffuse flattening (decremental activity) (Fusco & Vigeveno, 1993) (see Figs. 1 and 2). Spasms are variable in frequency; may be brief, sudden, and as subtle as a head nod; and may be easily missed (Hrachovy & Frost, 2003; Lux & Osborne, 2004). Parents substantially underestimate the number of spasms that their children are experiencing. In some cases the events are subtle and may not even be recognized. In those settings a home video of the events may prompt recognition and referral for the appropriate diagnostic workup and therapeutic intervention.

In most cases, there is an initial phasic component lasting less than 1–2 s, followed by a less intense, but generally more sustained tonic contraction, which could last up to 10 s. However, in some infants, the tonic phase may be absent and only the initial phasic component is seen. The number of spasms varies from as few as 2 to more than 100, and the duration of a cluster may vary from less than 1 min

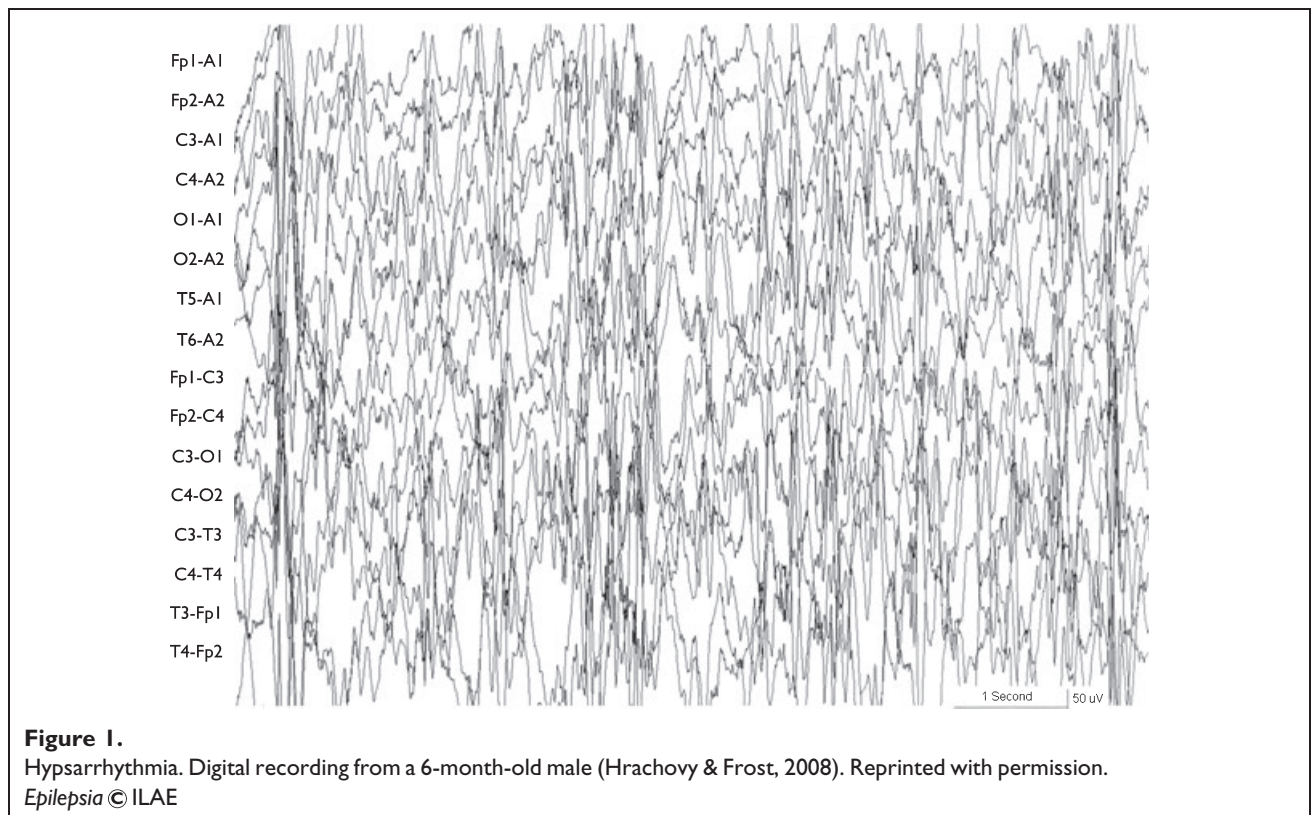
**Table 1. Animal models for infantile spasms**

Features	Model				
	TTX <sup>a</sup>	NMDA/GC <sup>b</sup>	CRH <sup>c</sup>	Triple hit	ARX <sup>d</sup>
Onset during early development	Yes	Yes	Yes	Yes	Yes
Biologic relevance	?	Yes	Yes	?	Yes
Spasms	Yes	Yes	No	Yes	No
Spontaneous spasms	Yes	No	No	No	No
Hypsarrhythmia	Yes	No	No	?	No
Cognitive deficits	?	?	Yes	?	Yes

<sup>a</sup>Tetrodotoxin; <sup>b</sup>*N*-methyl-D-aspartic acid/glucocorticoid; <sup>c</sup>Corticotropin-releasing hormone; <sup>d</sup>Aristaless-related homeobox.

Table courtesy of Tallie Baram, MD, PhD. Effects of hormonal therapy, vigabatrin, or other AEDs in these models are not yet well elucidated.





to more than 10 min. Coupling of different seizure types may occur—a focal electrographic seizure discharge may precede a spasm or cluster of spasms or follow a spasm and, in some cases, the focal electrographic seizure discharge may occur during a cluster (Plouin et al., 1993; Hrachovy et al., 1994a). Parents may notice a change in behavior that precedes the cluster and appears to announce the onset of the cluster.

In addition to clinical spasms, the defining features of IS include hypsarrhythmia and developmental regression. Interictal EEGs of IS are characterized by hypsarrhythmia with chaotic, nonrhythmic, asynchronous, disorganized, high-voltage spike and slow-wave activity (Wong & Trevathan, 2001; Lux & Osborne, 2004) (see Fig. 1). Classic hypsarrhythmia is described as random, high-voltage, slow waves and spikes in all cortical areas that vary from moment to moment in duration and location, and occasionally the spike discharge may become generalized. Variations in the classic hypsarrhythmia pattern include increased interhemispheric synchronization, asymmetry, a consistent focus of abnormal discharge, episodes of attenuation (local, regional, or general), high-voltage bilaterally asynchronous slow activity, excessive rapidity, excessive slowing, fragmentation, and increased periodicity (Hrachovy et al., 1984; Lux & Osborne, 2004). The hypsarrhythmic pattern is most frequent during non-rapid eye movement (REM) sleep, followed by waking and arousal, and it does not occur or is greatly reduced during REM sleep (Hrachovy et al., 1984;

Watanabe et al., 1993). However, patients with hypsarrhythmia often have very reduced non-REM sleep, which can, therefore, be difficult to recognize (Hrachovy et al., 1984). A full EEG evaluation will not only capture a full sleep-wake cycle but will also capture an ictal event (Hrachovy & Frost, 2003).

Evaluating the EEG is critical for the diagnosis of IS and for patient management (Drury et al., 1995; Haga et al., 1995; Hrachovy & Frost, 2003; Lux & Osborne, 2004). It is recommended that an EEG evaluation be conducted as soon as possible following the identification of spasms. Following EEG documentation of hypsarrhythmia or its variants, diagnostic procedures to determine IS etiology, including magnetic resonance imaging (MRI), are performed and treatment should be initiated. The recommended approach to EEG evaluation is an overnight inpatient 24-h video-EEG (Lux & Osborne, 2004), which may help to capture clinical events and document EEG while patient is awake and during all stages of sleep. If hypsarrhythmia does not occur, the EEG should be prolonged or repeated within 1 week or as clinically indicated. If an inpatient video-EEG is not available, a prolonged 2- to 4-h EEG during a waking and sleep period may be sufficient. It is particularly important to capture non-REM sleep.

Once spasms and hypsarrhythmic EEG have been documented, etiologic diagnosis becomes the focus of the IS clinical evaluation (Shields, 2002a,b; Hrachovy & Frost, 2003). Etiologic diagnosis is essential, as it may lead to

specific therapy (Hrachovy & Frost, 2003; Lux & Osborne, 2004), and the associated specific therapy may significantly alter the developmental outcome and treatment strategy. For example, a patient with IS and TSC is likely to receive VGB as a first-line treatment (though ACTH is also reported effective), whereas patients with cryptogenic IS or symptomatic IS without TSC are more likely to receive ACTH as a first-line treatment. Those with underlying brain malformations of cortical development may be candidates for surgical intervention if they do not respond promptly to medication (see subsequent text).

MRI is recommended to assist with the etiologic diagnosis of patients with IS. In children younger than 2 years, MRI including three-dimensional (3D) T<sub>1</sub>-weighted gradient-recalled-echo sequence, axial and coronal T<sub>2</sub>, and fluid-attenuated inversion recovery (FLAIR) sequences is recommended to assist with the etiologic differential diagnosis. For children who are younger than 1 year, FLAIR and 3D T<sub>1</sub>-weighted imaging is less helpful than high-resolution coronal and axial T<sub>2</sub>-weighted sequences with axial, coronal, and sagittal T<sub>1</sub> sequences (Gaillard et al., 2009). Magnetization transfer imaging may also be useful in identifying malformations of cortical development; magnetic resonance spectroscopy (MRS) may be helpful in identifying children with some inborn errors of metabolism. There are no class I or class II imaging studies in children with IS. Among class III and IV studies, 40–50% of patients showed clear migration abnormalities or syndromes, and 20% showed nonspecific abnormalities (e.g., atrophy) (Aydinli et al., 1998; Saltik et al., 2003). Early imaging is important to assist with etiologic differential diagnosis. Repeat imaging is recommended if the patient does not respond to treatment or does not follow the expected course associated with the etiologic diagnosis, and in cases where there is clinical deterioration (Gaillard et al., 2009). In addition, in very young infants, focal cortical dysplasia (FCD) may not be detectable at early imaging and only appears with maturation of myelination by age 24–30 months (Gaillard et al., 2009; Natsume et al., 1996). Fluorodeoxyglucose–positron emission tomography (FDG-PET) is recommended when surgical options are considered and especially when there is evidence for, or to seek evidence for, focality when MRI is normal (Gaillard et al., 2009).

Ideally, MRI should be obtained prior to the initiation of therapy, as ACTH treatment may cause transient abnormalities that may falsely be interpreted as brain atrophy (Konishi et al., 1992) and VGB treatment has been associated with T<sub>2</sub> changes. In the United States, children with IS are almost always evaluated at centers where MRI is available, and MRI is the procedure of choice. Therefore, computed tomography (CT) scans have a limited role. In cases where MRI will be delayed either due to lack of immediate availability or need for anesthesia, treatment should not be unduly delayed and imaging can be obtained at a later time.

Following completion of the history, physical, and neurologic examinations, and analysis of EEG and MRI, approximately 70% of patients will have an established etiologic diagnosis without the need to conduct extensive metabolic testing, saving valuable time to initiation of treatment and reducing evaluation costs (see Table 2). Of the remaining 30% of patients, a metabolic etiology will likely be established for less than 50%, and the rest will be labeled as cryptogenic. Potentially treatable and reversible causes of IS, such as pyridoxine-dependent seizures, should always be considered early. A challenge with pyridoxine dosed at 100 mg, i.v., may be administered to screen for pyridoxine-dependent seizures. However, unless an underlying metabolic disorder is diagnosed, there are few data to support pyridoxine as a first-line treatment for IS (Mackay et al., 2004). Infants without a determined etiologic diagnosis following the history, physical and neurologic evaluations, and EEG and MRI studies should be considered for further evaluation, which, depending on the individual circumstances, may include pyridoxine challenge; urine for organic acids; serum for amino acids; biotinidase determination; lumbar puncture to include neurotransmitters, lactic acid, amino acids, and folate metabolites, cerebrospinal fluid (CSF) glucose and glycine; and chromosomal studies (Table 2). Other biochemical testing may be suggested by a patient's clinical course and future study findings. In countries in which newborns are not routinely screened for metabolic disorders, such as phenylketonuria, a more comprehensive metabolic workup may be needed. Testing for gene mutations or rare chromosomal disorders, such as *ARX* in males or *CDKL5* in females, may also be considered in patients with suggestive characteristics.

## THERAPEUTIC OPTIONS FOR IS

The most recent practice parameter from the American Academy of Neurology (AAN) and the Child Neurology Society (CNS) for the medical treatment of IS, which is based on the available evidence as of 2004, concludes that ACTH is probably effective and VGB is possibly effective (Mackay et al., 2004). The practice parameter also states that VGB is possibly effective for children with TSC and IS. At the time that the practice parameter was published, there was insufficient evidence to recommend oral corticosteroids or valproic acid as first-line treatments in IS; however, high-dose oral prednisolone has recently been reported to possibly be effective (Lux et al., 2004). The ketogenic diet may be considered for refractory patients; however, no controlled trials are available to show its efficacy in IS. Surgery may also be an option.

Currently there is insufficient evidence to recommend protocols using new or emerging therapies for IS (Mackay et al., 2004). Rapamycin, currently being evaluated within animal models for TSC, is an emerging therapy under investigation for IS (Zeng et al., 2008). In addition, for many

Table 2. Etiologic differential diagnosis for infantile spasms

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<p><b>History</b></p> <ul style="list-style-type: none"> <li>Hypoxic-Ischemic Encephalopathy</li> <li>Perinatal HIE<sup>a</sup></li> <li>Near Miss SIDS<sup>b</sup></li> <li>Cardiac Arrest</li> <li>Near Drowning</li> <li>Maternal Toxemia</li> <li>Trauma</li> <li>Encephalitis (usually Herpes)</li> <li>Meningitis</li> <li>Cerebral Abscess</li> <li>Transplacental Infections</li> <li>Post Cardiac Surgery</li> <li>Neonatal Hypoglycemia</li> </ul>	<p><b>Neuroimaging/MRI</b></p> <ul style="list-style-type: none"> <li>Tuberous Sclerosis</li> <li>Aicardi Syndrome</li> <li>Cortical Dysplasias</li> <li>Lissencephaly</li> <li>Pachygyria</li> <li>Hemimegalencephaly</li> <li>Band Heterotopia</li> <li>Focal Cortical Dysplasia</li> <li>Porencephaly</li> <li>Hypoxic-Ischemic Encephalopathy</li> <li>Tumor</li> <li>AVM<sup>c</sup></li> <li>Stroke</li> <li>Leigh Disease</li> <li>Hydranencephaly</li> <li>Corpus Callosum Agenesis/Dysgenesis</li> <li>Septo-Optic Dysplasia</li> <li>Schizencephaly</li> <li>Holoprosencephaly</li> <li>Sturge-Weber Syndrome</li> <li>Multiple Pineal Cysts</li> <li>Transplacental Infections</li> <li>Periventricular Leukomalacia</li> <li>Krabbe Disease</li> </ul>	<p><b>Metabolic Evaluation</b></p> <ul style="list-style-type: none"> <li>Pyridoxine Dependent Seizures</li> <li>Phenylketonuria</li> <li>Maple Syrup Urine Disease</li> <li>Biotinidase Deficiency</li> <li>Menkes Disease</li> <li>Hyperammonemia disorders</li> <li>Non-ketotic Hyperglycinuria</li> <li>Leigh Disease</li> <li>Krabbe Disease</li> <li>ARX<sup>d</sup> and other emerging genes</li> <li>Others as indicated by patient course</li> </ul>
<p><b>Physical/Neurological Exam</b></p> <ul style="list-style-type: none"> <li>Neurocutaneous Disorders</li> <li>Tuberous Sclerosis</li> <li>Neurofibromatosis</li> <li>Sebaceous Nevus Syndrome</li> <li>Incontinentia Pigmenti</li> <li>Sturge-Weber Syndrome</li> <li>Epidermal Nevus Syndrome</li> <li>Hydrocephalus (+Imaging)</li> <li>Miller-Dieker Syndrome (+ Imaging)</li> <li>Down Syndrome</li> <li>Menkes Disease</li> </ul>		

<sup>a</sup>Hypoxic-ischemic encephalopathy; <sup>b</sup>Sudden infant death syndrome; <sup>c</sup>Arteriovenous malformation; <sup>d</sup>ARX aristaless-related homeobox.  
Table courtesy of W.D. Shields, MD.

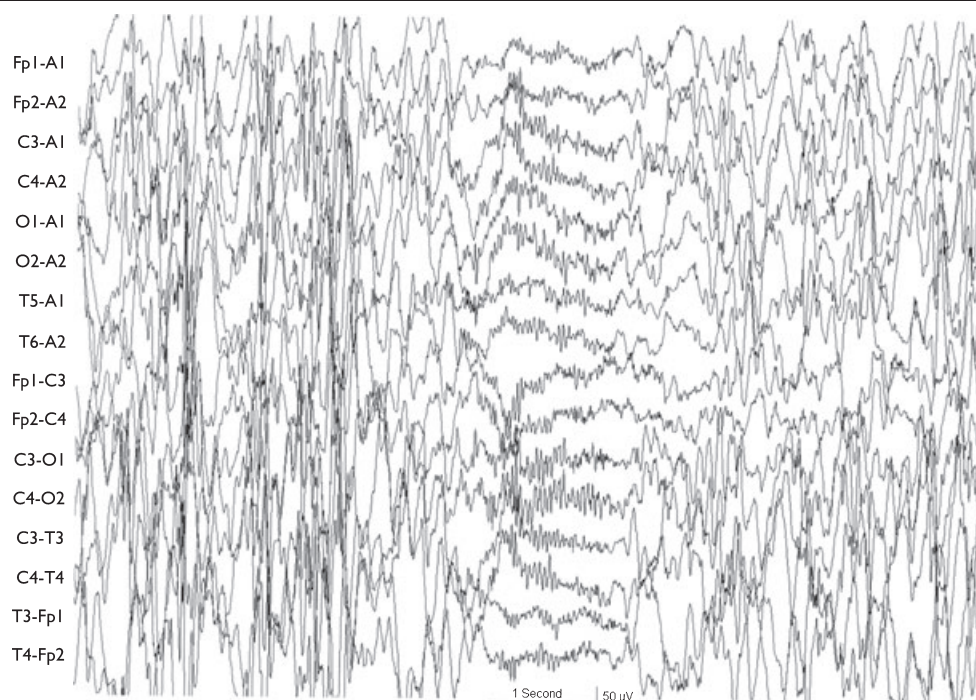
patients with IS, other forms of epilepsy may develop over time, requiring conventional AEDs. However, evidence does not support the clinical efficacy of benzodiazepines, phenobarbital, or most other conventional AEDs as effective treatments for IS (Mackay et al., 2004).

Goals for improving outcomes in IS include early recognition and diagnosis, short-duration therapy with a first-line treatment, timely EEG evaluation of treatment effectiveness, and, if indicated, prompt treatment modification. Effective treatment for IS should produce both cessation of spasms and normalization of the EEG in cryptogenic cases, and a resolution of hypsarrhythmia on EEG in symptomatic cases (Baram et al., 1996; Lux & Osborne, 2004; Mackay et al., 2004). Cessation of spasms and resolution of hypsarrhythmia are an “all-or-none” rather than a graded response to treatment (Baram et al., 1996; Hrachovy & Frost, 2003). This “all-or-none” treatment endpoint has been associated with the best cognitive and developmental outcomes, including reduced progression to other seizure disorders. Developmental outcomes are unclear, and it is not known if treatment produces a partial response in spasms and hypsar-

rhythmia. Effective short-duration treatment may avoid major side effects associated with first- and second-line treatments for IS (Partikian & Mitchell, 2007). Timely management of patients who are refractory to first-line therapy is critical (Hrachovy & Frost, 2003; Lux & Osborne, 2004). The dose of the chosen first-line agent should be adjusted to achieve the maximum effective dose in as short a period as clinically indicated. Treatment with the maximum dose of ACTH should be continued for 2 weeks, followed by taper, and then the treatment response should be evaluated (Baram et al., 1996; Hrachovy & Frost, 2003). This recommendation is based on the class 1 randomized clinical trial (Baram et al., 1996) that used both clinical and EEG response to evaluate outcomes, and had the highest reported efficacy rates using a relatively short period of high-dose treatment. Longer treatment periods have been used for prednisone and VGB prior to evaluation of treatment response (Elterman et al., 2001; Willmore et al., 2009); ongoing assessment of benefit versus risk of adverse events is critical.

If clinical improvement is reported or is unclear, a 24-h inpatient video-EEG is recommended. This will allow





**Figure 2.**

Digital recording from a 6-month-old male showing ictal EEG change associated with infantile spasms. Note the period of voltage attenuation associated with superimposed fast activity (Hrachovy & Frost, 2008). Reprinted with permission.

*Epilepsia* © ILAE

documentation of subtle persisting spasms, persistence of hypsarrhythmia, and change in seizure type. If an inpatient 24-h video-EEG is not available, a prolonged EEG, including full wake and sleep cycle over 4–6 h, may be conducted. It is essential to obtain the EEG in deep non-REM sleep in order to determine if hypsarrhythmia has been resolved (Watanabe et al., 1993). Data are lacking on the best approach to take if spasms recur following an initial clinical response to treatment (i.e., relapse). Possible treatment options include returning to the previously effective treatment agent and dose protocol, returning to the previously effective treatment agent but at the maximum dose, or implementing a new treatment agent. If there is no treatment response, the current drug should be tapered and a new drug should be administered. The patient should then be reevaluated as described earlier.

It is suggested that effective therapy initiated early in the disease course may improve developmental outcomes; therefore, it is important to identify IS patients early and to initiate effective treatment promptly (Lombroso, 1983; Eisermann et al., 2003; Goh et al., 2005; Primec et al., 2006; Sharma & Vishwanthan, 2008; Bombardieri et al., 2010). Class I studies of the effects of delayed treatment are not available, and clinical outcome is dependent on many factors, including response to therapy and underlying etiology of IS. However, some studies suggest that a delay in

effective treatment appears to be associated with poorer developmental outcomes (Lombroso, 1983; Darke et al., 2006; Kivity et al., 2004). One study showed that infants with cryptogenic IS who received ACTH within 1 month of onset of IS fared better on the outcomes of cognitive testing and incidence of seizures at 6 years than did infants with delayed treatment (Lombroso, 1983). Treatment prior to the onset of marked developmental regression was associated with favorable long-term cognitive outcomes among cryptogenic IS patients receiving high-dose ACTH (Kivity et al., 2004). Data from the United Kingdom Infantile Spasms Study (UKISS) study, which excluded patients with TSC, suggest that better initial control of spasms in patients allocated to hormonal treatment (i.e., ACTH or prednisolone) was associated with significantly better neurodevelopment at 14 months and 4 years of age in infants with no identified underlying etiology (Lux et al., 2004, 2005; Darke et al., 2006). However, comparison of various treatments for IS is complicated by the small number of participants in each report, differing definitions of IS (clinical spasms  $\pm$  EEG), and varying definitions of response.

#### **Adrenocorticotrophic hormone (ACTH)**

The practice parameter from AAP, AAN, and CNS recommended the use of ACTH for IS (Mackay et al., 2004). Outside the United States, tetracosactide, a synthetic ACTH



compound, is frequently used; however, there are no comparative studies of tetracosactide and natural ACTH. Among randomized controlled trials, the clinical spasm and hypsarrhythmic EEG response rate to natural or synthetic ACTH has ranged from 42–87% of patients (Hrachovy et al., 1983, 1994b; Baram et al., 1996; Vigevano & Cilio, 1997; Lux et al., 2004), and associations between genetic polymorphisms of the *MC2R* and *MC4R* genes and variability in ACTH responsiveness in IS are currently being examined (Liu et al., 2007, 2008b). The ongoing, NIH-funded Epilepsy Phenome Genome Project is collecting 250 cases of cryptogenic IS as well as cases of IS with specific errors in brain development for detailed genetic analysis and will ultimately yield important information in this area.

In a study of high-dose natural ACTH (150 IU/m<sup>2</sup>/day given twice daily) administered over a short duration (i.e., 2 weeks, followed by taper as follows: 30 IU/m<sup>2</sup> in the morning × 3 days, 15 IU/m<sup>2</sup> in the morning × 3 days, 10 IU/m<sup>2</sup> in the morning × 3 days, and then 10 IU/m<sup>2</sup> every other morning for 6 days), Baram et al. (1996) reported that 87% of subjects responded with both clinical cessation of spasms and abolition of hypsarrhythmia on EEG. Natural ACTH at this regimen was superior to prednisone 2 mg/kg/day. A study by Lux et al. (2004), where the primary outcome measure was clinical cessation of spasms without EEG confirmation of the abolition of hypsarrhythmia, reported that synthetic ACTH given at the equivalent of 20 IU per day [40 IU alternate days tetracosactide] resulted in the cessation of spasms in 76% of patients. A similar response was seen using high-dose prednisolone (40–60 mg/day); however, this study was not powered to compare the two hormonal treatments. The combined hormonal therapy arm (tetracosactide or prednisolone) was reported to be superior to VGB in clinical cessation of spasms and other outcomes among cryptogenic patients in this cohort from which TSC cases were

excluded (see Table 3) (Lux et al., 2004, 2005; Darke et al., 2006). In both studies, the clinical response in 76–87% of patients within 2 weeks occurred without major adverse side effects (Baram et al., 1996; Lux et al., 2004). The most frequent adverse events were irritability and increased appetite.

Hrachovy et al. compared high-dose and low-dose natural ACTH. Dosing regimen for the high-dose group was as follows: 150 IU/m<sup>2</sup>/day for 3 weeks; 80 IU/m<sup>2</sup>/day for 2 weeks; 80 IU/m<sup>2</sup> every other day for 3 weeks; and then 50 IU/m<sup>2</sup> every other day for 1 week. The low-dose group received 20 IU/day for 2 weeks, then increased to 30 IU/day for 4 weeks if no response. Primary outcome measurement was cessation of clinical spasms and the abolition of hypsarrhythmia on EEG. There were no differences in efficacy for each dosing group, with 50% responders in the high-dose group and 58% response in the low-dose group (Hrachovy et al., 1994b). It should be noted that nonresponders to the lower dose were escalated to a higher dose after a few weeks, making comparisons among treatment arms challenging. The adverse effect profile was similar except for a higher rate of hypertension in the high-dose group.

ACTH studies have shown clinical effectiveness in treating IS using differing treatment protocols. The practice parameter from the AAP/AAN/CNS states that ACTH is probably effective for the short-duration treatment of IS and the resolution of hypsarrhythmia; however, there is insufficient evidence to recommend optimal dosage and duration of treatment with ACTH (Mackay et al., 2004). Effective short-duration treatment may be preferred in light of serious adverse events associated with long-duration exposure to ACTH (Riikonen & Donner, 1980), such as fulminant infections secondary to immunosuppression, hypertension, Cushingoid features, glucosuria, and metabolic abnormalities. A small study of six patients with TSC

**Table 3. IS clinical trial treatment protocols**

References	N	Agent	Dose	Duration of full dose (weeks)	% Patients spasms stopped	% Patients resolution hypsarrhythmia
Baram et al. (1996)	15	ACTH (native)	150 IU/m <sup>2</sup> /day, divided b.i.d.	2	93	87
Hrachovy et al. (1994b)	24	ACTH (native)	20–30 IU/day or	2–6	58	58
	26	ACTH (native)	150 IU/m <sup>2</sup> /day	3	50	50
Lux et al. (2004)	25	ACTH <sub>1–24</sub> (synthetic)	40–60 IU (0.5–0.75 mg), alternate days	2	76	89 <sup>a</sup>
Elterman et al. (2001)	75	VGB	18–36 mg/kg/day or	2	11	11
	67	VGB	100–148 mg/kg/day	2	36 <sup>b</sup>	36
Lux et al. (2004)	52	VGB	100–150 mg/kg/day	2	54	56 <sup>c</sup>
Hrachovy et al. (1983)	12	Prednisone	2 mg/kg/day	2–6	33	33
Lux et al. (2004)	30	Prednisolone	40–60 mg/day	2	70	71 <sup>d</sup>

<sup>a</sup>16 of 18 patients showed resolution of hypsarrhythmia; <sup>b</sup>65% of total patients responded, as determined by caregiver report, by 3 months ongoing treatment follow-up; <sup>c</sup>20 of 36 patients showed resolution of hypsarrhythmia; <sup>d</sup>10 of 14 patients showed resolution of hypsarrhythmia. Adverse events reported are detailed in the text.

demonstrated that the use of corticotropin in two patients may have been associated with enlargement of cardiac rhabdomyoma (Hishitani et al., 1997). Based on these results, it is suggested that the use of hormonal treatment such as ACTH or corticosteroids in patients with TSC and cardiac rhabdomyoma be closely monitored. As is noted below, patients with TSC and IS may be particularly responsive to VGB (Chiron et al., 1997; Elterman et al., 2001).

There was consensus in the ISWG that use of ACTH is effective as first-line therapy for IS. There was insufficient evidence to precisely define the optimum ACTH dose and duration of treatment for IS, although short duration was preferable (i.e., approximately 2 weeks followed by taper).

### Vigabatrin (VGB)

VGB has been used for treatment of IS in the European Union (EU) and other countries since the 1990s, and the drug was approved in the United States in August 2009 (Willmore et al., 2009). In the EU, VGB is regarded as the drug of first choice for children with IS secondary to TSC or with other symptomatic or cryptogenic IS (Wheless et al., 2007). In the United States, VGB is considered a drug of first choice for IS comorbid with TSC, and is the drug of second or third choice for children with other symptomatic or cryptogenic IS (Wheless et al., 2005). Insufficient evidence exists to recommend a specific dose and therapy duration for VGB, and there is no consensus among pediatric neurologists regarding optimal dosage. Although evaluation of treatment response at 12 weeks has been suggested (Willmore et al., 2009), clinical response, or lack thereof, may be realized earlier. In a review of nine prospective studies, VGB dosages ranged from 18–200 mg/kg/day and time to cessation of spasms following initiation of therapy ranged from 12–35 days (Mackay et al., 2004). However, the AAN/CNS practice parameter concluded that VGB appeared to be effective within 14 days of initiation of therapy (Mackay et al., 2004). The single class 1 study that was reviewed found that 35% of patients were spasm free and 25% had resolution of hypsarrhythmia at treatment day 5 (Appleton et al., 1999). Studies examining VGB as a first-line treatment for patients with IS comorbid with TSC show a 50–90% clinical response rate (Mackay et al., 2004). The typical dosing escalation includes an initial dose of 50 mg/kg/day escalated up to 100–150 mg/kg/day (Chiron et al., 1997; Appleton et al., 1999; Elterman et al., 2001; Lux et al., 2004).

Limited data suggest that VGB therapy can be safely withdrawn in children who have been seizure free for 6 months (British Medical Journal & Vigabatrin Paediatric Advisory Group, 2000). However, there is some evidence to suggest that children with TSC/FCD may relapse after VGB withdrawal and become refractory to the drug (Kroll-Seger et al., 2007). Concentric permanent visual field defects may be a possible adverse effect associated with VGB treatment and have been reported in 10–40% of patients (Mackay

et al., 2004). However, a recent study of IS patients treated with VGB in early infancy found that only one in 16 patients (6%) showed VGB-attributed visual field loss when evaluated at age 6–12 years (Gaily et al., 2009), compared with an estimated 30% in older patients (Willmore et al., 2009). The pediatric studies (Gaily et al., 2009) need to be replicated in a larger number of children treated in infancy and old enough to cooperate with detailed testing to confirm these preliminary data. The duration of therapy, cumulative dose, and daily dose have been implicated as risk factors for visual field changes with VGB use (Kalviainen & Nousiainen, 2001; Vanhatalo et al., 2002; Conway et al., 2008; Durbin et al., 2009). Accurate assessment of visual field changes in infants is challenging, and no consensus exists on a protocol for visual evaluation for infants on VGB. Therefore, it is recommended that patients on VGB have periodic ophthalmic evaluations beginning with a baseline evaluation at initiation of therapy as well as 3–6 months after cessation of treatment. It is also recommended that the drug be withdrawn if there is no clinical response after 2 weeks following escalation of therapy. Unfortunately, the optimal method of ophthalmologic assessment in this age group is unclear, as the children are too young to assess visual fields, and electroretinogram (ERG) are insensitive to visual field defects and require sedation. Other adverse effects with VGB therapy include sedation, irritability, insomnia, and hypotonia (Chiron et al., 1997; Vigevano & Cilio, 1997; Appleton et al., 1999; Elterman et al., 2001). MRI abnormalities were recently identified in 7 (32%) of 22 infants treated with VGB for IS. The abnormalities were characterized by new-onset and reversible T<sub>2</sub>-weighted hyperintensities and restricted diffusion in thalami, globus pallidus, dentate nuclei, brainstem, or corpus callosum (Pearl et al., 2009). A large retrospective review of cranial MRIs for patients with IS or complex partial seizures showed similar outcomes (Wheless et al., 2009). The clinical significance of these reversible changes is not yet known. A recent case report described a single infant with a suspected, but unproven, metabolic disorder, who was being treated with topiramate and the ketogenic diet. The patient developed pathologically confirmed white matter vacuolation and died shortly after the initiation of low-dose VGB (50 mg/kg/day) (Horton et al., 2009). Although this is only a single report, it is of concern as the pattern of intramyelinic edema was similar to that seen in animal models of VGB toxicity (Cohen et al., 2000; Gibson et al., 1990).

There was consensus among those in the ISWG about the use of VGB as effective first-line therapy for IS, particularly in patients with IS and TSC. VGB dose should begin at 50 mg/kg/day and escalate up to 100–150 mg/kg/day in those patients requiring escalation. Efficacy should be assessed within 2 weeks following dose titration. Infants who respond to therapy with VGB may be continued on the drug for 6–9 months, with continued ophthalmic evaluation and periodic reevaluation of risk and benefit.

### Corticosteroids

From 1958–2002, 24 studies or case reports examined corticosteroid therapy, and prednisone was the most common agent used (Hrachovy & Frost, 2003). Dosages of prednisone ranged from 1–8 mg/kg/day and therapy duration ranged from 2–32 weeks. Two randomized controlled trials, using prednisone 2 mg/kg/day for 2–6 weeks, found that cessation of spasms was 29% (4 of 14 patients in a 2-week trial) (Baram et al., 1996) and 33% (4 of 12 patients in a 6-week trial) (Hrachovy et al., 1983) (see Table 3). More recently, a high-dose prednisolone treatment regimen produced high clinical efficacy for cessation of spasms in IS using 40 mg oral prednisolone per day over 2 weeks (see Table 3) (Lux et al., 2004). Patients were given 10 mg, 4 times a day for 2 weeks, or 20 mg, 3 times a day after 1 week if spasms continued. Seventy percent of patients (21 of 30 patients receiving prednisolone) showed a clinical response. However, response was based purely on parental report of spasm frequency. Patients with TSC were excluded from this trial. The most frequent adverse events were increased irritability and appetite, and two infants were given diuretics due to increased blood pressure. However, there were some deaths in the study and there is a concern about adrenal suppression with the use of high-dose prednisolone.

Common side effects reported in IS patients receiving corticosteroids are similar to those with ACTH (Hrachovy et al., 1983, 1994b; Baram et al., 1996; Vigeveno & Cilio, 1997; Yanagaki et al., 1999). A small retrospective study examined high-dose oral prednisolone (40–60 mg/day) in 15 infants with new-onset and previously treated IS and found equivalent treatment of spasms (10 of 15 spasm free) compared with 15 infants who had received ACTH (13 of 15 spasm free) (Kossoff et al., 2009). However, a randomized controlled study comparing high-dose ACTH (150 IU/m<sup>2</sup> given twice a day) with prednisone (1 mg/kg twice a day) found significantly better clinical outcomes for patients receiving ACTH. In this study, 13 of 15 infants receiving ACTH responded, by EEG and clinical criteria, compared with 4 of 14 infants receiving prednisone (Baram et al., 1996). No consensus was reached in the ISWG regarding oral steroids as first-line therapy for IS, or regarding preparation, dose, or duration of oral steroids.

### Ketogenic diet

The ketogenic diet is a high-fat, restricted-carbohydrate diet with a fat to carbohydrate and protein ratio of 3:1 or 4:1. A modified version of the diet uses medium chain triglycerides as the fat source. The diet may work by enhancing GABA synthesis and improves energy utilization in the brain. There is renewed interest in the role of ketogenic diet in refractory pediatric epilepsy (Kossoff et al., 2008; Neal et al., 2008); however, currently there is insufficient class I evidence to recommend the ketogenic diet as a first-line

intervention in IS. The ketogenic diet may be an option in drug-resistant epilepsy as an adjunct to pharmacologic therapy. The diet is contraindicated in children with pyruvate carboxylase deficiency and fatty acid oxidation defects, and is not recommended in organic acidurias or carnitine deficiency. However, studies suggest it can be used, with caution, in the context of mitochondrial disorders (Kang et al., 2007). Gastrointestinal symptoms such as nausea, vomiting, renal stones, and fatty liver, are some complications with the ketogenic diet. At the present time there is insufficient evidence with respect to safety and efficacy to recommend the ketogenic diet as a first-line treatment in IS, but it can be considered as an alternative when first-line treatments (ACTH and VGB) fail or are deemed inappropriate for a given patient. There was consensus in the ISWG for the use of the ketogenic diet as one of the second-line therapies for IS.

### Surgery

Patients with spasms or seizures refractory to medical treatment, concomitant partial seizures, or focal abnormality on EEG may be evaluated for surgery (Shields et al., 1992). Criteria for focal resection in IS include the following: IS refractory to medical management (with/without partial seizures), developmental arrest (or regression), no evidence of diffuse brain damage on imaging studies, localized (focal) abnormality on MRI/PET, remainder of the brain is normal, focal EEG abnormality, no evidence of metabolic or degenerative disease, and no undue risk of “unacceptable deficit” postresection.

## OUTCOMES IN INFANTILE SPASMS

Outcomes are most dependent on etiology and may be more favorable in cryptogenic IS. Among 22 patients with cryptogenic IS and early effective treatment (i.e., within 1 month of IS onset), normal cognitive development was documented in all 22 patients during a 6- to 21-year follow-up period. Only one patient showed subsequent epilepsy, which then resolved (Kivity et al., 2004). Poor outcomes associated with IS, including development of refractory epilepsy, MR, and ASD, impose a significant long-term cost burden on families, the healthcare system, and society. Total lifetime costs associated with epilepsy and ASD are estimated in the billions of dollars (Ganz, 2007; Pugliatti et al., 2007). Learning disorders and MR have been identified as the most consistent predictors of poor long-term social outcome (Camfield & Camfield, 2007). Other comorbidities such as cerebral palsy may add to the long-term cost of IS. According to a report from the Centers for Disease Control and Prevention (CDC), the estimated lifetime cost in 2003 dollars was \$11.5 billion for persons with cerebral palsy born in the year 2000 (Centers for Disease Control and Prevention et al., 2004). A study of average per capita medical expenses for “usual care” in children with special

healthcare needs noted that expenses for children with MR when compared to special needs children without MR were substantially higher with respect to physician care, prescribed medication, emergency care, and hospitalization (Liu et al., 2008a). According to a recent report, the total public spending on intellectual disability in the United States was estimated to be \$82.57 billion in 2004 (Braddock, 2007). Resources allocated to research and training have declined significantly in recent years; only a small fraction (0.4%) of the spending on intellectual disability was allocated to biomedical, behavioral, and rehabilitation research (Braddock, 2007).

A review of 67 published studies with an average follow-up period of 31 months found that only 16% of patients with IS had normal development (Hrachovy & Frost, 2003). Poor outcomes included mortality, presence of seizure disorders, and cognitive and developmental problems. Classification into the cryptogenic category was associated with good prognostic outcomes. Other prognostic indicators, including the features of normal prior development, absence of causative features, normal imaging studies, absence of other seizure types, and sustained response to therapy without relapse were also associated with favorable prognostic outcomes (Hrachovy & Frost, 2003; Riikonen, 2010). Moderate or severe learning difficulties may be present in 70–90% of patients at follow-up (Riikonen, 1982, 1996; Trevathan et al., 1999; Riikonen, 2001b; Goh et al., 2005). In addition, in a small population-based study of IS in Iceland, approximately one-third of children were diagnosed with ASD (Saemundsen et al., 2007). In children with TSC, the occurrence of IS is a risk factor for ASD (Goh et al., 2005; Winterkorn et al., 2007). Seizure disorders are also common, and reports show that 94% of IS patients have active epilepsy at age 10 years, 50% of children with IS develop Lennox-Gastaut syndrome (LGS) before age 11, and a history of IS was found in approximately 39% of children with LGS (Trevathan et al., 1997, 1999). Patients with IS carry an increased risk of mortality due to the underlying etiologic disease and comorbid conditions. In the studies of Riikonen, 31% of the Finnish cohort died during the follow-up period of 20–35 years (Riikonen, 1996, 2001b). Trevathan and colleagues examined IS in an Atlanta birth cohort (1975–1977)

and found that 15% died by age 11 and 35% died by age 25 (Trevathan et al., 1999).

## UNMET NEEDS AND FUTURE TRENDS

The establishment of a continuum of care for patients with IS is critical for improving outcomes. A comprehensive approach is needed for the optimal management of children with IS and its associated comorbidities, including access to and evaluation by a variety of professionals—such as child neurologists, pediatricians, psychiatrists, pediatric nurse practitioners, rehabilitation services (physical, occupational and speech therapy), nurses, vocational rehabilitation counselors, neuropsychologists, social workers, and pharmacists. Although there are a number of organizations working to improve services for patients and families, there is an urgent need for a reliable, web-based, central resource for the practicing pediatrician and neurologist to access updated medical information, as well as for families in search of medical and other support services. Table 4 lists organizations that provide information about IS and family resources.

An IS patient registry also needs to be established. As a rare disorder with no absolute standard to treat all patients, treatment decisions—such as the duration of treatment, when to consider surgery, and how best to proceed from failed intervention attempts—vary by patient. In addition, there is no clear guideline concerning the treatment of patients with later recurrence of IS. A patient registry will allow a standard format for gathering important clinical data, including what therapy was administered, short-term and long-term developmental outcomes, side effects, and rates of IS recurrence, from a large sample of IS patients.

Further studies are required to determine the optimal treatment of children with IS (Mackay et al., 2004). ICISS is an international multicenter, randomized parallel group trial investigating the medical treatment of IS that began recruitment in 2007 (<http://www.bath.ac.uk/health/research/iciss/about/summary.php>). ICISS will compare hormonal treatment (either tetracosactide depot or prednisolone) and VGB given together (combined treatment) to hormonal treatment alone. The objective is to evaluate control

**Table 4. U.S. Organizations providing information and resources to families and caregivers of patients with infantile spasms or epilepsy**

Organization	Website	Telephone
American Epilepsy Society	<a href="http://www.aesnet.org">http://www.aesnet.org</a>	
CURE	<a href="http://www.cureepilepsy.org/home.asp">http://www.cureepilepsy.org/home.asp</a>	312-255-1801
Epilepsy Foundation	<a href="http://www.epilepsyfoundation.org">http://www.epilepsyfoundation.org</a>	301-459-3700 or 800-332-1000
Epilepsy Therapy Project	<a href="http://www.epilepsy.com">http://www.epilepsy.com</a>	
National Organization for Rare Disorders (NORD)	<a href="http://www.rarediseases.org">http://www.rarediseases.org</a>	203-744-0100 or 800-999-6673 (voicemail only)
NYU faces	<a href="http://faces.med.nyu.edu/">http://faces.med.nyu.edu/</a>	646-558-0900
Tuberous Sclerosis Alliance	<a href="http://www.tsalliance.org">http://www.tsalliance.org</a>	301-562-9890 or 800-225-6872



of spasms in the short term and developmental progress at 18 months of age. Whenever possible, the patient's epilepsy and developmental outcome will also be assessed at 42 months of age. Studies of new agents and AEDs to assess efficacies are needed, with long-term evaluation of cognitive outcomes using standardized psychometric assessments. Standardized dosage and duration of treatment are essential to allow comparison of short- and long-term outcomes.

Further studies are needed on whether specific causes or genetic mutations respond best to specific treatments similar to the way TSC appears to respond well to VGB. As VGB is relatively newer, long-term outcome studies are needed in children treated with VGB to assess the possible long-term consequences of treatment with a GABAergic agent early in life. The new animal models can be used both to study these issues and to improve our understanding of the pathophysiology of IS and identify novel targets for therapeutic development. As an example, animal models suggest that mammalian target of rapamycin (mTOR) inhibitors may have a potential therapeutic role in IS (Wong, 2010; Zeng et al., 2009) and can also serve to screen other agents.

## CONCLUSIONS

IS is a major form of severe epileptic encephalopathy of early childhood that results in neurodevelopmental regression and imposes a significant health burden. Early recognition and prompt treatment are mandatory and may improve outcomes in some patients, particularly in those with cryptogenic IS. The ISWG began with a discussion of the AAP/AAN/CNS consensus statement and reviewed literature (Mackay et al., 2004), with further discussion of the additional literature published since the practice parameter. Vigorous discussion and debate of the available evidence followed. Although the ISWG did not reach consensus on initial treatment dosage levels, there was strong consensus on the following conclusions:

1. The need for a broad clinical evaluation, including detailed clinical neurophysiology, is strongly recommended.
2. At this time, ACTH and VGB are the only drugs with proven efficacy to suppress clinical spasms and abolish the hypsarrhythmic EEG in a randomized clinical trial setting (Mackay et al., 2004) and thus remain first-line treatments.
3. Regardless of the chosen medication, timely assessment of treatment efficacy (i.e., 2 weeks for ACTH followed by taper; 2 weeks or less following dose titration for VGB) and, if indicated, prompt treatment modification, is strongly recommended as longer treatment trials (i.e., greater than 2 weeks for ACTH; greater than 3 months for VGB) are not likely to be effective and may come at the expense of serious adverse events.

4. Effective treatment for IS should produce both cessation of spasms and resolution of hypsarrhythmia on EEG and is an "all-or-none" response.

Given the finding of cessation of spasms in 70% of IS patients receiving high-dose prednisolone (Lux et al., 2004), prednisolone appears promising and warrants further study. However, because the primary outcome of the study was parental report of clinical spasm cessation without EEG confirmation, the data to recommend oral prednisolone as a first-line treatment are suboptimal. Finally, there is an urgent need for further research, including new animal models and long-term clinical research studies involving developmental outcomes. Currently available studies in patients with IS are not large enough to examine comorbid variabilities, other than TSC, that may be important determining factors in treatment response, neurologic development, and risk for further evolution to epilepsy. Because IS is a rare entity, carefully controlled comparative studies or patient registries, similar to those currently used in pediatric cancer trials, are urgently needed. Clinical and basic science research in IS is poorly funded at present. Significant increase in research dollars allocated to IS is needed to develop novel therapies that can improve outcomes in this devastating disease.

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## CONFLICTS OF INTEREST

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JMP is a consultant for Eisai, Jazz, King Pharmaceuticals, KV Pharmaceuticals, Marinus Pharmaceuticals, Neupace, Ortho-McNeil/Johnson & Johnson, Lundbeck, Pfizer, Questcor, UCB Pharmaceuticals, and Valeant; has participated in an advisory board for Eisai, Ortho-McNeil/Johnson & Johnson, Lundbeck, Questcor, UCB Pharmaceuticals, and Valeant; is a lecturer for Eisai, Ortho-McNeil/Johnson & Johnson, Lundbeck, Questcor, UCB Pharmaceuticals, and Valeant; is a researcher for Eisai, Marinus Pharmaceuticals, Ortho-McNeil/Johnson & Johnson, Lundbeck, Pfizer, Questcor, UCB Pharmaceuticals, and Valeant; and has received honoraria and reimbursement for travel expenses from Questcor. RH has received honoraria and reimbursement for travel expenses from Questcor. SS has served on an advisory board for Valeant and Questcor, is a consultant for Questcor, Eisai, King, Jazz, and Valeant; has received grants from Questcor; has received honoraria from Questcor, Eisai, and UCB; has received payment for development of educational presentations from Questcor, Eisai, UCB, and Valeant; and has reimbursement for travel expenses from Questcor. TZB is a board member for AES; has received research funding from Questcor; has participated in a symposium for Pfizer; has received grants from NIH and EFA; and has received honoraria and reimbursement for travel expenses from Questcor. DB is a consultant for and has received grants and reimbursement for travel expenses from Questcor and Ovation. DJD has received a NIH

grant and served as coinvestigator on a study of infantile spasms; and has received honoraria and reimbursement for travel expenses from Questcor. WDG has received honoraria and reimbursement for travel expenses from Questcor. PAG has received grants from Questcor, Ovation, Valeant, Eisai, Ortho-McNeil, and GlaxoSmithKline; and has received honoraria and reimbursement for travel expenses from UCB Pharmaceuticals, Questcor, and Ovation. DB is a consultant for Questcor; and has received grants and reimbursement for travel expenses from Questcor and Ovation. GLH is a member of the Data Safety Monitoring Board for Eisai; has received grants from Lundbeck and Eisai for clinical trials; and has received honoraria and reimbursement for travel expenses from GlaxoSmithKline and Questcor. DRN has received honoraria and reimbursement for travel expenses from Questcor. CO is a consultant for and has received honoraria and payment for development of education presentations from Ovation and Questcor; and has received grants and reimbursement for travel expenses from Questcor. WDS is a consultant for and has received grants from Lundbeck and Questcor; has received royalties from Lundbeck; and has received honoraria and reimbursement for travel expenses from Lundbeck and Questcor. ET is a full-time employee of the Centers for Disease Control and Prevention, US Department of Health and Human Services. JWW has received grants from NIH, the Shainberg Foundation, UCB Pharmaceuticals, Ovation, Questcor, Marinus, Ortho-McNeil, King Pharmaceuticals, Cyberonics, and Eisai; is a consultant for UCB Pharmaceuticals, Ovation, Questcor, Marinus, Ortho-McNeil, King Pharmaceuticals, Cyberonics, Pfizer, Eisai, Valeant, Cydex, Inc, and Neurelis, Inc; is a member of a speakers bureau for UCB Pharmaceuticals, GlaxoSmithKline, Ortho-McNeil, Cyberonics, Pfizer, Eisai, Shire, and Valeant; and has received honoraria and reimbursement for travel expenses from Questcor.

The opinions expressed in this publication are those of the authors, and do not necessarily represent the policy opinion of the Centers for Disease Control and Prevention.

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