



Treatment of Infantile Spasm Syndrome: Update from the Interdisciplinary Guideline Committee Coordinated by the German-Speaking Society of Neuropediatrics

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Abstract

Objectives The manuscript serves as an update on the current management practices for infantile spasm syndrome (ISS). It includes a detailed summary of the level of current evidence of different treatment options for ISS and gives recommendations for the treatment and care of patients with ISS.

Methods A literature search was performed using the Cochrane and Medline Databases (2014 to July 2020). All studies were objectively rated using the Scottish Intercollegiate Guidelines Network. For recommendations, the evidence from these studies was combined with the evidence from studies used in the 2014 guideline.

Recommendations If ISS is suspected, electroencephalography (EEG) should be performed within a few days and, if confirmed, treatment should be initiated immediately. Response to first-line treatment should be evaluated clinically and electroencephalographically after 14 days. The preferred first-line treatment for ISS consists of either hormone-based monotherapy (AdrenoCorticoTropic Hormone [ACTH] or prednisolone) or a combination of hormone and vigabatrin. Children with tuberous sclerosis complex and those with contraindications against hormone

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treatment should be treated with vigabatrin. If first-line drugs are ineffective, second-line treatment options such as ketogenic dietary therapies, sulthiame, topiramate, valproate, zonisamide, or benzodiazepines should be considered. Children refractory to drug therapy should be evaluated early for epilepsy surgery, especially if focal brain lesions are present. Parents should be informed about the disease, the efficacy and adverse effects of the medication, and support options for the family. Regular follow-up controls are recommended.

Introduction

Infantile spasms (IS) are an age-related epileptic syndrome that significantly impacts the development of affected children. Recently, the term “Infantile Spasm Syndrome” (ISS) has been proposed by the Nosology and Definitions Task Force of the ILAE (International League Against Epilepsy) to encompass both West syndrome as well as infants presenting with epileptic spasms (ES) who do not fulfill all criteria for West syndrome (available online at: <https://pubmed.ncbi.nlm.nih.gov/35503712/>).

ES are mandatory for diagnosis and consist of a sudden flexion, extension, or mixed extension–flexion of predominantly proximal and truncal muscles that is usually more sustained than a myoclonic jerk but not as sustained as a tonic seizure.¹ In addition, symptoms can occasionally be subtle (e.g., serial tonic contraction of single muscles or muscle groups, grimacing, head nodding, chin movements, eye movements) and may only be identifiable on ictal electroencephalography (EEG) recordings. ES usually occur in series or clusters, often on awakening, with an increasing prominence of motor features through the cluster, often over minutes, though clusters may last 30 minutes or longer. Non-serial, single ES may also be observed but should only be attributed to ISS (“infantile spasm single variant”) when the ictal or interictal EEG is compatible.² ES may be symmetric or asymmetric. It should be noted that focal seizures may also co-occur independently of spasms or even preceding spasms, especially in a structural etiology, such as tuberous sclerosis complex (TSC) or focal cortical dysplasia. “West syndrome” is classically defined by the triad of ES, hypsarrhythmia, and developmental stagnation or regression. However, the terms “Infantile spasms” and “West Syndrome” are often used interchangeably. Children with ISS often lack one of three criteria of West syndrome, e.g., the developmental stagnation or regression may not be apparent or typical hypsarrhythmia may not be present. Some infants may not be diagnosed with hypsarrhythmia, although the EEG is clearly abnormal. Not only is the interrater reliability for the assessment of hypsarrhythmia low,³ but hypsarrhythmia may also be absent very early in the course of the disease or in older children. Furthermore, there is no consensus on whether treatment should differ for ISS with and without hypsarrhythmia. While the time to resolution of ES is directly correlated with 18-month developmental outcomes,⁴ the effect of timing of resolution of hypsarrhythmia is less clear.

Therefore, we opted to use ISS as an umbrella term for this guideline. The current report is the second update of the guideline on ISS, first published in 2009 and updated in 2014,⁵ and exclusively refers to the treatment of acute, new-onset ISS. Other types of seizures preceding or occurring during the course of ISS are not addressed in this guideline.

ISS may occur due to a wide spectrum of etiologies. In older studies, three etiological subgroups of ISS were differentiated:

- Idiopathic: no identifiable underlying cause at the absence of other neurological signs or symptoms.
- Cryptogenic (Greek term for “of hidden origin”): a symptomatic etiology is suspected, but no structural or metabolic cause has been identified. A symptomatic etiology may be alleged, e.g., in pre-existing developmental delay, neurological signs or symptoms or epileptic seizures preceding ISS manifestation.
- Symptomatic: the underlying disorder has been confirmed.

The *ILAE Commission on Classification and Terminology* recommends to replace the terms “idiopathic,” “symptomatic” and “cryptogenic” with “genetic,” “structural/metabolic” and “unknown etiology.”⁶ However, the available information on ISS etiology only rarely allows such a precise distinction across studies. Since the terminology of epilepsies and epilepsy syndromes has undergone major changes in the last decade(s) and studies on ISS have thus used widely variable classifications of ISS etiology, we opted for the terms “no identified etiology” (tantamount with “idiopathic” and “cryptogenic”) and “identified etiology” (tantamount with “symptomatic”), as used in the seminal study of Lux et al.⁷

The aim of this updated guideline is to define treatment goals and to summarize the evidence level (EL) of different treatment options, both in terms of efficacy and adverse effects. Recommendations to improve current practice are proposed even at low EL. This guideline should enable the treating physician to select the therapeutic option most likely to result in a rapid and sustained treatment response and, consequently, in an optimal developmental trajectory for the affected infant. The following aspects of ISS management are assessed in our guideline:

- Which conditions are most likely to lead to a successful treatment?

- Which treatment leads to a quick and sustainable cessation of ES and resolution of hypsarrhythmia?
- Which treatment has the fewest adverse effects?
- Which treatment is the most effective in certain etiological subgroups?
- Which treatment leads to the best neurological and cognitive/developmental outcomes?
- Which quality indicators are suitable for the assessment of treatment success?

In addressing these questions, it is important to acknowledge that there is currently a lack of high-level evidence in the form of randomized controlled studies. Other limitations to be considered are inconsistent outcome measures, small cohorts with highly variable etiologies, short follow-up duration, and the diverse dose and duration for different treatments. Freedom from ES, the main goal of ISS treatment, is not to be equated with freedom from all other epileptic seizure types that may present in the context of ISS. If the latter persists, additional treatment approaches are needed that are not elaborated here. For similar reasons, the normalization of the EEG is not a treatment goal. The authors are aware that “resolution of hypsarrhythmia” leaves room for interpretation.

Methods

For this update we performed a literature search (2014 to July 2020) using the Cochrane and Medline databases. MESH terms used included “Spasms, Infantile” OR “Blitz-Nick-Salaam,” “Humans,” “English,” “German,” which generated 690 new references. All references considered for this guideline (including those considered for the previous versions of this guideline) are listed in ►**Supplementary References** (available in the online version). A search in the international database for medical guidelines (<https://g-i-n.net>) did not yield any other guidelines on the subject of “Infantile Spasms” or “West syndrome” apart from the present one. For publications to be considered, the following inclusion criteria had to be fulfilled:

- Definite diagnosis of ISS.
- Age mainly below 2 years.
- Study population of at least five patients.

The results of the previously published *AAN Practice Parameters*,^{8,9} and the Cochrane Review regarding the *Treatment of infantile spasms*¹⁰ were also considered for our analysis both in terms of included references and meta-analysis data. Reported spontaneous remission rates of 2% 1 month after onset and 25% 12 months after onset were taken into account.^{11,12} Rating the level of evidence followed the principles of the Scottish Intercollegiate Guidelines Network (SIGN) www.sign.ac.uk/methodology/index.html. We defined four levels of evidence (► **Table 1**).

The authors of the current guideline appreciate that the assessment of the EL of individual publications (► **Supplementary Tables**, available in the online version) may leave room for interpretation. However, for the previous (2014) version of the guideline, no members of the German-speaking Society of Neuropediatrics or users of the guideline raised any justified objections to the classification of evidence, as performed in the scope of the guideline.

The grading of recommendations (► **Table 2**) incorporates the expected benefit and a risk-benefit analysis. Corresponding explanations are given for each recommendation.

For the formal recommendations, a written, three-step Delphi process was used to establish consensus amongst the guideline authors and the delegates of the involved medical societies and of the parent association (see Acknowledgments). The grades of recommendation and the strength of agreement within the guideline group were classified as described in ► **Table 3**.

The revised version of the guideline, *Therapie der Blitz-Nick-Salaam Epilepsie (West Syndrome)*, was published in October 2021 on the website of the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of the Scientific Medical Societies) (<https://www.awmf.org/leitlinien/detail/II/022-022.html>) together with a *Patients Guideline*. The present paper summarizes

Table 1 Levels of evidence (SIGN grading system)

1 ²⁺	High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias.
1 ⁺	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1 ⁻	Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
2 ²⁺	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2 ⁺	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2 ⁻	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3	Non-analytic studies, e.g., case reports, case series.
4	Expert opinion

^aScottish Intercollegiate Guidelines Network SIGN 50. A guideline developer's handbook. Edinburgh: SIGN, 2008.

Table 2 Grade of recommendation

Quality of evidence	Recommendation	Symbol
High mostly EL 1 ++ and 1 +, in justified cases EL 2 ++ or 2+	Strong recommendation: “we recommend” or “it is recommended”	↑↑
Moderate mostly EL 2 ++ and 2 +, in justified cases EL 3 or downgraded EL 1 ++ or 1+	Recommendation: “we suggest” or “it is suggested”	↑
Low mostly EL 3, in justified cases also downgraded to EL 2 ++ or 2+	Open recommendation: may be considered/no specific recommendation	⇔

Table 3 Classification of consensus strength according to the AWMF

Strong consensus	Agreement amongst >95% of participants.
Consensus	Agreement amongst >75–95% of participants.
Majority consensus	Agreement amongst >50–75% of participants.
No consensus	Agreement amongst <50 of participants.

this guideline. References cited in the original German version (273 citations) and tables with the EL assessment are provided as **►Supplementary References** and **►Supplementary Tables** (available in the online version).

Summary of Reviewed Drugs

Adrenocorticotrophic Hormone

Fifteen randomized (**►Supplementary Table S1**, available in the online version), 14 uncontrolled prospective (**►Supplementary Table S2** available in the online version), and 31 retrospective studies (**►Supplementary Table S3** available in the online version) were identified.

- No placebo-controlled studies were found.
- Adrenocorticotrophic hormone (ACTH) is probably effective in ISS of identified etiology and in ISS of no identified etiology (EL 1 +). The initial efficacy of ACTH appears to be superior to its long-term efficacy.
- On average, time to response is 1 to 2 weeks (EL 1 +).
- In almost all studies, the response rate was higher in ISS with no identified etiology than in those with identified etiology. No differences in treatment response related to different etiologies could be identified (EL 1).
- The different ACTH formulations (natural, synthetic, and synthetic depot) appear to be equivalent.
- High-dose ACTH is not more effective than low-dose ACTH (EL 1 +).
- There is no data showing any superiority of a long-term over a short-term (2 week) treatment duration (EL 1 +). However, there is data suggesting that longer treatment duration (months) reduces the relapse rate (EL 3).
- In case of a relapse after short-term treatment, patients with ISS can benefit from a second course of ACTH, glucocorticoids or vigabatrin (EL 2 –).
- There is no proof of an additive/supra-additive effect of pyridoxine/pyridoxal phosphate or MgSO₄, when administered concurrently with ACTH.
- ACTH is probably not superior to oral glucocorticoids. Recent studies (EL 1 +) and a meta-analysis¹³ show that prednisolone and ACTH are equivalent for sufficiently high prednisolone doses. The inferiority of prednisone to ACTH in an older study (EL 1 –) may be attributed to the low dosage. In their Cochrane review, Hancock et al¹⁰ mention, albeit without citation, that prednisone and prednisolone cannot be considered equivalent in infants because prednisone metabolism is reduced due to a reduced HSD11B1 capacity.
- Patients with no identified etiology, recent onset of ISS, and subsequent early treatment (within 4 weeks) respond better to ACTH in terms of seizure freedom (EL 1 +) and cognitive development (EL 1 +) (**►Supplementary Tables S4** and **S5**, available in the online version).
- There is a small body of evidence deriving from the UKISS (United Kingdom Infantile Spasms Study)⁷ that in ISS with no identified etiology, cognitive development is better when using ACTH or prednisolone than vigabatrin. However, if vigabatrin is combined with ACTH or prednisolone, there is no difference in cognitive development compared with the group treated exclusively with hormones.⁴
- Adverse effects (**►Supplementary Table S6**, available in the online version), such as arterial hypertension, agitation, sedation, hypokalemia, hyperglycemia, infections, cataracts, Cushing’s syndrome, brain volume loss, reversible hypertrophic cardiomyopathy (without significant left ventricular outflow obstruction), and nephrocalcinosis are reported with variable frequency. Severe side effects are reported at 13% and deaths are very rare (exception: one retrospective study with very high doses and a death rate of 4.5%).

- Hypertension and brain-volume loss are dose-dependent adverse effects of ACTH (EL 1+). No other dose-dependent adverse effects have been reported. There is limited data on the occurrence of adrenocortical insufficiency after ACTH discontinuation. Furthermore, there is no data on whether and which scheme of tapering or whether and which scheme of temporary steroid substitution can prevent adrenocortical insufficiency.

Glucocorticoids

There were 29 studies on the efficacy and adverse effects of glucocorticoids in ISS (► **Supplementary Table S7A + B**, available in the online version) including nine randomized, four prospective, and 11 retrospective studies. Four did not fulfil the inclusion criteria.

- Glucocorticoids are probably effective in treating ISS with identified etiology and in those with no identified etiology (EL 1+).
- Higher doses of glucocorticoids are more effective than lower doses.
- ISS with no identified etiology respond better to therapy than those with identified etiology (EL 1+).
- A short time interval between ISS manifestation and treatment initiation seems to have a positive effect on both seizure and developmental outcomes (EL 1+).
- There is no data demonstrating the superiority of any particular glucocorticoid, route of administration, or duration of treatment.
- The available data are insufficient for a conclusive assessment of pulsatile therapy with glucocorticoids.
- Similar to ACTH, glucocorticoids have potentially life-threatening adverse effects (► **Supplementary Table S6**, available in the online version). There is insufficient data to assess whether glucocorticoids have a better safety profile than ACTH.
- There is no data on endocrine disorders after discontinuation of glucocorticoids following ISS treatment and there is no data on whether and what kind of tapering or whether and what kind of temporary glucocorticoid substitution can prevent these disorders.

Vigabatrin seven randomized (► **Supplementary Table S8**, available in the online version), nine prospective (► **Supplementary Table S9**, available in the online version) and 15 retrospective studies (► **Supplementary Table S10**, available in the online version) were reviewed.

- Vigabatrin is probably effective for the treatment of ISS with identified etiology and in those with no identified etiology (EL 1+).
- Higher dosages (100–150 mg/kg) are more effective than lower dosages of vigabatrin (18–36 mg/kg) (EL 1+).
- Vigabatrin response is usually seen within 1 to 2 weeks (EL 1+).
- A treatment period of only 6 months does not appear to increase relapse rates, including ISS with identified etiology (EL 3).

- Response to vigabatrin is better in infants with TSC (EL 1+) (► **Supplementary Table S11**, available in the online version).
- Vigabatrin is overall well tolerated. Adverse effects include fatigue, irritability and hyperactivity, gastrointestinal problems, sleep disorders, muscular hypo- or hypertonia, and weight gain (► **Supplementary Table S12**, available in the online version).
- Vigabatrin-associated brain abnormalities on magnetic resonance imaging (MRI) (► **Supplementary Table S13B**, available in the online version) are reversible and mostly asymptomatic. In infants treated with the combination of vigabatrin and hormones, vigabatrin-associated brain abnormalities on MRI can be accompanied by reversible movement disorders, encephalopathy, and dysautonomia. This may be more common in infants with trisomy 21.¹⁴
- There is evidence that the preventive use of vigabatrin in TSC leads to better long-term outcomes with regards to seizure and cognitive outcome.¹⁵ However, further studies are needed to provide clarity on the full extent of preventive treatment benefits.
- Visual field defects due to vigabatrin (► **Supplementary Table S13A**, available in the online version)
- Children with ISS show a high percentage of ophthalmological disorders and retinal damage even without vigabatrin therapy.^{16,17}
- Studies do not allow a clear risk assessment of visual field impairments or retinal damage in patients with ISS treated with vigabatrin.
- Ophthalmological studies performed with variable methodologies show significant differences regarding visual field impairments and retinal damage between vigabatrin-treated children and a control group. There is, however, currently no consensus regarding the clinical relevance of these findings.
- The risk of visual field defects from vigabatrin appears to be lower in children than in adults. The risk may be even lower in very young children.
- Clinically relevant visual field defects due to vigabatrin are only rarely reported in children.
- A higher total cumulative dose and a longer duration of vigabatrin treatment may play a role in the development of visual field defects.¹⁸ Therefore, children with TSC are at increased risk for developing visual field defects.
- The risk of clinically relevant visual field impairment due to vigabatrin cannot be ruled out. The risk, however, does seem to be low if the treatment is limited to less than 6 months (or 3–4 months, as practiced in recent studies).

Other Drugs

The studies (► **Supplementary Tables S14 - S19**, available in the online version) on sulthiame (one study EL 1-), benzodiazepines (eight studies EL 1-, EL3), immunoglobulins (three studies EL 3), levetiracetam (three studies EL 3), topiramate (20 studies EL 1+ - EL 3), felbamate (three studies EL 3), valproate (seven studies EL 3), pyridoxine/pyridoxal phosphate (nine studies EL 1- - EL 3) and zonisamide (nine studies EL 1+ - EL 3) provide insufficient evidence to

Table 4 Therapeutic goals

Evidence	Recommendation 1	Recommendation level
High	The aim of the treatment should be the rapid cessation of epileptic spasms and the rapid resolution of hypsarrhythmia on the EEG (both awake and asleep) as a prerequisite for the best possible cognitive development of the affected child.	↑↑

Source: Adapted from O'Callaghan et al, 2011, 2017, 2018 (EL 1 +),^{4,21,22} and ► **Supplementary Tables S4, S5** (available in the online version).
Note: Strong consensus (>95%).

recommend these therapies for the first-line treatment of ISS. These agents should thus only be considered in selected cases. For example, a therapeutic trial with these agents may be justified in ISS refractory to first-line treatments. Valproate requires probably high doses (>60 mg/kg) and a longer duration of treatment to show efficacy. Metabolic, particularly mitochondrial diseases should be ruled out before starting valproate. Pyridoxine 30 mg/kg/d for 3 to 5 days can be considered if pyridoxine-dependent epilepsy is suspected or if the first-line drugs are not effective. The vast majority of infants with pyridoxine-dependent epilepsy promptly respond to the first administration of pyridoxine. There is currently no data that supports the use of tetrahydrocannabinol/cannabidiol or everolimus to treat ISS.

Ketogenic Dietary Therapies

The use of dietary treatments such as ketogenic dietary therapies (KDTs) to treat ISS is supported by a limited body of evidence consisting of one randomized (EL 1 –/EL 2 –),¹⁹ five prospective (EL 2 +/EL 3), and 12 retrospective (EL 2 –/EL 3) studies (► **Supplementary Table S20**, available in the online version).

- KDT are a therapeutic option for the treatment of ISS (EL 1 –, EL 3) when glucocorticoids/ACTH and vigabatrin are not successful.
- KDT may be considered in addition to vigabatrin when vigabatrin is not sufficiently effective and hormonal therapy is contraindicated.
- In individual cases, a rapid response to KDT can be achieved.
- There are indications that the response to KDT can be seen within 2 to 4 weeks. It appears reasonable to evaluate the efficacy after 2 weeks and to change therapy in case of no response.
- The clinical improvement often precedes the EEG changes.
- The duration of KDT may be limited to 6 to 8 months.

Table 5 Indication for EEG

Evidence	Recommendation 2	Recommendation level
High	If infantile spasms syndrome is suspected, an EEG should be performed within a few days.	↑↑

Source: Adapted from O'Callaghan et al., 2011, 2017, 2018 (EL 1 +),^{4,21,22} and ► **Supplementary Tables S4, S5** (available in the online version).
Note: Strong consensus (>95%).

Epilepsy Surgery and Vagal Nerve Stimulation

In 10 studies (EL 3, four of which draw from the same patient cohort), 6 to 39 children with ISS underwent epilepsy surgery. Another five retrospective studies included infants with ISS but did not explicitly present their findings and outcomes in a subgroup analysis. After focal resection or hemispherectomy, 65 to 100% of children were seizure free.

No studies exist on the efficacy of vagal stimulation in ISS. A retrospective analysis considering 129 children with vagal nerve stimulation reported 10 infants, all without improvement of their seizures.²⁰

- Epilepsy surgery is a therapeutic option for ISS, but is only indicated in selected cases of ISS with structural etiology (EL 3).
- The development of the affected children benefits from early epilepsy surgery.³⁸
- The Commission for Pediatric Epilepsy Surgery stated that no recommendation can be made for vagal nerve stimulation in ISS.

Recommendations

Therapeutic Goals

► **Table 4.**

Treatment Initiation and Ongoing Patient Care

Diagnostic work-up and treatment initiation as well as the ongoing care of the affected child is usually undertaken by a pediatrician specialized in child neurology. Treatment is usually initiated in inpatient status directly following diagnosis. In exceptional cases, treatment can be started on an outpatient basis by an experienced pediatric neurologist/epileptologist. When starting glucocorticoid or ACTH treatment, thorough knowledge of their adverse effects is required, and support from a pediatric endocrinologist and a pediatric cardiologist should be considered. Drug-resistant ISS should be referred to a pediatric neurology center with a wide range of diagnostic and therapeutic options (► **Tables 5 and 6**).

Table 6 Timing of treatment initiation

Evidence	Recommendation 3	Recommendation level
High	Once the diagnosis has been confirmed, treatment with proven rapid efficacy should be initiated as soon as possible.	↑↑

Source: Adapted from O’Callaghan et al., 2011, 2017, 2018 (EL 1 +),^{4,21,22} and ► **Supplementary Tables S4, S5** (available in the online version). Note: Strong consensus (>95%).

Comment on Recommendation 1, 2, and 3

These three strong recommendations are based on several well-documented studies (EL 1 +, EL 2 +, EL 3),^{4,21,22} which show that a rapid diagnosis and a rapid initiation of an effective treatment are essential for a good therapeutic result (response to treatment, epilepsy outcome, and cognitive outcome). This is especially true for patients with no identified etiology, but also for those with identified etiology.^{4,23,24}

Non-epileptic paroxysmal events or other types of seizures can mimic ISS. Home-video documentation of the suspicious events must be confirmed by video EEG recordings. Sleep EEG is recommended. During the EEG registration, it is important to capture the time period after waking up, as ES often present during this time. The presence of hypsarrhythmia is not mandatory for the diagnosis. If in doubt, a longer video EEG recording with the goal to capture ES is recommended (► **Table 7**).

Comment on Recommendation 4

The recommendation to review the treatment efficacy after 14 days corresponds to the primary outcome criteria of recent treatment studies in ISS. No studies have compared different time periods. This suggestion is based on the need for a rapid and sustained therapeutic success. Clinical success can be assumed if no ES has occurred for 48 hours. A reduction of ES does not qualify for a sufficient treatment response.

Table 7 Evaluation of treatment efficacy

Evidence	Recommendation 4	Recommendation level
Low	The efficacy of first-line drugs should be evaluated clinically and electroencephalographically (EEG in wakefulness and sleep) after approximately 14 d.	↑

Note: No specific studies; Strong consensus (>95%).

Table 8 Parental information and support

Evidence	Recommendation 5	Recommendation level
Expert consensus	Parents should be informed about all aspects relating to the disease, the chosen management plan and potential adverse effects. In addition, parents should be made aware of relevant support structures that may assist them in caring for their child. This requires repeated consultations in simple language. The parents should have sufficient opportunity to discuss questions and concerns. A child psychologist could be engaged to facilitate this process. In addition, the parents can be offered written information about ISS and treatment options. It is recommended to involve a social worker with experience in epilepsy care.	↑↑↑ ↑

Note: No specific studies on ISS; Strong consensus (>95%).

An electroencephalographic response requires a hypsarrhythmia-free EEG in wakefulness and sleep. Clinical improvement can precede the response seen electroencephalographically. The role of the EEG in patient management is controversial. If hypsarrhythmia persists despite cessation of ES, subclinical or subtle symptoms of ISS should be carefully excluded. This may include conducting a long-term video EEG study. Whether the persistence of hypsarrhythmia alone warrants a change of treatment remains an unanswered question. In these cases, adaptation of treatment should be considered and the patient should be closely monitored (► **Table 7**).

Comment on Recommendation 5

In the absence of ISS-specific studies, a “recommendation” or “suggestion” is made within the frame of an expert consensus. Informing the parents about the disease and the adverse effects of the medication as well as about support options is an essential task of the treating physician. In our experience, parents of ISS patients are in a very emotional and vulnerable psychological state. Parents are rarely able to obtain all the information that they require at the first consultation. Repeated consultations with the care provider about the treatment options, their mode of action and adverse effects, as well as about the funding and support options available for the child and the family, help to stabilize the family, increase compliance and prevent the parents from overburdening (► **Table 8**).

Since informing the parents about the diagnosis is often accompanied by considerable anxiety, offering psychological support can be helpful. The involvement of a social worker with specific epilepsy expertise and the prescription of socio-medical aftercare can contribute significantly to reducing the psychosocial burden on the parents. Providing written information on ISS (e.g., a patient information pamphlet) and handing out copies of the child's clinical record (with proper guidance by the care provider) may help to educate parents about the child's condition.

Recommendation of Treatment

► Table 9.

Comment on Recommendation 6

There are sufficiently high-quality studies demonstrating the efficacy of hormones (ACTH, prednisolone,^{7,25} and other glucocorticoids) and the combination of hormones and vigabatrin.^{4,21} This corresponds with the appraisal of ACTH and prednisolone in a Cochrane review¹⁰ and of ACTH in the 2012 updated American guideline for ISS treatment.⁹

ACTH is only available in German-speaking countries as a synthetic product (Synacthen, Depot-Synacthen). Low ACTH doses seem equally effective as high doses^{26,27} and good therapeutic success can be achieved even with short-term therapy protocols.^{21,25}

Glucocorticoids: Prednisolone in doses of 40 to 60 mg/d (corresponding to approximately 7.5 mg/kg/d) is the most extensively studied glucocorticoid. In addition to prednisolone, other glucocorticoids with different dosages and regimens can also be effective in ISS (► **Supplementary Table S7A, B**, available in the online version). Lower doses of prednisone²⁸ are probably less effective than higher doses of prednisolone.²⁵ The total duration of treatment with glucocorticoids studied was 4 to 16 weeks.

In non-responders to hormone therapy (defined as ongoing ES after completing a two-week trial) a shift to another treatment and tapering of the hormone is recommended.

Combination of vigabatrin with ACTH or prednisolone:

This recommendation is based on the result of the International Collaborative Infantile Spasms Study (EL 1+).^{4,21} In this study, vigabatrin combined with ACTH or prednisolone showed significantly better results in stopping ES after 2 weeks than monotherapy with ACTH or prednisolone. However, there was no superiority of the combined therapy on developmental and epilepsy outcomes in the follow-up examination at the age of 18 months. The authors have attributed this discrepancy to the fact that non-responders to hormone monotherapy received vigabatrin after 2 weeks and thus were actually switched to the combined therapy.⁴ There are some reports (EL 3) about adverse effects of the combined therapy (e.g., movement disorders, encephalopathy, and dysautonomia),²⁹ especially in children with trisomy 21.¹⁴ It is, therefore, prudent to exercise caution when prescribing combination therapy, especially in children with trisomy 21, until further data are available (► **Table 10**).

Comment on Recommendation 7

TSC is a common cause of ISS. High efficacy of vigabatrin in patients with TSC presenting with ISS has been widely reported.^{30,31}

If hormone treatment is inappropriate, vigabatrin is the preferred alternative first-line treatment for ISS. Its efficacy has been demonstrated in three EL 1+ studies.^{25,32,33} However, two EK 1+ studies have shown that hormone therapy (ACTH or prednisolone) is more effective in stopping spasms than vigabatrin.^{25,33} This is reflected in the U.S. guideline for the treatment of ISS that mentions that ACTH is superior to vigabatrin.⁹

In most studies, vigabatrin is given in doses of 75 to 150 mg/kg, introduced in one to two steps up to 75 to 100 mg/kg and, if not successful, increased after a week to 100 to 150 mg/kg. Because of the potential risk of visual field defects, vigabatrin should be discontinued rapidly if the efficacy is insufficient. For the same reason, vigabatrin should be withdrawn after 6 months if the course is favorable (► **Table 10**).^{34,35}

Table 9 Recommendation of treatment

Evidence consensus (>75%)	Recommendation 6	Recommendation level
High	Children with infantile spasm syndrome should be treated primarily with hormones (ACTH or prednisolone) or with a combination of hormones and vigabatrin.	↑↑

Source: Adapted from Go et al., 2012; Hancock et al., 2013; Lux et al., 2004, 2005; O'Callaghan et al., 2017, 2018^{4,7,9,10,21,25}; and

► **Supplementary Tables S1–S3** and **S7–S10** (available in the online version).

Note: Consensus (>75%).

Table 10 First-line treatment with vigabatrin

Evidence	Recommendation 7	Recommendation level
High	Children with a diagnosis of tuberous sclerosis complex and children with contraindications to hormone treatment should be treated first-line with vigabatrin.	↑↑

Source: Adapted from Chiron et al., 1997; Hancock and Osborne, 1999^{30,31}; and ► **Supplementary Tables 8–11** (available in the online version).

Note: Consensus (>75%).

Table 11 Suggested treatment regimens

Evidence	Recommendation 8	Recommendation level
High	We suggest the following treatment regimens: Oral prednisolone 40–60 mg/d: 2 wk + 2 wk gradual withdrawal or <ul style="list-style-type: none"> ● Depot ACTH (Tetracosactide): 40–60 IU, i.m., for 2 wk, every 2nd day + 2-wk gradual withdrawal via oral prednisolone or/or combined with ● Vigabatrin 100–150 mg/kg/d: 3 mo + 1-mo gradual termination 	↑

Source: Adapted from: Prednisolone and ACTH Depot regimen: (EK 1 +)^{4,7,21,25,34,35}; Vigabatrin-regimen: (EK 1 +)^{4,7,21,25,33,34,35}; and (EL 2, EL 3) in ► **Supplementary Tables S8–S11 (available in the online version)**.

Note: Strong consensus (>95%).

Table 12 Other treatment options

Evidence	Recommendation 9	Recommendation level
Low	If first-line drugs are ineffective, other treatment options such as ketogenic dietary therapies, sulthiame, topiramate, valproate, zonisamide or benzodiazepines should be considered.	↑↑

Source: Adapted from EL 1, EL 2, and EL 3 (► **Supplementary Tables 14–20**, available in the online version).

Note: Consensus (>75%).

Comment on Recommendation 8

Even though there is a high level of evidence to support “Recommendation 8,” we chose to propose it as a “suggestion.” This is due to the fact that other treatment regimens using ACTH, glucocorticoids, and vigabatrin are also effective. The short duration of treatment has the advantage of fewer adverse effects compared with a longer treatment. Before application, it is recommended for physicians to gain detailed knowledge of the regimens (► **Table 11**).

Comment on Recommendation 9

While the evidence to support these alternative treatment regimens is low, we recommend their use in view of the unfavorable prognosis of drug-resistant ISS. All therapies listed showed an effect in some infants with ISS, which is why they represent a further treatment option in patients refractory to ACTH, glucocorticoids, and vigabatrin (► **Table 12**).

Comment on Recommendation 10

Current studies support that epilepsy surgery in children with ISS caused by structural brain lesions may be related to superior developmental outcomes (► **Table 13**).^{36,37} The higher the preoperative cognitive status and the shorter the interval between the epilepsy onset and operation, the

better the developmental outcome of affected children.³⁸ Therefore, in the case of drug resistance, the option of epilepsy surgery should be evaluated at an early stage, especially at the presence of an MRI-detectable focal brain lesion.³⁹ Prerequisites for epilepsy surgery in ISS are:

- Drug-resistant ISS.
- No evidence of a degenerative or metabolic disease.
- No contraindications for surgery and no unacceptable new neurological deficits that would be caused by surgery. The benefits of improved epilepsy control must be weighed against possible neurological deficits that may result from surgery.^{40,41}

Findings that suggest considering a surgical approach:

- Focal seizures before and during ISS.
- Focal structural lesions on MRI.
- Interictal focal hypometabolism or ictal focal hypermetabolism in PET (only in conjunction with MRI or EEG findings).
- Focal EEG findings before ISS, interictal focal EEG findings during ISS: subclinical focal epileptic discharges, predominant focal spike wave focus, focal slowing, and focally reduced β frequencies.
- Focal neurological signs.

Table 13 Epilepsy surgery

Evidence	Recommendation 10	Recommendation level
Low	In children who do not respond to first-line treatment, the option of epilepsy surgery should be evaluated early, especially if focal brain lesions are present.	↑↑

Source: Adapted from several EL 3 studies.

Note: Strong consensus (>95%).

Table 14

Evidence	Recommendation 11	Recommendation level
Expert consensus	Therapeutic approaches which have not been validated through a prospective randomized controlled trial are considered to have been inadequately tested and should not be the primary treatment option. On a larger scale, such therapeutic approaches should only be used within the setting of randomized control trials.	↑

Note: Strong consensus (>95%).

The presurgical assessment should be performed at an epilepsy center with pediatric expertise. If drug resistance is proven, the timing for the operation should be chosen as early as possible (–Table 14).

Comment on Recommendation 11

The evidence for this recommendation relates to the availability of first-line drugs which have been proven rapidly effective in several EL 1 studies. Therefore, the expert consensus is that “trying out” of unproven therapies as first-line treatment is not justified. On a larger scale, new treatment options should be used only in the setting of studies that offer the appropriate controls to ensure patient safety is upheld.

Special Considerations Before, During, and After Treatment

Follow-up Appointments during Treatment

- Weekly contact (i.e., by phone) with the parents in the first week of treatment.
- For the first-line drugs, the treatment success should be evaluated clinically and by EEG (in wakefulness and sleep) after at least 14 days.
- After the 2nd week of treatment, follow-up intervals depend on the course of the epilepsy and the neurological development of the child.

Monitoring and Follow-up When Using ACTH and Glucocorticoids

The threshold for hospital admission should be low whenever complications or side effects are suspected. Hospital admission can be indicated also if caregivers are distressed or overwhelmed.

Before Treatment

- No vaccination with live vaccines (MMR, varicella) from 4 weeks (at least two weeks) prior to 8 weeks after hormone therapy (risk of severe complications due to attenuated vaccination viruses).⁴²
- Inactivated vaccines can be administered up to 1 week before therapy and commence again 1 week post therapy. During hormone therapy vaccination with inactivated vaccines is possible, but immune response may be limited.
- Brain MRI (if not already available), physical examination, blood pressure, blood count, blood sugar, serum electrolytes, liver and kidney function test and echocardiography.

During Treatment

- Consider gastric protection.
- Early and appropriate antibiotics in case of infection.
- Prevention of varicella exposure. Post varicella exposure blood test for varicella IgG titers and passive immunization (within 72 hours post exposure) without waiting for blood results.
- Regular physical examination, echocardiography in case of hypertension and clinical symptoms, blood pressure initially once per week and after 4 weeks twice per week, blood sugar weekly.

Tapering ACTH/glucocorticoid—Endocrine Perspective

- After hormone treatment, cortisol response to physical stress (e.g., fever, trauma, surgery) may be insufficient due to a suppressed hypothalamus-pituitary-adrenal axis. This can be observed up to 1 year after the end of ACTH/glucocorticoid therapy and can lead to severe complications. The longer the duration of the hormone therapy, the higher the risk.
- In infants with ISS, no data is available regarding endocrine disorders after discontinuation of ACTH or glucocorticoids. After a short (< 4-week) treatment duration no complications associated with the discontinuation of ACTH or prednisolone have been described.^{21,25}
- The available data are insufficient for a general recommendation of ACTH/glucocorticoid tapering. Especially after prolonged treatment, endocrinological tapering below the physiological prednisolone dose of 2.5 to 3 mg/m²/d, Synacthen tests, and morning cortisol measurements can be used to provide guidance. Support from a pediatric endocrinologist in this process could be considered.
- Every patient should receive a “steroid treatment card” for 1 year, in which the ACTH/glucocorticoid therapy and a possible insufficient stress response (Addison’s disease) are mentioned.

Monitoring for Vigabatrin Adverse Effects

It remains unclear whether ophthalmological examinations should be recommended after vigabatrin treatment. Visual field examination cannot be reliably performed before a developmental age of 8 years.¹⁸ Electroretinography can provide evidence of retinal damage in infants, but requires sedation. Visual field examinations can be recommended for cooperative children with a cognitive age of at least 8 years. Pathological findings should be always double-checked. Consultation with an ophthalmologist should be considered

in any case, because children with ISS are at risk of developing visual disorders even without vigabatrin.

Monitoring Development

Motor and cognitive development represents an essential quality control of the treatment. Developmental assessment should include a neurological examination and standardized neuropsychological tests (e.g., Bayley scales, Griffith score, etc.). Detailed documentation is required regarding the development status and any deficits should be clearly described. Assessments are recommended at the age of 18 months and before schooling. Additional assessments and therapies may be necessary and should be scheduled depending on the child's development.

Open Questions and Future Developments

The optimal dosage of ACTH and glucocorticoids as well as their termination and the necessary controls afterward are still unclear. It is also still unclear whether children have a better cognitive development after ACTH or glucocorticoid therapy than after vigabatrin. Safety concerns related to vigabatrin remain. The consequences of persistent ISS and the prompt efficacy of vigabatrin may outweigh the risk for potential adverse effects such as visual field defects. It remains unknown whether the combination of hormone therapy and vigabatrin is advantageous. Initial results²¹ indicated an improved response, but in the long term the benefits could not be confirmed.⁴ There are some reports on side effects due to the combined treatment of hormones and vigabatrin.^{14,29,43,44} Whether these findings will lead to a reassessment of the combined treatment remains to be seen.

Looking ahead, we should look into treatments that are tailored to the underlying etiology of IS. This would include treatments that target specific genetic or metabolic abnormalities.

February 2022 Update

Twenty-two relevant articles have been found in Medline (search date February 1, 2022) since the initial search for this updated guideline (search date July 2, 2020): 12 on ACTH/glucocorticoids, four on vigabatrin, and six on other treatment options (► **Supplementary References**, available in the online version). None of these studies required the reassessment of our recommendations. Of interest are the results of the EPISTOP trial in infants with TSC which show that the preventive treatment with vigabatrin significantly delayed the onset of seizures and reduced the occurrence of IS and of drug resistant epilepsy. Developmental outcome, however, did not differ between TSC infants who received preventive treatment and those who received conventional treatment.¹⁵

Authors' Contributions

G.R. contributed toward drafting the initial manuscript, revising the manuscript, analysis and interpretation of

data, and acquisition of data. She approved the final manuscript as submitted. B.K.B., M.A., J.K., R.K., G.K., D. T., and M.W. revised the manuscript, did the analysis or interpretation of data, and acquisition of data. They approved the final manuscript as submitted. B.S. drafted the initial manuscript, revised the manuscript, contributed to the study concept, analysis and interpretation of data, acquisition of data, and study supervision. He approved the final manuscript as submitted.

Conflict of Interest

B.K.B. received speaker's honoraria from Nutricia; J.K. received speaker's honoraria from Nutricia and Vitaflo GmbH; G.K. obtained honoraria for speaking engagements from Desitin Arzneimittel, Eisai, UCB Pharma, Takeda, Zogenix, Neuraxpharm Arzneimittel, Stada Arzneimittel, and GW Pharmaceuticals companies. The following authors do not have any conflict of interest: R.K., B. S., G.R., D.T., and M.W.

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