SPECIAL REPORT

Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics

Working Group: *Jo M. Wilmshurst, †William D. Gaillard, ‡Kollencheri Puthenveettil Vinayan, §Tammy N. Tsuchida, ¶Perrine Plouin, #Patrick Van Bogaert, **Jaime Carrizosa, ††Maurizio Elia, ‡‡§§Dana Craiu, ¶¶Nebojsa J. Jovic, ##Doug Nordli, ***Deborah Hirtz, †††‡‡‡Virginia Wong, §§§Tracy Glauser, ¶¶¶###Eli M. Mizrahi, and ****J. Helen Cross

Epilepsia, 56(8):1185–1197, 2015
doi: 10.1111/epi.13057

Jo Wilmshurst is head of pediatric neurology at Red Cross War Memorial Children's Hospital (RCWMCH) and chairs the ILAE Pediatric Commission.

Summary

Evidence-based guidelines, or recommendations, for the management of infants with seizures are lacking. A Task Force of the Commission of Pediatrics developed a consensus document addressing diagnostic markers, management interventions, and outcome measures for infants with seizures. Levels of evidence to support recommendations and statements were assessed using the American Academy of Neurology Guidelines and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The report contains recommendations for different levels of care, noting which would be regarded as standard care, compared to optimal care, or "state of the art" interventions. The incidence of epilepsy in the infantile period is the highest of all age groups (strong evidence), with epileptic spasms the largest single subgroup and, in the first 2 years of life, febrile seizures are the most commonly occurring seizures. Acute intervention at the time of a febrile seizure does not alter the risk for subsequent epilepsy (class I evidence). The use of antipyretic agents does not alter the recurrence rate (class I evidence), and there is no evidence to support initiation of regular antiepileptic drugs for simple febrile seizures (class I evidence). Infants with abnormal movements whose routine electroencephalography (EEG) study is not diagnostic, would benefit from video-EEG analysis, or home video to capture events (expert opinion, level U recommendation). Neuroimaging is recommended at all levels of care for infants presenting with epilepsy, with magnetic resonance imaging (MRI) recommended as the standard investigation at tertiary level (level A recommendation). Genetic screening should not be undertaken at primary or secondary level care (expert opinion). Standard care should permit genetic counseling by trained personal at all levels of care (expert opinion). Genetic evaluation for Dravet syndrome, and other infantile-onset epileptic encephalopathies, should be available in tertiary care (weak evidence, level C recommendation). Patients should be referred from primary or secondary to tertiary level care after failure of one antiepileptic drug (standard care) and optimal care equates to referral of all infants after presentation with a seizure (expert opinion, level U evidence). Infants with recurrent seizures warrant urgent assessment for initiation of antiepileptic drugs (expert opinion, level U recommendation). Infantile encephalopathies should have rapid introduction and increment of antiepileptic drug dosage (expert opinion, level U recommendation). There is no high level evidence to support any particular current agents for use in infants with seizures. For focal seizures, levetiracetam is effective (strong evidence); for generalized seizures, weak evidence supports levetiracetam, valproate, lamotrigine, topiramate, and clobazam; for Dravet syndrome, strong evidence supports that stiripentol is effective (in combination with valproate and clobazam), whereas weak evidence supports that topiramate, zonisamide, valproate, bromide, and the ketogenic diet are possibly effective; and for Ohtahara syndrome, there is weak evidence that most antiepileptic drugs are poorly effective. For

epileptic spasms, clinical suspicion remains central to the diagnosis and is supported by EEG, which ideally is prolonged (level C recommendation). Adrenocorticotropic hormone (ACTH) is preferred for short-term control of epileptic spasms (level B recommendation), oral steroids are probably effective in short-term control of spasms (level C recommendation), and a shorter interval from the onset of spasms to treatment initiation may improve long-term neurodevelopmental outcome (level C recommendation). The ketogenic diet is the treatment of choice for epilepsy related to glucose transporter I deficiency syndrome and pyruvate dehydrogenase deficiency (expert opinion, level U recommendation). The identification of patients as potential candidates for epilepsy surgery should be part of standard practice at primary and secondary level care. Tertiary care facilities with experience in epilepsy surgery should undertake the screening for epilepsy surgical candidates (level U recommendation). There is insufficient evidence to conclude if there is benefit from vagus nerve stimulation (level U recommendation). The key recommendations are summarized into an executive summary. The full report is available as Supporting Information. This report provides a comprehensive foundation of an approach to infants with seizures, while identifying where there are inadequate data to support recommended practice, and where further data collection is needed to address these deficits.

KEY WORDS: Infants, Seizures, Recommendations, Guidelines, Standard care, Optimal care.

Evidence-based guidelines that clarify the optimal management of seizures in the infantile period are incomplete, and those that exist are based on individual preferences and expert panel opinion. The aim of this document is to recommend a logical, viable approach to the standard and optimal management of the infant with seizures, wherever possible according to evidence-based data.

Methods

A committee of child neurologists was recruited from members of the International League Against Epilepsy (ILAE) under the auspices of the Commission for Pediatrics. This working group compiled a list of management areas for an infant with seizures from the point of presentation through to the investigation, treatment, and outcome interventions. The existing literature on each management area was documented using systematic reviews.

Search terms were documented (see full supplemental report in Supporting Information Data S1) and databases were searched—namely Medline, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Cabi Global Health Service, National Library of Medicine (NLM) gateway, Centre for Reviews and Dissemination (CRD plus National Health Service [NHS]), conference proceedings (abstracts), and the International Registers of On-going Clinical Trials (ISRCTN). The committee was multilingual, and as such, articles in all languages were included.

Accepted May 11, 2015; Early View publication June 30, 2015.

*Paediatric Neurology, Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa; †Pediatrics and Neurology, Division Epilepsy and Neurophysiology, Comprehensive Pediatric Epilepsy Program, George Washington University, Washington, District of Columbia, U.S.A.; ‡Division of Pediatric Neurology, Department of Neurology, Amrita Institute of Medical Sciences, Cochin, Kerala, India; §Department of Neurology, Children's National Medical Center, Washington, District of Columbia, U.S.A.; ¶Clinical Neurophysiology Department, INSERM U663, Hospital for Sick Children, Paris, France; #Paediatric Neurology, Department of Pediatrics, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium; **Pediatric Department Child Neurology Service, University of Antioquia, Medellín, Colombia; ††Unit of Neurology and Clinical Neurophysiopathology, IRCCS Italy Oasi Institute for Research on Mental Retardation and Brain Aging, Troina, EN, Italy; ‡‡Department of Neurology, Pediatric Neurology, Psychiatry, Neurosurgery, "Carol Davila" University of Medicine Bucharest, Bucharest, Romania; §§"Alexandru Obregia" Clinical Hospital, Bucharest, Romania; ¶¶Neurology, Clinic of Neurology and Psychiatry for Children and Youth, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; ##Epilepsy Center, Children's Memorial Hospital, Chicago, Illinois, U.S.A.; ***Office of Clinical Research, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Rockville, Maryland, U.S.A.; †††Department of Paediatrics and Adolescent Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, Hong Kong; ‡‡‡Division of Paediatric Neurology/Developmental Behavioural Paediatrics/NeuroHabilitation, Duchess of Kent Children Hospital, Queen Mary Hospital, Hong Kong, Hong Kong; §§§Comprehensive Epilepsy Center, Division of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, U.S.A.; ¶¶¶Peter Kellaway Section of Neurophysiology, Department of Neurology, Baylor College of Medicine, Houston, Texas, U.S.A.; ###Section of Pediatric Neurology, Department of Pediatrics, Baylor College of Medicine, Houston, Texas, U.S.A.; and ****Childhood Epilepsy, Paediatric Neurology, UCL-Institute of Child Health, Great Ormond Street Hospital for Children NHS Trust, NHS Foundation Trust, London, United Kingdom

Address correspondence to Jo M. Wilmshurst, Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town 7700, South Africa. E-mail: Jo.wilmshurst@uct.ac.za

Key Points

- Evidence-based guidelines for the management of seizures in infants are lacking
- Incidence of epilepsy in the infantile period is the highest of all age groups
- Epileptic spasms are the largest subgroup and, in the first 2 years of life, febrile seizures are the most commonly occurring seizures
- Infants with recurrent seizures warrant urgent assessment for initiation of antiepileptic drugs
- There is no high-level evidence to support any particular current agents for use in infants with seizures.

Recommendations were graded according to level of the evidence-based data (Table 1). Where no evidence was available, the committee acknowledged that these recommendations were based on "expert opinion" and "standard practice." The level of evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (descriptive studies) and the American Academy of Neurology (AAN) Practice Guidelines grading system (comparison studies).[1–3]

Antiepileptic drugs (AEDs) were analyzed based on their efficacy, or lack of efficacy, according to the AAN guidelines, with the recommendation for effective, ineffective, or exacerbation of seizures equating to level A recommendation; probably effective, or probably ineffective, equated to level B; and possibly effective, or possibly ineffective, to level C recommendation. Whether these recommendations were based on strong or weak data was documented. Where lack of data precluded analysis, the outcome "no data" was documented, which equated to level U recommendation.

Where possible, the standard and the optimal level of care at primary/secondary and tertiary/quaternary facility level was recommended. Standard care was defined as intervention appropriate for all infants regardless of which center they attended, and equated to "safe care." Inevitably some recommendations would be infrequently available in resource-poor settings (RPS), but children should be entitled to access appropriate health care in order to enable them to reach their full potential. By documenting a "standard" level of care, centers can lobby for improved facilities. Optimal care equated to the "state of the art" management for infants with seizures. A primary or secondary level was defined as a center able to provide basic clinical assessment (history, examination, and interpretation), baseline investigations (infection and electrolyte screens), and identification of an infant who would benefit from referral to the next level of care. In selected cases these centers were also regarded as appropriate to initiate first-line AEDs. Tertiary or quaternary level was defined as centers with access to doctors with experience in the management of infants with epilepsy, with access to specific investigations relevant to understanding the etiology of the epilepsy and with access to relevant extended AEDs and alternative treatments.

Table 1. Definitions used to grade the quality of the evidence for the proposed recommendations[1–3]

Evidence tool used			
AAN practice parameters	Quality of the research	Class I	A statistical, population-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. All patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations
		Class 2	A statistical, nonreferral-clinic–based sample of patients studied at a uniform point in time (usually early) during the course of the condition. Most (>80%) patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations
		Class 3	A selected, referral-clinic–based sample of patients studied during the course of the condition. Some patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation by someone other than the treating physician
		Class 4	Expert opinion, case reports, or any study not meeting criteria for class I–III
AAN practice parameters	Strength of the practice recommendation based on the reviewed literature	Level A	Established as effective, ineffective, or harmful, or as useful/predictive or not useful/predictive
		Level B	Probably effective, ineffective, or harmful, or as useful/predictive or not useful/predictive
		Level C	Possibly effective, ineffective, or harmful, or as useful/predictive or not useful/predictive
		Level U	Data are inadequate or conflicting; treatment, test or predictor unproven
GRADE	Grade of the recommendation	1A	Strong recommendation/high-quality evidence
		1B	Strong recommendation/moderate quality evidence
		1C	Strong recommendation/low or very low quality evidence
		2A	Weak recommendation/high quality evidence
		2B	Weak recommendation/moderate quality evidence
		2C	Weak recommendation/low or very low quality evidence
Committee consensus	Expert opinion		Group consensus in the setting where the AAN and GRADE assessments failed to provide an adequate level of evidence to direct intervention

Table 2. Executive summary of key recommendations and findings

Topic	Recommendation
Epidemiology	The incidence of epilepsy in the infantile period is highest of all age groups (strong evidence);[43–51] estimated 70.1 per 100,000[51]
	Overall, infantile (epileptic) spasms constitute the largest single epilepsy subgroup, representing 13–45.5% of infantile population-based incidence studies[44,47,52–56]
	For other seizure types there are limited data beyond case series (class 3 and 4 studies)
	The outcomes reported in typically class 4 studies suggest that seizures in infancy are predictive of comorbidities as well as complex and poor outcomes[52,53,55]
Clinical semiology/ types of epileptic events	The first stage in the clinical management is to recognize if abnormal movement or behavior has an epileptic origin (Fig. 1)
	Data S1, Table 4.3.1 summarizes the clinical appearance of seizures, disease manifestations, specific neurophysiology findings and the severity, or morbidity, of the epilepsy
Febrile seizures	Acute intervention at the time of simple febrile seizures does not alter the subsequent risk of epilepsy (class I evidence)
	Antipyretic intervention does not affect the recurrence rate of subsequent febrile seizures (class I evidence)
	There is no indication for initiation of chronic antiepileptic drugs for simple febrile seizures (class I evidence) (Table 3)
	In the acute treatment of febrile seizures it is important to treat seizures lasting 10 min or longer (expert opinion)
	Although initial management of infants with complex febrile seizures is often at the primary or secondary level, there should be a low threshold for referral of these infants to a pediatrician (secondary/tertiary setting) for further management and exclusion of underlying etiologies (level of evidence U, expert opinion)
Investigations	
The role of EEG	In any child with undiagnosed repeated abnormal events, where EEG analysis has failed to delineate the condition, video-EEG monitoring is recommended (standard care at tertiary and quaternary level)[30]
	At primary and secondary levels, carers are strongly encouraged to utilize home video (level of evidence U; expert opinion)
The role of neuroimaging	Neuroimaging is recommended at all levels of care for infants presenting with epilepsy
	At a primary or secondary level of care, optimal care would be MRI screening, but at the very least CT scan imaging (standard care)
	At tertiary or quaternary level, MRI is recommended as the standard investigation (level A). Optimal care could consist of more advanced imaging modalities for epilepsy surgical evaluation, such as PET, MEG, or SPECT (level B)
Metabolic investigations	In any infant with medication-resistant seizures, or in whom a structural or syndromic cause is not evident, underlying metabolic disease should be considered
	Infants with a positive family history of epilepsy, features reported in Table 4, myoclonic seizures, neuroregression, encephalopathic episodes, and when there is no structural or infective explanation, and those who do not comply with the known categories, should undergo metabolic evaluation
	Table 5 provides the recommended standard screening at primary and secondary level and at tertiary and quaternary level, as well as the optimal levels of intervention
	Table 5 summarizes the interventions whereby empirical treatment should be initiated as soon as possible independently of disease confirmation based on care at primary and secondary care level, inclusive of referral to a tertiary center
	Level of evidence—weak recommendation, level B—based mainly on case reports and expert center opinions
Genetic testing	Genetic screening should not be undertaken at a primary or secondary level of care, as the screening to identify those in need of specific genetic analysis is based on tertiary settings
	Standard care should permit genetic counseling by trained personnel to be undertaken at all levels of care (primary to quaternary)
	Genetic evaluation for Dravet syndrome and other infantile-onset epileptic encephalopathies should be available at tertiary and quaternary levels of care (optimal intervention would permit an extended genetic evaluation) (level of evidence—weak recommendation, level C)
	Early diagnosis of some mitochondrial conditions may alter long-term outcome, but whether screening at quaternary level is beneficial is unknown (level of evidence U)
Approach to therapy/ interventions in infantile seizures	
Where to treat	To avoid delays in intervention, as standard level of care, patients should be referred from primary or secondary level to tertiary or quaternary level after failure of one AED
	Optimal care would consist of referral of all infants from primary or secondary level to tertiary or quaternary level after presentation with a first nonfebrile seizure (expert opinion, level of evidence U)

Continued

Table 2. Continued.

Topic	Recommendation
When to treat	In an otherwise well infant, a policy of "wait and see" is reasonable after the first afebrile seizure
	In reality this is a rare event; close monitoring is essential, as the risk of recurrence is high in infants with epilepsy
	At this stage, as a standard level of care, urgent referral to a specialist and plan to initiate therapy should be considered (expert opinion, level of evidence U)
How to treat	Treatment for infantile epileptic encephalopathies should be considered with rapid introduction of incremental AED doses
	Treatment should be coordinated as standard practice through a tertiary or quaternary center, but introduction of therapy not delayed
	Optimal tertiary care would permit the infant to have up to daily review to monitor the response to acute therapy (expert opinion; level of evidence U).
What to treat with	See Table 6 (main text) and Data S1, Tables 6.3.1–6.3.7
	There is no high-level evidence to support any of the current agents used
How long to treat for	No clear evidence-based recommendation possible—dependent on seizure type
Definition of medical intractability	Drug-resistant epilepsy has been defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom[57]
	One third of children presenting with epilepsy before 36 months of age will be medically intractable,[58] the largest group with West syndrome (epileptic spasms)[59]
	Children with focal or hemispheric lesions also carry a high risk of medical intractability[60]
Ketogenic diet	Ketogenic diet is the treatment of choice for glucose transporter 1 deficiency syndrome and pyruvate dehydrogenase deficiency (expert opinion; class 4 data, level of evidence U)
	Ketogenic diet should be offered to infants with selected epileptic encephalopathies and a subset with medically refractory seizures at optimal level care at tertiary/quaternary facilities (expert opinion and standard practice ; level of evidence U)
Epilepsy surgery	Infants with focal-onset seizures, particularly those with a unilateral structural brain abnormality, or those with persistent seizures despite two antiepileptic drugs should be assessed in a specialist epilepsy unit with access to epilepsy surgery
	The identification of patients as potential candidates for epilepsy surgery should be part of standard practice at primary/secondary level care, whereas the actual evaluation or detailed screening as to whether they could be an epilepsy candidate is the role of tertiary/quaternary settings
	Depending on the resources of the region, this may be regarded as a standard level of care, whereas in resource-limited settings, this may be limited to an optimal level of care at quaternary level facilities only
	Such interventions are undertaken only in facilities with appropriate capacity and experience to provide safe care (level of evidence U; expert opinion)
Vagus nerve stimulation	There are insufficient data to conclude if there is a benefit from intervention with vagus nerve stimulation in infants with seizures
	Infants with medically refractory seizures who are not suitable candidates for epilepsy surgery may be considered for vagus nerve stimulation (expert opinion and standard practice; optimal level care at tertiary/quaternary facilities) (level of evidence U)
Epileptic spasms	
Diagnosis and investigation	Clinical suspicion remains the cornerstone of diagnosis of epileptic spasms
	An EEG of sufficient length to capture wakefulness, sleep, and awakening is sufficient as the minimum standard level of care and is mandatory for the diagnosis and management of epileptic spasms.[61] However, there are insufficient data to support the exact type and duration of the EEG study. Twenty-four hour video-EEG recording has the best chance for detecting hypsarrhythmia and recording the spasms. As such prolonged video-EEG recording may be recommended as the optimal level of care in centers where the facility is available. In practice centers with capacity for prolonged studies often monitor suspected patients for 3–12 hours until enough data is collected to confirm the diagnosis. Common practice (level C evidence)
	MRI of the brain should be performed in all children (level A evidence-based on data for all infantile epilepsies)
	Genetic and metabolic studies should be performed in children with a high index of clinical suspicion for a genetic or metabolic disorder. However, there is insufficient evidence to recommend any specific tests in all infants with spasms (level U evidence)
Treatment and management	ACTH is preferable in the short-term control of spasms[36] (level B evidence)
	Oral steroids are probably effective in the short-term control of spasms (level C evidence)[32]
	Data are insufficient to comment on the optimal preparation, dosage, and duration of treatment of steroids (level U evidence)
	Low-dose ACTH may be considered as an alternative to high-dose ACTH for treatment of epileptic spasms (level B evidence)
	Vigabatrin is possibly effective in the short-term control of spasms (level C evidence), especially in the case of tuberous sclerosis complex (level C evidence)

Continued

Table 2. Continued.

Topic	Recommendation
	Treatment with ACTH/oral steroids may result in a better long-term neurodevelopmental outcome than treatment with vigabatrin in children with epileptic spasms due to unknown etiologies (level C evidence)
	A shorter interval from the onset of spasms to treatment initiation may improve the long-term neurodevelopmental outcome, especially in cases where there is no identified etiology (level C evidence)
Which treatment gives the best long-term seizure and developmental outcome	Meaningful improvement in cognition and behavior may be achieved if the spasms and interictal epileptiform abnormalities are controlled relatively early in the clinical course[62]
	The shorter the "lag time" (time from spasms onset to commencement of therapy) the better the developmental outcome[38]
Outcome tools for infants with seizures	Early neurodevelopmental screening is essential at the tertiary/quaternary level (expert opinion, standard level care)
	Current studies suggest that epilepsy, autism, and intellectual disability commonly coexist
Inclusive of early screening for autism spectrum disorder (ASD)	In addition, these recent studies suggest that early onset seizures may index a group of infants at high risk for developing autism, usually with associated intellectual deficits; as a result autism should be considered as a major comorbidity
	Screening for autism spectrum disorders, as recommended by the American Academy of Pediatrics[39] in this high-risk population is strongly suggested (expert opinion, standard level care)

Results

A key summary and recommendations of the areas covered by this review are provided in Table 2. A more detailed account of the discussion and the level of evidence can be found in the full document available in Data S1. Added areas of qualification are provided below.

Clinical semiology/types of epileptic events

Data S1, Table 4.3.1 summarizes the characteristics of the main infantile seizure syndromes, and Figure 1 provides a stepwise approach to the initial presentation of an infant with suspected seizures (expert opinion, level U evidence).

Febrile seizures

Febrile seizures, as the most commonly occurring seizures in the first 2 years of life, were specifically addressed with regard to investigations and interventions. Events are defined as seizures accompanied by a fever, without central nervous system infection, which occur in children between 6 and 60 months of age.[4] They are generally benign with normal cognitive outcome. Table 3 illustrates the excep-

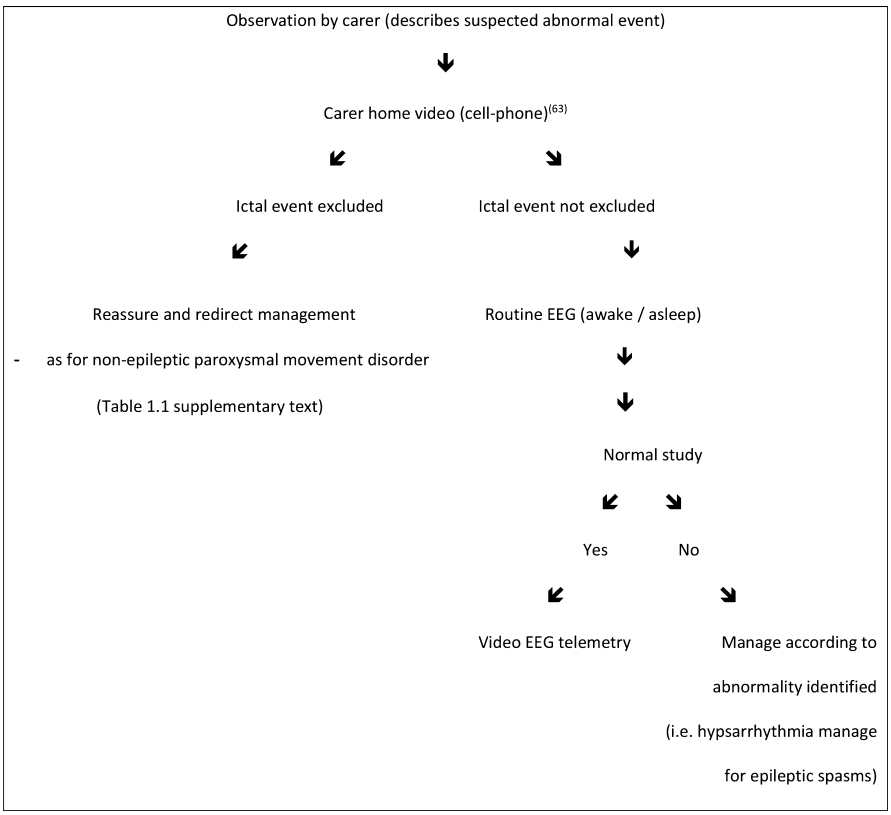

Figure 1.
Approach to the assessment of a paroxysmal event.
Epilepsia © ILAE

Table 3. Febrile seizure–related risk factors

Recurrence after an initial febrile seizure
Early age of onset (<15 or 18 months)[64,65] (<12 months)[66,67]
Epilepsy in first-degree relatives
Febrile seizures in first-degree relatives[67,68]
Frequent febrile illness
Low temperature at the onset of the febrile seizure, close to 38°C[67]
Temperature <104°F (40°C)[68]
Shorter duration of fever (<1 h) before the seizures
Subsequent development of epilepsy after a complex febrile seizure (CFS)[5,65,66,69–74]
Low Apgar scores at 5 min
History of at least one complex feature
Prolonged febrile seizures (>15 min)
Multiple seizures in 24 h
Focal features of seizures
Short duration of fever (<1 h) before the seizure
Neurologic abnormality (neurodevelopmental delay, cerebral palsy)
Family history of epilepsy
Focal epileptiform discharges
Temperature in the lower febrile range at the time of the CFS
Younger ages

tions.[5–7] Class 1 studies support that active intervention is rarely required for simple febrile seizures (Table 2), whereas early seizure termination (within 10 min) for complex febrile seizures is associated with a better outcome (strong recommendation; weak level of evidence).

The key investigations for infants with seizures were reviewed, including electroencephalography (EEG) and neuroimaging (Table 2). EEG screening is recommended for an infant with undefined movements, but more especially to capture the events on available video devices (level U recommendation). There are sufficient data to support a level A recommendation for neuroimaging of an infant with afebrile seizures. Where the cause is already known (e.g., chromosomal abnormality, hypoxic-ischemic encephalopathy), the usefulness of the study findings must be balanced against whether the investigation will alter management.

A number of epilepsy types are closely associated with specific metabolic conditions (Table 4),[8–10] and some metabolic conditions, if identified early, can respond well to specific interventions.[8] Namely glucose transporter 1 deficiency syndrome (GLUT1) deficiency when managed with the ketogenic diet, and cofactor dependent epilepsy, according to the deficiency, will respond to pyridoxine, pyridoxal phosphate, folinic acid, and biotin. The list of potential conditions is exhaustive and beyond the capacity of this text, as is stipulating detailed investigations for specific subconditions. Instead, the report provides a guide to the standard investigations undertaken in most units when first assessing an infant with a possible metabolic disorder, but acknowledges that other more focused analyses may be required (Table 5) (expert opinion, level U recommendation). A review of the benefits and risks of genetic testing relevant to the field of epilepsies is represented by the Report of the ILAE Genetics Commission (expert opinion).[11] The points raised in this report are especially relevant for infants with Dravet syndrome and those with early infantile epileptic encephalopathies.

Approach to therapy and interventions in infantile-onset seizures

Due to the lack of evidence-based data (Table 6), an international survey was undertaken and the outcomes are reported separately (Wilmshurst et al.[75]). Table 2 expands on the key approaches to therapy, namely, to refer infants early to tertiary/quaternary services, to initiate AEDs after the second seizure event, and to initiate AEDs rapidly in most cases (expert opinion, level U recommendation). There are no data to support standard weaning of AEDs, especially as this is often situation or syndrome specific. With regard to which agent to treat with, again there is a lack of data, but the agents that have been studied are summarized in Table 6.

Evidence to support the use of other therapies included the ketogenic diet. Class 4 evidence supports the role of the

Table 4. Epilepsy types associated with specific metabolic conditions with onset in the infantile period (expert opinion; class 4 data)

Epilepsy type	Metabolic condition
Epileptic spasms	Biotinidase deficiency, Menkes' disease, organic acidurias, amino acidopathies, mitochondrial respiratory chain diseases
Early onset absence epilepsy	Glucose transporter 1 deficiency syndrome (GLUT1) deficiency
Early myoclonic epilepsy group	Consider vitamin-dependent diseases (pyridoxine or pyridoxal-phosphate), amino acid disorders such as nonketotic hyperglycinemia, methylene tetrahydrofolate reductase (MTHFR) deficiency, γ-aminobutyric acid (GABA) transaminase deficiency, serine deficiency, congenital glutamine deficiency, defects of purine metabolism, sulfite oxidase deficiency, peroxisomal disorders and Carbohydrate-deficient glycoprotein syndromes; often the etiology remains unknown
Epilepsy with myoclonic seizures	Nonketotic hyperglycinemia, mitochondrial disorders, GLUT1-deficiency, and storage disorders
Epilepsy with generalized tonic–clonic seizures	GLUT1 deficiency, neuronal ceroid lipofuscinosis type 2 (NCL2) , other storage disorders, mitochondrial disorders
Epilepsy with myoclonic-astatic seizures	Consider GLUT1 deficiency and NCL2
Epilepsy with (multi-)focal seizures	Consider GLUT1 deficiency
Epilepsy partialis continua	Alpers' disease, other mitochondrial disorders

Table 5. Recommendations for approach to the infant with epilepsy suspected to have a metabolic condition. These screens are a guide only, and specific findings, such as hypoglycemia, may focus the investigations further. Level of evidence—weak recommendation, level B evidence—based mainly on case reports and expert center opinions

	Primary/Secondary	Tertiary/Quaternary
Investigations Standard level of care	Glucose Basic hematologic screening Liver function tests Ammonia Urine analysis pH Arterial gases Plasma electrolytes (sodium [Na], Potassium [K], chloride [Cl] for anion gap measurement), cerebrospinal fluid (CSF) and plasma lactate, CSF glucose (paired with blood glucose)	Amino acid and organic acid chromatography or tandem mass spectrometry Specific enzymatic studies Molecular quantifications[a] Genetic testing[b] Liver, skin, muscle, and bone marrow biopsies
Investigations Optimal		Extended genetic screens inclusive of next-generation sequencing and linkage analysis
Empirical treatment interventions	Maintain adequate pH Hydro electrolyte balance High metabolic glucose flow and protein restriction should be started Secure referral to a tertiary center where specific studies and interventions are possible	Specialized treatments should be initiated

[a]Molecular quantification of substances not identified by standard studies already listed, for example, for mucopolysaccharidosis analyzing chondroitin sulfate, heparan sulfate, and so on.

[b]Genetic testing strategy can vary according to the suspected underlying condition affecting the infant, that is, full-gene sequencing indicated for conditions such as *SCN1A* genes for children with FS + or Dravet syndrome; targeted mutation analysis for mutations of the glucocerebrosidase *GBA* gene in conditions such as Gaucher disease; multiplex ligand dependent probe amplification for conditions such as Rett syndrome; chromosome, oligo, and single-nucleotide polymorphism) array analysis for conditions such as 15q13.3 deletion syndrome; karyotype for conditions such as Down syndrome; fluorescence in situ hybridization for deletions associated with conditions such as Miller-Dieker syndrome; methylation analysis for conditions such as imprinting alterations in Angelman syndrome; and whole genome sequencing for a research protocol in an infant with an undiagnosed condition.

ketogenic diet for infants younger than 1 year of age, and class 3 evidence for children aged 12–24 months.[12–20] There is evidence that ketosis can be sustained in infants.

Studies relating to surgery for infants with epilepsy suggest good outcome with regard to seizure control in carefully selected cases (class 4 evidence). Maintenance of neurodevelopmental progress is seen, if not gains, in the longer term (level U evidence). Expert consensus recognizes infants as a high-risk group, and that all infants should be assessed for possible epilepsy surgery early in their natural history (class 4 evidence).[21]

Vagus nerve stimulation (VNS) is approved by the U.S. Food and Drug Administration (FDA); for patients older than 12 years of age with medically refractory epilepsy who are not suitable for epilepsy surgery. Data related to infants are sparse, and limited to either small proportions of larger case series, or small case reports of up to six infants.[22–26]

Because epileptic spasms are the more common single seizure type to occur in infancy, this condition was assessed in isolation. West syndrome is characterized by an electroclinical triad of (1) epileptic spasms, (2) hypsarrhythmia on EEG study, and (3) developmental stagnation or regression. The incidence is estimated to be around 2–3 per 10,000 live births.[27,28] Detailed meta-analyses already exist and were incorporated into the text, supporting the development of a practical algorithm for the management of children with suspected spasms (Fig. 2).

The onset of epilepsy in the infantile age range is associated with poor outcome. There are increased comorbidities of intellectual disability and autism. Autism is often not detected early and this leads to delay in potential early interventions. As a result, promotion of outcome tools for infantile seizures is important, especially the early screening for autism spectrum disorder (ASD) in infantile seizures (expert opinion, level U recommendation) (Table 2).

Discussion of the Recommendations

This report was compiled with the intention of presenting a guideline for the best care practice in the management of infants with seizures. The document was intended to be relevant to clinical practice, to be easy to follow, and to leave clinicians with insight into the existing evidence for the management of infants with seizures. Care that should be available at primary or secondary level facilities, compared to tertiary and quaternary, was recommended (Table 2). Furthermore, where appropriate, a statement was made relating to a standard level of care compared to optimal or "state of the art" intervention. The report did not address well-described electroclinical descriptions of seizures, which occur in the infantile period, or the extensive assessments typically undertaken for an infant with abnormal movements prior to the diagnosis of seizures, or the extended investigations for an infant with a suspected metabolic condition.

Much of the interpretation was limited due to the lack of consistency (for example, different age ranges used to

Table 6. Summary of published studies addressing AED treatment for infants with seizures

Epilepsy type	AED therapy	Recommendation Seizures	Strength Efficacy	AAN recommendations A, B, C, U
Focal seizures	Levetiracetam	**Effective**	**Strong**	**A**
	Topiramate	**Ineffective**	**Strong**	**A**
	Lamotrigine	**Ineffective**	**Strong**	**A**
	Gabapentin	**Ineffective**	**Strong**	**A**
	Oxcarbazepine	**Ineffective**	**Strong**	**A**
	Felbamate	No data		U
	Tiagabine	No data		U
	Zonisamide	No data		U
Generalized seizures	Levetiracetam	Possibly effective	Weak	C
	Valproate	Possibly effective	Weak	C
	Lamotrigine	Possibly effective	Weak	C
	Topiramate	Possibly effective	Weak	C
	Clobazam	Possibly effective	Weak	C
Epileptic spasms	Low dose ACTH	Probably effective	**Strong**	**B**
	High dose ACTH	Probably effective	**Strong**	**B**
	Prednisone	Possibly effective	Weak	C
	Vigabatrin	Possibly effective	Weak except tuberous sclerosis complex	C
Benign infantile convulsions	Carbamazepine	Possibly effective	Weak	C
	Phenobarbital	Possibly effective	Weak	C
	Valproate	Possibly effective	Weak	C
Dravet syndrome	Stiripentol[a]	**Effective**	**Strong**	**A**
	Topiramate	Possibly effective	Weak	C
	Zonisamide	Possibly effective	Weak	C
	Valproate	Possibly effective	Weak	C
	Bromide	Possibly effective	Weak	C
	Ketogenic diet	Possibly effective	Weak	C
	Lamotrigine	**Exacerbate**	**Strong**	**A**
	Carbamazepine	**Exacerbate**	**Strong**	**A**
	Phenytoin	**Exacerbate**	**Strong**	**A**
Benign myoclonic epilepsy of infancy	Valproate	Possibly effective	Weak	C
	Topiramate	Possibly effective	Weak	C
	Lamotrigine	Possibly effective	Weak	C
	Clonazepam	Possibly effective	Weak	C
Ohtahara syndrome	Topiramate	Poorly effective	Weak	C
	Conventional AEDs	Poorly effective	Weak	C
	ACTH, prednisone	Poorly effective	Weak	C
	Pyridoxine	Poorly effective	Weak	C
Provoked or situational seizures	Carbamazepine	Possibly effective	Weak	C
	Phenobarbital	Ineffective	Weak	B

Columns marked in bold correlate where recommendations are supported by strong level of evidence.
[a]In combination with valproate and clobazam.

define the studied period of infancy) and directness (for example, not addressing the question under investigation) of the studies, as well as the poor study quality (for example, retrospective observational studies and small study sizes) for many of the areas under investigation. Although class 1 studies were available for some areas such as management of simple febrile seizures, the optimal outcome of febrile status remained under investigation, awaiting studies such as those from the FEBSTAT (Consequences of Prolonged Febrile Seizures) study group to collate prospective and longitudinal data.[29]

EEG is most useful when confirmatory data are recorded, but failure to detect epileptiform activity may not exclude epilepsy without good clinical correlation.[30] Access to EEG, with accurate interpretation, is challenging even in resource-equipped settings, and would often be considered a tertiary intervention. The recommendation to perform EEG in this group promotes the need for increased access to centers equipped to perform accurate studies. Similarly for neuroimaging, although findings may drastically alter patient management, access is precluded in many settings, due to resources, costs, and interpretation skills. As such, the recommendation that neuroimaging should be available "at all levels of care," although unrealistic for many settings, enables lobbying to health care authorities to attempt to improve access to such resources. Raising awareness of treatable metabolic diseases at primary and secondary levels, and the precautions that should be put into place are essential as part of standard care and also reflect an underresourced area that

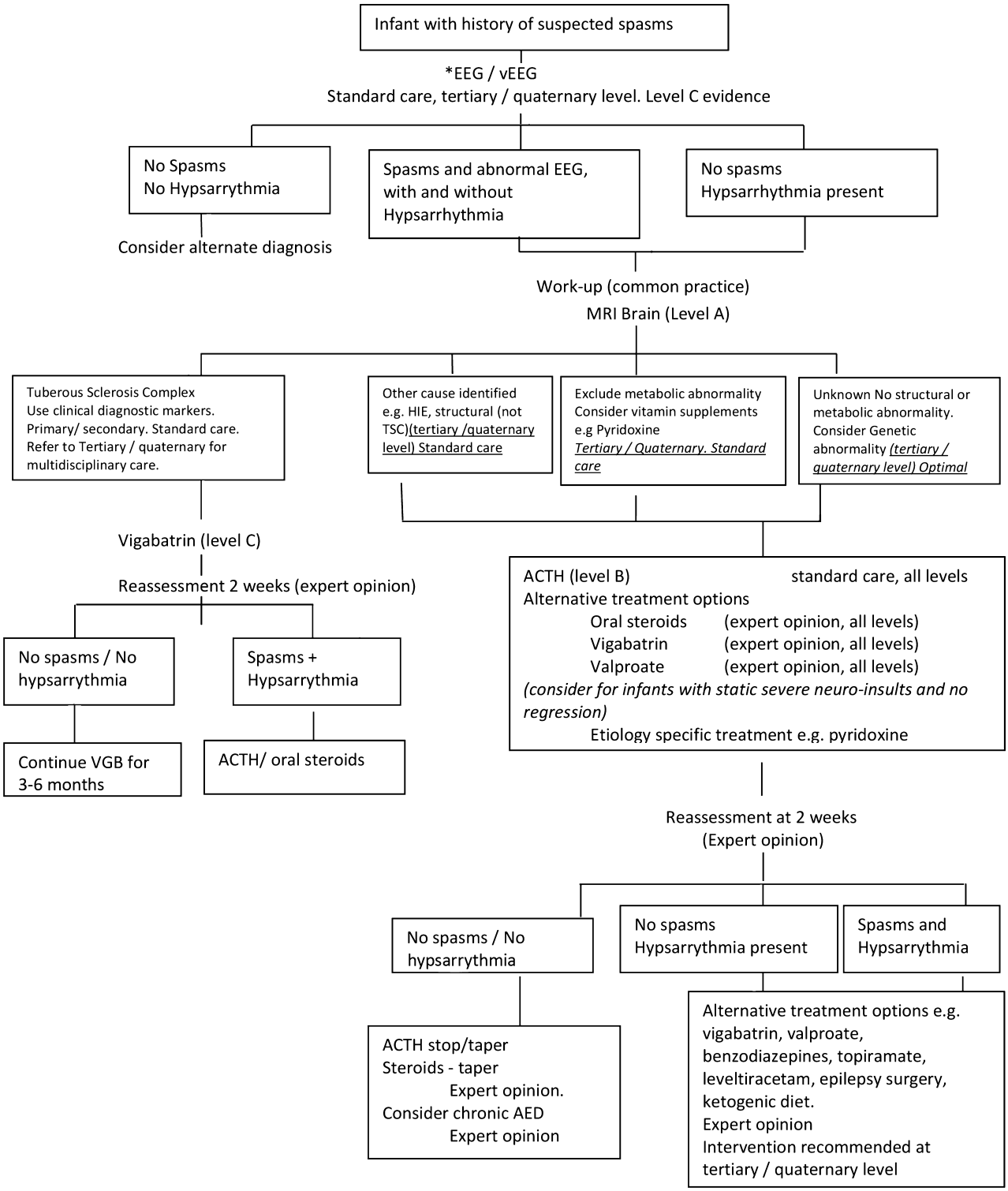

Figure 2.
Clinical approach to an infant with suspected epileptic spasms. *In facilities with no access to EEG, empirical treatment intervention must not be delayed and care will need to be approached based on clinical suspicion
Epilepsia © ILAE

could use this statement to lobby for improved capacity to allow early intervention and to identify patients for specialist referral.

The recommendation of promoting genetic testing in Dravet syndrome and early onset epileptic encephalopathies at tertiary centers could be considered contentious, as at pres-

ent most genetic findings have no immediate influence on patient management. Although these screens were supported as relevant at a tertiary level, access to genetic counseling by trained personnel was considered to be part of standard care that should be undertaken at all levels of care. This would enable at-risk groups, either with or without a definitive diagnosis, to be counseled, even if a definitive diagnosis could not be made.

Infants differ from other age groups in that they are more likely to have a more complex and adverse course with medically refractory epilepsy in a high proportion of the affected group. The management differs with regard to conventional introduction of AEDs compared to that seen in the older patient and in adult practice. Therapy tends to be introduced more aggressively and rapidly, with the aim of attaining early seizure control and based on this, improved long-term outcomes. There are limited data to support this for conditions such as Dravet syndrome and mostly this is a standard practice approach.[31] Such approaches to care are not without risk; therefore, careful observation of patients would be important. Consequently, it is recommended that whenever possible these infants are managed initially with frequent assessment for efficacy and AED tolerance. One could debate that a study of, for example, the deferred treatment optimization of an infant with epileptic spasms, would be unethical.

Evidence to support specific treatments in infants is lacking, so a survey was undertaken (Wilmshurst et al.[75]). For some of the newer AEDs, there was limited data to draw conclusions relating to efficacy, for example, levetiracetam. This did not equate to other commonly used agents being ineffective; the studies have not been performed using these AEDs in this age group. Epileptic spasms, however, is one of the few infantile epilepsy conditions for which there are insufficient data to allow stronger recommendations to be made. The United Kingdom Infantile Spasms Study (UKISS) study, the American Academy recommendations, and the Cochrane meta-analyses have aided focus on the condition.[32–38]

The comorbidities of epilepsy are vast, and there are increasing data to raise the profile of this additional aspect of the condition. Epilepsies with onset in the infantile period are especially associated with autism and intellectual disability, supporting the screening for autism spectrum disorders.[39]

The recommendations drawn from this analysis are predominantly based on low level evidence and are often expert opinion. There is a lack of comparative data of the older AEDs against the newer AEDs. With concerns regarding the safety and influences on brain maturation of some of the older AEDs, such as phenobarbital, it is frustrating to have limited longitudinal data to determine definitively whether prescribing such a product in infants is indeed doing them a disservice.[40] Again, if sufficient evidence was established then there could be a stronger case to lobby for improved access, and viable rates for the newer generation AEDs to make them accessible to low and middle income countries. Further studies are needed, for example, to address the role of high dose oral prednisone in the management of epileptic spasms, and the use of the ketogenic diet in medically refractory epileptic spasms.[16,41,42] Although this report has provided a series of recommendations, for the most part it has identified the significant lack of evidence to support a standard of care with regard to the management of infants with epilepsy and the need for more targeted randomized controlled trials (RCTs) across all management areas, especially with respect to the role of AEDs. This report, initially intended as a guideline, was re-termed a recommendation, due to the lack of evidence-based data to support guideline statements. For the areas of expert opinion throughout the report, readers could elect to adapt this data to ensure the best care possible for their patients. These statements are not rigid but fluid, we are waiting for further studies to consolidate an improved evidence base to enable a definitive comment on common practice.

Acknowledgement

The authors wish to thank Roberto Tuchman for his suggestions to the outcome tools section.

Disclosure of Conflict of Interest

All authors were members of the Infantile Seizures Task Force, under the Pediatric Commission of the ILAE.

JM Wilmshurst and WD Gaillard are associate editors of *Epilepsia*.

JM Wilmshurst is a member of the Tuberous Sclerosis Complex advisory board for South Africa, which is sponsored by Novartis.

Tammy Tsuchida is a site primary investigator for a multicenter study Prevent West syndrome and has funding from Epilepsy Foundation New Therapy Research Grant for Dry Sensor-based Neonatal EEG Monitoring (NEMO).

WD Gaillard's income derives from clinical revenue generated for Children's National Medical Center (CNMC) clinical care. Federal support provided by the National Institute of Neurological Disorders and Stroke (NINDS) 1P30HD40677-01, 2K12NS052159-06A1; the National Institute of Mental Health (NIMH) RO1 MH084961, 1R21MH092615, the National Science Foundation (NSF) 095998; the Centers for Disease Control and Prevention (CDC) 1UO1DP003255; Department of Defense/United States Army Medical Research Acquisitions Activity (DOD/USAMRAA) W81XWH-11-2-0198: and Patient-Centered Outcomes Research Institute (PCORI) 527. Foundation support from the Epilepsy Foundation of America, American Epilepsy Society, Infantile Epilepsy Research Foundation (Lundbeck), and Citizens United for Research in Epilepsy (CURE). The CNMC conducts industry-supported trials form which no salary support is derived including from Ovation Pharmaceuticals, King Pharmaceuticals, PRA International/Eisai. Stock (held with spouse): Johnson and Johnson; Lily, Glaxo Smith Kline, Pfizer, Siemens, and General Electric. Editorial board of *Epilepsia* and *Epilepsy Research*.

J. Helen Cross holds an endowed Chair through University College, London. She has sat on Advisory Panels for Eisai, GW Pharma, and

Viropharma, for which remuneration has been paid to her department. Her department has received honoraria from Nutricia and UCB for speaking. Her Department has received a research grant from Vitaflo. She currently holds grants for research as from Action Medical Research, Epilepsy Research United Kingdom, Sparks – Children's Medical Research Charity, National Institute for Health and Research, the Great Ormond Street Hospital Children's Charity, and the European Union. She worked as clinical advisor to the update of the National Institute for Health and Care Excellence (NICE) guidelines on the diagnosis and management of epilepsy (2009–12) and is currently clinical advisor to the Children's Epilepsy Surgery Service (England and Wales), for which remuneration is made to her department. She is currently Secretary General to the ILAE.

Kollencheri Puthenveettil Vinayan, Virginia Wong, Deborah Hirtz, Nebojsa J Jovic, Patrick Van Bogaert, Dana Craiu, and Maurizio Elia have no disclosures or conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

1. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490.
2. Edlund W, Gronseth G, So Y, et al. (Eds) *Clinical practice guideline process manual*. St Paul, MN: American Academy of Neurology; 2004.
3. Gronseth G, French J. Practice parameters and technology assessments: what they are, what they are not, and why you should care. *Neurology* 2008;71:1639–1643.
4. Subcommittee on Febrile Seizures, American Academy of Pediatrics. Neurodiagnostic evaluation of the child with a simple febrile seizure. *Pediatrics* 2011;127:389–394.
5. Berg AT, Shinnar S. Complex febrile seizures. *Epilepsia* 1996;37:126–133.
6. Sapir D, Leitner Y, Harel S, et al. Unprovoked seizures after complex febrile convulsions. *Brain Dev* 2000;22:484–486.
7. Nelson KB, Ellenberg JH. Predisposing and causative factors in childhood epilepsy. *Epilepsia* 1987;28:S16–S24.
8. Wolf NI, Bast T, Surtees R. Epilepsy in inborn errors of metabolism. *Epileptic Disord* 2005;7:67–81.
9. Arsov T, Mullen SA, Damiano JA, et al. Early onset absence epilepsy: 1 in 10 cases is caused by GLUT1 deficiency. *Epilepsia* 2012;53:e204–e207.
10. Suls A, Mullen SA, Weber YG, et al. Early-onset absence epilepsy caused by mutations in the glucose transporter GLUT1. *Ann Neurol* 2009;66:415–419.
11. Ottman R, Hirose S, Jain S, et al. Genetic testing in the epilepsies–report of the ILAE Genetics Commission. *Epilepsia* 2010;51:655–670.
12. Nordli DR Jr, Kuroda MM, Carroll J, et al. Experience with the ketogenic diet in infants. *Pediatrics* 2001;108:129–133.
13. Kossoff EH, Pyzik PL, McGrogan JR, et al. Efficacy of the ketogenic diet for infantile spasms. *Pediatrics* 2002;109:780–783.
14. Eun SH, Kang HC, Kim DW, et al. Ketogenic diet for treatment of infantile spasms. *Brain Dev* 2006;28:566–571.
15. Kossoff EH, Hedderick EF, Turner Z, et al. A case–control evaluation of the ketogenic diet versus ACTH for new-onset infantile spasms. *Epilepsia* 2008;49:1504–1509.
16. Hong AM, Turner Z, Hamdy RF, et al. Infantile spasms treated with the ketogenic diet: prospective single-center experience in 104 consecutive infants. *Epilepsia* 2010;51:1403–1407.
17. Numis AL, Yellen MB, Chu-Shore CJ, et al. The relationship of ketosis and growth to the efficacy of the ketogenic diet in infantile spasms. *Epilepsy Res* 2011;96:172–175.
18. Kang HC, Lee YJ, Lee JS, et al. Comparison of short- versus long-term ketogenic diet for intractable infantile spasms. *Epilepsia* 2011;52:781–787.
19. Hopkins IJ, Lynch BC. Use of ketogenic diet in epilepsy in childhood. *Aust Paediatr J* 1970;6:25–29.
20. Kayyali HR, Gustafson M, Myers T, et al. Ketogenic diet efficacy in the treatment of intractable epileptic spasms. *Pediatr Neurol* 2014;50:224–227.
21. Cross JH, Jayakar P, Nordli D, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery. *Epilepsia* 2006;47:952–959.
22. Blount JP, Tubbs RS, Kankirawatana P, et al. Vagus nerve stimulation in children less than 5 years old. *Childs Nerv Syst* 2006;22:1167–1169.
23. Shahwan A, Bailey C, Maxiner W, et al. Vagus nerve stimulation for refractory epilepsy in children: more to VNS than seizure frequency reduction. *Epilepsia* 2009;50:1220–1228.
24. Cersosimo RO, Bartuluchi M, De Los Santos C, et al. Vagus nerve stimulation: effectiveness and tolerability in patients with epileptic encephalopathies. *Childs Nerv Syst* 2011;27:787–792.
25. Cersosimo RO, Bartuluchi M, Fortini S, et al. Vagus nerve stimulation: effectiveness and tolerability in 64 paediatric patients with refractory epilepsies. *Epileptic Disord* 2011;13:382–388.
26. Zamponi N, Rychlicki F, Corpaci L, et al. Vagus nerve stimulation (VNS) is effective in treating catastrophic 1 epilepsy in very young children. *Neurosurg Rev* 2008;31:291–297.
27. Cowan LD, Hudson LS. The epidemiology and natural history of infantile spasms. *J Child Neurol* 1991;6:355–364.
28. Riikonen R. Epidemiological data of West syndrome in Finland. *Brain Dev* 2001;23:539–541.
29. Shinnar S, Hesdorffer DC, Nordli DR Jr, et al. Phenomenology of prolonged febrile seizures: results of the FEBSTAT study. *Neurology* 2008;71:170–176.
30. Yu HJ, Lee CG, Nam SH, et al. Clinical and ictal characteristics of infantile seizures: EEG correlation via long-term video EEG monitoring. *Brain Dev* 2013;35:771–777.
31. Brunklaus A, Dorris L, Ellis R, et al. The clinical utility of an SCN1A genetic diagnosis in infantile-onset epilepsy. *Dev Med Child Neurol* 2013;55:154–161.
32. Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2012;78:1974–1980.
33. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. *Cochrane Database Syst Rev* 2008;4:CD001770.
34. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. *Cochrane Database Syst Rev* 2013;6:CD001770.
35. Lux AL, Edwards SW, Hancock E, et al. The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. *Lancet* 2004;364:1773–1778.
36. Lux AL, Edwards SW, Hancock E, et al. The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. *Lancet Neurol* 2005;4:712–717.
37. Darke K, Edwards SW, Hancock E, et al. Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for infantile spasms: a multi-centre randomised trial. *Arch Dis Child* 2010;95:382–386.
38. O'Callaghan FJ, Lux AL, Darke K, et al. The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study. *Epilepsia* 2011;52:1359–1364.
39. Johnson CP, Myers SM; American Academy of Pediatrics Council on Children With Disabilities. Identification and evaluation of children with autism spectrum disorders. *Pediatrics* 2007;120:1183–1215.
40. Kim JS, Kondratyev A, Tomita Y, et al. Neurodevelopmental impact of antiepileptic drugs and seizures in the immature brain. *Epilepsia* 2007;48:S19–S26.
41. Wanigasinghe J, Arambepola C, Sri Ranganathan S, et al. The efficacy of moderate-to-high dose oral prednisolone versus low-to-moderate dose intramuscular corticotropin for improvement of hypsarrhythmia in West syndrome: a randomized, single-blind, parallel clinical trial. *Pediatr Neurol* 2014;51:24–30.
42. Hussain SA, Shinnar S, Kwong G, et al. Treatment of infantile spasms with very high dose prednisolone before high dose adrenocorticotropic hormone. *Epilepsia* 2014;55:103–107.
43. Freitag CM, May TW, Pfafflin M, et al. Incidence of epilepsies and epileptic syndromes in children and adolescents: a population-based prospective study in Germany. *Epilepsia* 2001;42:979–985.

44. Dura-Trave T, Yoldi-Petri ME, Gallinas-Victoriano F. Incidence of epilepsies and epileptic syndromes among children in Navarre, Spain: 2002 through 2005. *J Child Neurol* 2008;23:878–882.
45. Kurtz Z, Tookey P, Ross E. Epilepsy in young people: 23 year follow up of the British national child development study. *BMJ* 1998;316:339–342.
46. Olafsson E, Ludvigsson P, Gudmundsson G, et al. Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study. *Lancet Neurol* 2005;4:627–634.
47. Verity CM, Ross EM, Golding J. Epilepsy in the first 10 years of life: findings of the child health and education study. *BMJ* 1992;305:857–861.
48. Camfield CS, Camfield PR, Gordon K, et al. Incidence of epilepsy in childhood and adolescence: a population-based study in Nova Scotia from 1977 to 1985. *Epilepsia* 1996;37:19–23.
49. Doose H, Sitepu B. Childhood epilepsy in a German city. *Neuropediatrics* 1983;14:220–224.
50. Granieri E, Rosati G, Tola R, et al. A descriptive study of epilepsy in the district of Copparo, Italy, 1964–1978. *Epilepsia* 1983;24:502–514.
51. Eltze CM, Chong WK, Cox T, et al. A population-based study of newly diagnosed epilepsy in infants. *Epilepsia* 2013;54:437–445.
52. Datta AN, Wirrell EC. Prognosis of seizures occurring in the first year. *Pediatr Neurol* 2000;22:386–391.
53. Masri A, Badran E, Hamamy H, et al. Etiologies, outcomes, and risk factors for epilepsy in infants: a case–control study. *Clin Neurol Neurosurg* 2008;110:352–356.
54. Korff C, Nordli DR Jr. Do generalized tonic-clonic seizures in infancy exist? *Neurology* 2005;65:1750–1753.
55. Matsumoto A, Watanabe K, Sugiura M, et al. Long-term prognosis of convulsive disorders in the first year of life: mental and physical development and seizure persistence. *Epilepsia* 1983;24:321–329.
56. Hsieh DT, Chang T, Tsuchida TN, et al. New-onset afebrile seizures in infants: role of neuroimaging. *Neurology* 2010;74:150–156.
57. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010;51:1069–1077.
58. Wirrell E, Wong-Kisiel L, Mandrekar J, et al. Predictors and course of medically intractable epilepsy in young children presenting before 36 months of age: a retrospective, population-based study. *Epilepsia* 2012;53:1563–1569.
59. Geerts A, Brouwer O, Stroink H, et al. Onset of intractability and its course over time: the Dutch study of epilepsy in childhood. *Epilepsia* 2012;53:741–751.
60. Dhamija R, Moseley BD, Cascino GD, et al. A population-based study of long-term outcome of epilepsy in childhood with a focal or hemispheric lesion on neuroimaging. *Epilepsia* 2011;52:1522–1526.
61. Korff CM, Nordli DR Jr. The clinical-electrographic expression of infantile seizures. *Epilepsy Res* 2006;70:S116–S131.
62. Trevathan E, Murphy CC, Yeargin-Allsopp M. The descriptive epidemiology of infantile spasms among Atlanta children. *Epilepsia* 1999;40:748–751.
63. Zeiler SR, Kaplan PW. Our digital world: camera phones and the diagnosis of a seizure. *Lancet* 2009;373:2136.
64. Knudsen FU. Febrile seizures: treatment and prognosis. *Epilepsia* 2000;41:2–9.
65. Sadleir LG, Scheffer IE. Febrile seizures. *BMJ* 2007;334:307–311.
66. Bast T, Carmant L. Febrile and other occasional seizures. *Handb Clin Neurol* 2013;111:477–491.
67. Sfaihi L, Maaloul I, Kmiha S, et al. Febrile seizures: an epidemiological and outcome study of 482 cases. *Childs Nerv Syst* 2012;28:1779–1784.
68. Graves RC, Oehler K, Tingle LE. Febrile seizures: risks, evaluation, and prognosis. *Am Fam Physician* 2012;85:149–153.
69. Annegers JF, Hauser WA, Shirts SB, et al. Factors prognostic of unprovoked seizures after febrile convulsions. *N Engl J Med* 1987;316:493–498.
70. Vestergaard M, Pedersen CB, Sidenius P, et al. The long-term risk of epilepsy after febrile seizures in susceptible subgroups. *Am J Epidemiol* 2007;165:911–918.
71. Capovilla G, Mastrangelo M, Romeo A, et al. Recommendations for the management of "febrile seizures": Ad Hoc Task Force of LICE Guidelines Commission. *Epilepsia* 2009;50:S2–S6.
72. Nagase H, Nakagawa T, Aoki K, et al. Therapeutic indicators of acute encephalopathy in patients with complex febrile seizures. *Pediatr Int* 2013;55:310–314.
73. Kim H, Byun SH, Kim JS, et al. Clinical and EEG risk factors for subsequent epilepsy in patients with complex febrile seizures. *Epilepsy Res* 2013;105:158–163.
74. Hesdorffer DC, Shinnar S, Lewis DV, et al. Risk factors for febrile status epilepticus: a case–control study. *J Pediatr* 2013;163:1147–1151.
75. Wilmshurst JM, Burman R, Gaillard WD, Cross JH. Treatment of infants with epilepsy: Common practices around the world. *Epilepsia* 2015;56:1033–1046.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Main data collection document with complete data analysis.

Tables

1.1: The differential diagnosis of mimics of seizures in infants.

4.3.1: Diagnostic markers of key infantile seizures and syndromes.

6.3.1: Summary of published studies addressing AED treatment for infants with seizures.

6.3.2: Studies addressing management of focal seizures of infants.

6.3.3: Studies addressing generalized seizures in infancy.

6.3.4: Studies addressing severe myoclonic epilepsy in infancy.

6.3.5: Studies addressing benign infantile convulsions.

6.3.6: Studies addressing provoked or situational seizures.

6.3.7: Summary of the survey results (n=733).

Figures

4.3.1: Hypsarrhythmia in an 8-month-old male infant demonstrating the chaotic high-amplitude multifocal discharges throughout all regions with one short burst of suppression.

4.3.2: Migrating partial seizures of infancy: Serial EEG studies recorded in the same patient, which sequentially demonstration the migrations of seizures from the left to the right hemispheres and vice versa.

4.3.3: Generalized spike wave activity recorded in a 14-month-old child with myoclonic jerks supported by the correlation with electromyographic lead activity.

4.3.4: Myoclonic status recorded in a patient with infantile-onset neuronal ceroid lipofuscinosis.

4.3.5: EEG recording from a 2-year-boy with Angelman syndrome demonstrating the high-amplitude, symmetrical, synchronous and monorhythmic bilateral spike and wave activity with slow wave component at 2 Hz evident on eye closure.