



Response to second treatment after initial failed treatment in a multicenter prospective infantile spasms cohort

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SUMMARY

Objective: Infantile spasms (IS) represent a severe epileptic encephalopathy presenting in the first 2 years of life. Recommended first-line therapies (hormonal therapy or vigabatrin) often fail. We evaluated response to second treatment for IS in children in whom the initial therapy failed to produce both clinical remission and electrographic resolution of hypsarhythmia and whether time to treatment was related to outcome.

Methods: The National Infantile Spasms Consortium established a multicenter, prospective database enrolling infants with new diagnosis of IS. Children were considered nonresponders to first treatment if there was no clinical remission or persistence of hypsarhythmia. Treatment was evaluated as hormonal therapy (adrenocorticotropic hormone [ACTH] or oral corticosteroids), vigabatrin, or “other.” Standard treatments (hormonal and vigabatrin) were compared to all other nonstandard treatments. We compared response rates using chi-square tests and multivariable logistic regression models.

Results: One hundred eighteen infants were included from 19 centers. Overall response rate to a second treatment was 37% (n = 44). Children who received standard medications with differing mechanisms for first and second treatment had higher response rates than other sequences (27/49 [55%] vs. 17/69 [25%], $p < 0.001$). Children receiving first treatment within 4 weeks of IS onset had a higher response rate to second treatment than those initially treated later (36/82 [44%] vs. 8/34 [24%], $p = 0.040$).

Significance: Greater than one third of children with IS will respond to a second medication. Choosing a standard medication (ACTH, oral corticosteroids, or vigabatrin) that has a different mechanism of action appears to be more effective. Rapid initial treatment increases the likelihood of response to the second treatment.



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KEY WORDS: Infantile spasms, Adrenocorticotrophic hormone, Vigabatrin, Second-line treatment.

KEY POINTS

- More than one third of children with IS will respond to a second medication
- Rapid initiation of first treatment for IS increases the likelihood of response to a second treatment
- Standard medications are more effective than nonstandard medications for IS

Infantile spasms (IS) are an age-specific seizure type that occurs in the first 2 years of life. IS are associated with severe epileptic encephalopathy with an incidence of 2–5 per 10,000 live births.^{1–4} Treatment is recommended urgently; delays in diagnosis and treatment are associated with subsequent intellectual impairment.⁵ Sixty percent of children with IS will develop other seizure types,⁶ and 75–87% will develop intellectual impairment.^{6,7} There has been little improvement in outcome of these children over the past 30 years.⁸ Despite this, there is continued debate regarding initial treatment and there are limited data addressing treatment following failure of initial treatment.

Steroid treatment with adrenocorticotrophic hormone (ACTH) and oral corticosteroids (OCS) have demonstrated efficacy since 1958,^{9,10} with more recent studies showing a response rate between 55%¹¹ and 73%.¹² The United Kingdom Infantile Spasms study observed similar response rates between OCS and tetracosactide, the synthetic form of ACTH, and these were considered superior to vigabatrin.¹² Vigabatrin is effective in 38–48% of children without tuberous sclerosis complex.^{13,14} Evidence-based guidelines developed in 2004 state that “ACTH is probably effective for the short-term management of IS,” and an update in 2012 adds that vigabatrin “*may* be useful for short term treatment of IS with ACTH considered preferentially over vigabatrin.”^{15,16} Despite guidelines, there is little uniformity among providers’ practices.^{17,18} This could be due in part to variation in outcome measures among the studies, with clinical cessation of IS as the most oft-used primary outcome measure, but relapse rates and electroencephalography (EEG) improvement must also be considered in assessing efficacy. Nonetheless, relapse rates and failure rates remain high, with all standard treatments leaving a large percentage of children without successful treatment.

Many studies report the use of nonstandard therapies for IS in infants for whom traditional medications have been ineffective. In a single study comparing topiramate and

levetiracetam as second therapy after failure of oral steroids, there was a poor response to either medication given sequentially.¹⁹ Long-term use of high-dose topiramate has been reported, but again after there had been failure of several medications.²⁰ Felbamate,²¹ lamotrigine,^{22,23} and zonisamide²⁴ responses have been reported in similar small studies as well as the use of the ketogenic diet.²⁵ Recent guidelines suggest several alternative treatments based on expert opinion.²⁶

This study evaluates treatment response after failure of initial medication in a large national prospective database. We hypothesized that children prescribed standard second treatments would have higher response rates than children prescribed nonstandard second treatments, given the superiority of standard treatments (ACTH, OCS, and vigabatrin) as first-line therapy and the poor response rate of IS to anything else. We also hypothesized that a second standard treatment with a mechanism of action different from that of the failed first treatment would result in higher cumulative response rates due to evidence that medications with different mechanisms of action are often effective for epilepsy.^{27,28}

METHODS

Standard protocol approvals, registrations, and patient consents

The study was approved by all participating site institutional review boards (IRBs). The parents or guardians provided written informed consent for participation via center-specific IRB requirements.

In 2012, The Pediatric Epilepsy Research Consortium (PERC) developed the National Infantile Spasms Consortium (NISC) database. NISC is a multicenter database enrolling children in a prospective manner. Children with new-onset infantile spasms between 2 months and 2 years of age were eligible for the study. Clinical information was collected at time of diagnosis and 3 months after diagnosis. Medication dosing was standardized based on published experience and guidelines for ACTH, OCS, and vigabatrin, as reported previously,¹¹ although compliance with these recommendations was not necessary for inclusion. Treatment decisions for individual children were deferred to the treating clinicians.

Data collected from June 2012 to July 2014 were used for this study. These children’s demographic profile and initial treatment responses have been reported elsewhere.^{11,29} Children with an early infantile epileptic encephalopathy

(Ohtahara syndrome/early myoclonic encephalopathy) were excluded from the analysis, as this represents a different disease process. Records with missing treatment or response data due to loss to follow-up or incomplete data entry were also excluded, as outcome could not be determined.

Data collected for each child included age at onset of IS, gestational age at birth, sex, presence of seizures prior to spasms, etiology, height, weight, magnetic resonance imaging (MRI), genetic and metabolic testing, developmental assessment, presence of hypsarhythmia at onset, IS medication, and dosage. Hypsarhythmia was assessed at individual institutions and defined as multifocal spikes, disorganization, and >200 μV (trough-to-peak) in any epoch on a bipolar longitudinal montage, and included modified hypsarhythmia variants.³⁰ At 3 months after study enrollment, we collected new MRI findings, new genetic and metabolic testing, developmental assessment, response to medication(s), EEG findings and assessment of etiology. Clinical response was assessed at 2 weeks and at 3 months following treatment initiation using both electrical and clinical data.

Standard therapy was defined as ACTH, OCS, or vigabatrin. All other treatments were considered nonstandard therapy for the purposes of this study. Children initiated on simultaneous standard and nonstandard therapy (e.g., ACTH and levetiracetam) had response attributed to the standard medication. For primary statistical analyses, a treatment sequence variable was constructed looking at first and second treatments simultaneously. We grouped children into two categories: (1) those prescribed two standard treatments as first and second therapy, but with different mechanisms of action (e.g., first treatment ACTH, second treatment vigabatrin); and (2) all other treatment sequences (e.g., combination of standard and nonstandard therapies or OCS with ACTH).

Response to first spasms treatment (FST) was initially classified into one of two response categories: responders and nonresponders. Responders were defined as those who had resolution of both clinical spasms and hypsarhythmia/modified hypsarhythmia (if present at onset) within 2 weeks of IS treatment, which was sustained at the 3-month follow-up, and no second treatment for IS was introduced during this interval. Nonresponders included children who did not have resolution of clinical IS and/or hypsarhythmia, or who initially met response criteria and then had return of either clinical spasms or hypsarhythmia within the 3-month study period. Nonresponders to FST were the subjects of this analysis.

Response to second spasm treatment (SST) was classified into responders and nonresponders. Responders included those who had resolution of clinical spasms and hypsarhythmia (if present at diagnosis) within 2 weeks of initiation of the second medication without subsequent relapse of clinical IS or hypsarhythmia at the time of the 3-month data collection point; however, the true interval of follow-up after SST was variable. Nonresponders were all others.

Development was recorded as the clinician's perception of overall development, motor, and cognitive status, with each defined as normal, mild or equivocal delay, or definite abnormality. These three domains were then used to create an overall assessment of development categorized as normal, mild, moderate, and severe delay. Children with no domain marked as abnormal were classified as having normal development. If one domain was marked as mild, the child was included in the mild developmental delay group. The moderate developmental delay group consisted of children with two or more domains marked as mild or one domain marked as a definite abnormality. Severe developmental delay included children with two or more domains marked as definite abnormality.

Etiology was classified into five primary etiologic classifications: genetic/metabolic, malformation of cortical development, prior acquired injury, other structural, and unknown. Tuberous sclerosis was classified as other structural according to International League Against Epilepsy (ILAE) guidelines.³¹ For data analysis, those with unknown etiology were further categorized into normal and abnormal development. Unknown etiology with normal development was analyzed as a separate category, whereas genetic/metabolic was combined with unknown etiology and abnormal development. The latter group likely represents presumed genetic causes, but without an identified etiology in the 3-month follow-up period (either due to late diagnosis, decreased utilization of testing, or genetic influences that are non-Mendelian). In addition, malformations of cortical development, prior injury, and other structural were categorized together as a structural cause of epilepsy.

Statistical analysis

We compared demographic and clinical characteristics by treatment group (ACTH, oral steroid, vigabatrin, or other) using chi-square tests for categorical covariates and Kruskal-Wallis tests for continuous covariates. To understand the association of demographic and clinical covariates with treatment response, we used chi-square tests to compare the proportions of responders in each group. Next, we fit multivariable logistic regression models to estimate crude and adjusted relative risk of responding to a specified treatment sequence using the method of Kleinman and Norton.³² All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, U.S.A.).

RESULTS

Figure 1 shows the flow diagram of participants included in our analyses. First spasms treatment failed in 136 (59%) of 230 children with infantile spasms. Of these, 18 were excluded, leaving 118 children in the cohort for our current analysis (see Table 1 for baseline demographics). We did not observe any significant differences in demographics, etiology, development, or treatment delay between children

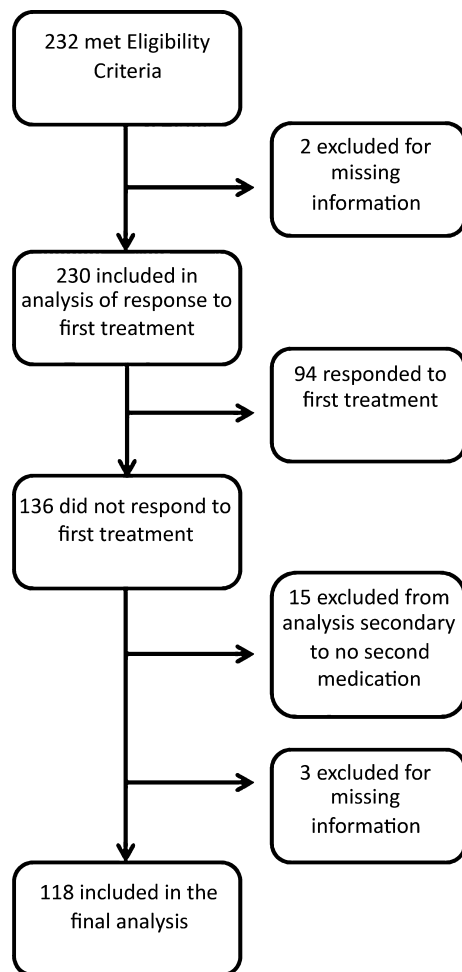


Figure 1.
Flow chart of participant eligibility and inclusion.
Epilepsia © ILAE

included in our analysis versus those excluded. Hypsarhythmia was present in 47% (48/103), modified hypsarhythmia in 28% (29/103), and 25% (26/103) had EEG findings that were abnormal but not considered hypsarhythmia. Hormonal therapy (ACTH and OCS) was used as a second medication in 41 children, vigabatrin in 38, and other treatments (topiramate, rufinamide, clonazepam, valproic acid, gabapentin, clobazam, oxcarbazepine, levetiracetam, zonisamide, pyridoxine, ketogenic diet, and phenobarbital) in 39 children. We did not observe differences in demographics based on second treatment choices, with the exception of development at onset of IS, with a higher percentage of infants exhibiting severe delay being more likely to be on a hormonal therapy or nonstandard therapy as their second treatment than vigabatrin, which may reflect bias of choice of FST. Clinicians followed NISC dosing recommendations in 23 (79%) of 29 ACTH-treated children, 11 (92%) of 12 OCS-treated children, and 24 (63%) of 38 of those treated with vigabatrin. Time to initiation of FST and time to

initiation of SST were similar between the treatment groups (Table 1).

Forty-four (37%; 95% confidence interval [CI] 29–46%) of the 118 children responded to their second treatment, 36 of 79 (46%; CI 35–57%) to a standard treatment, and 8 of 39 (21%; CI 8–33%) to a nonstandard treatment ($p = 0.008$, chi-square test). Table 2 shows the response rates to all observed treatment sequences. Three (21%) of 14 children who received repeated hormonal therapy responded. Children who were treated initially with a nonstandard treatment and were subsequently treated with a standard therapy had an overall response rate of 37% (6/16), whereas all of those treated with nonstandard treatments for both first and second therapy failed to respond to either treatment (0/7, Table 2).

When first and second spasms treatments were standard medications but with different mechanisms of action (e.g., hormonal therapy followed by vigabatrin, or vigabatrin followed by hormonal therapy), there was a response rate of 55% (27/49 CI 41–69%), which was superior to the 25% (17/69 CI 14–35%) overall response rate to all other treatment sequences ($p < 0.001$, chi-square test, Table 3). This result corresponds to an absolute risk reduction of 30% (95% CI 13–48%), and number needed to treat of 3.28 (95% CI 2.10–7.56). We observed a significantly higher response rate to SST in children who had initially been treated more rapidly, even though FST failed. Specifically, children who received FST within 4 weeks of their first clinical spasm had a 44% (36/82 CI 33–55%) response rate to SST, whereas children who were not initiated on FST until after 4 weeks had only a 24% (8/34 CI 9–38%) response rate to SST ($p = 0.040$, chi-square test, Table 3). The interval between IS onset and initiation of SST was not a significant predictor of response. We observed a lower response rate in children with severe developmental issues than in children with less severe developmental issues (30% [20/67 CI 19–41%] vs. 47% [23/49 CI 33–61%] $p = 0.06$, chi-square test) (Table 3), but this result was not statistically significant. The relative probability of response between groups, estimated via logistic regression modeling, is shown in Table 3. Even after adjustment for developmental category and time to treatment initiation, the treatment sequence remained a significant predictor of response. Children prescribed two standard treatments—the second with a different mechanism of action—had approximately twice the probability of responding as children prescribed other treatment sequences (Table 3).

We did not observe significant differences in response to second treatment based on the child's sex, race, ethnicity, gestational age, age at spasm onset, etiology, or prior seizures (Table 4). Of five children with tuberous sclerosis who failed first treatment, two responded to a second therapy (vigabatrin and topiramate).

Table 1. Baseline characteristics by type of second treatment for spasms

Characteristic	Second treatment for spasms			Total N = 118	p-Value ^a
	ACTH or oral steroid N = 41	Vigabatrin N = 38	Other N = 39		
Sex					
Male	24 (59)	22 (58)	18 (46)	64 (54)	0.46
Race					0.13
Black	5 (13)	4 (11)	8 (22)	17 (16)	
White	30 (79)	28 (80)	20 (56)	78 (72)	
Other	3 (8)	3 (9)	8 (22)	14 (13)	
Ethnicity					0.54
Hispanic	4 (12)	3 (9)	6 (18)	13 (13)	
Gestational age					0.31
Weeks	38 (34, 40)	40 (38, 40)	39 (37, 40)	39 (37, 40)	
At least 37 weeks	28 (70)	32 (84)	31 (80)	91 (78)	
Age at spasm onset					0.93
Months	6.5 (3.9, 8.2)	5.0 (4.2, 7.0)	5.7 (4.0, 9.0)	5.6 (4.0, 7.8)	
<12 months	35 (88)	34 (90)	34 (87)	103 (90)	
First spasm to treatment start					0.28
Days	12 (6, 25)	9 (4, 29)	18 (6, 61)	14 (5, 36)	
Within 4 weeks	31 (78)	27 (73)	24 (62)	82 (71)	
First treatment to second treatment					0.50
Days	28 (18, 41)	25 (16, 35)	24 (17, 34)	25 (17, 36)	
Within 4 weeks	21 (51)	24 (63)	24 (62)	69 (59)	
First spasm to second treatment					
Days	49 (31, 68)	43 (24, 70)	48 (28, 104)	44 (27, 79)	
Prior seizures	19 (46)	11 (29)	16 (41)	46 (39)	0.27
History of AED use	21 (51)	11 (29)	17 (44)	49 (42)	0.13
Etiology ^b					0.76
Genetic/metabolic	10 (24)	6 (16)	10 (26)	26 (22)	
Prior brain injury	11 (27)	9 (24)	7 (18)	27 (23)	
MCD/other structural	9 (22)	5 (13)	7 (18)	21 (18)	
Unknown abnormal	8 (20)	12 (32)	10 (26)	30 (25)	
Unknown normal	3 (7)	6 (16)	5 (13)	14 (12)	
Developmental issues					<0.001
None/mild/moderate	12 (30)	25 (68)	12 (31)	49 (42)	
Severe	28 (70)	12 (32)	27 (69)	67 (58)	

Values are N (column %) or median (Q1, Q3).
^aChi-square test.
^bMCD, malformations of cortical development. There were five participants with tuberous sclerosis complex (TSC) (included in the MCD/other structural etiology group).
The following variables had missing values: race (9), ethnicity (16), gestational age (1), age at spasm onset (4), time between first spasm and treatment start (2), time between first spasm and second treatment (2), and development (2).

DISCUSSION

This is the largest prospective study that evaluates response to second treatment for IS. Our data demonstrate that 37% of children for whom a first IS treatment fails will subsequently respond to a second medication. Response rates to standard medications (ACTH, oral steroids, and vigabatrin) were greater than that to nonstandard medications. Timing of SST did not significantly affect outcome, whereas initiation of FST within 4 weeks of IS onset did. Characteristics of the child such as development, etiology, and prior seizures did not have an impact on response to SST, and therefore perhaps should not be considered in making treatment choices. Etiology has been associated with long-term cognitive outcomes,⁷ which were not measured in this study.

Similar to prior studies, the use of standard medications demonstrated a greater response rate. ACTH, vigabatrin, and OCS have been well studied in the treatment of IS as initial treatment, but have not been studied in children for whom initial medication is ineffective. This study supports the view that standard therapies are also more successful for second-line treatment, regardless of whether the initial therapy was standard or nonstandard. A prior smaller study similarly demonstrated a low response to nonstandard medication after failure of initial treatment with oral steroids, with only 2 of 18 children responding.¹⁹ An additional study demonstrated that a protocol with sequential standard medications led to improved outcomes compared to patients who were treated with a nonstandard medication (52% vs. 25%), although all subjects were initially treated with vigabatrin.³³ Fedak et al.

Table 2. Treatment sequence effect on response

First treatment	Second treatment	Response to second treatment	
		Response N = 44	Nonresponse N = 74
ACTH/oral steroid	ACTH/Oral steroid	3 (21)	11 (79)
	Vigabatrin	17 (55)	14 (45)
	Other	6 (23)	20 (77)
Vigabatrin	ACTH/Oral steroid	10 (56)	8 (44)
	Other	2 (33)	4 (67)
Other	ACTH/Oral steroid	5 (56)	4 (44)
	Vigabatrin	1 (14)	6 (86)
	Other	0 (0)	7 (100)

Values are N (row %).

demonstrated an overall improvement in response rates to initial medications when a protocol was instituted using standard therapies for IS. These data further support the ongoing use of clinical care guidelines encouraging the use of standard therapies, although the response rates in our standardized treatment group are not as high as the 78% reported by that group.³⁴ Other factors may have played a role in the higher response rate in the Fedak study, such as all patients received standardized care and early changes in ineffective treatment.

Timing of initiation of first spasms treatment did not significantly predict outcome after FST,¹¹ but was related to response to SST. Of interest, timing of second medication (either related to spasm onset or duration between first and second medication) was not associated with a change in 3-month outcome. Other studies have demonstrated improved outcomes with initiation of treatment within 4 weeks of spasms present as well as early response to treatment.^{6,35–39} Cohen et al.³⁷ have reported improved seizure and cognitive outcome with early initiation of ACTH. The majority of

these studies have cohorts that are exclusively “cryptogenic children,” who have no prior developmental delay and no identifiable etiology. Koo et al.⁴⁰ demonstrated that lag in treatment was related to a poor cognitive outcome, but not seizure outcome. Our study design did not allow for assessment of developmental outcome.

The highest response rate was achieved when the SST was switched from a steroid therapy to vigabatrin or vice versa. This may be attributable to presenting a treatment with a different mechanism of action. Further investigation is required to determine if different responses are attributable to complementary or even additive mechanisms of action, or alternatively, this may reflect individualized responses to single treatments due to a myriad of pharmacogenomic and epigenetic factors. If the former is true, this would suggest that combination therapy at initiation may lead to overall improved response rates. A better understanding of these factors may help to further new drug development (novel mechanisms are sought for those have not responded to currently available seizure medications) as well as rational polypharmacy.

Previous studies have evaluated the importance of early spasm resolution to improved neurodevelopmental outcome. While recognizing that prognosis, in part, is heavily linked to the underlying etiology, resolution of an epileptic encephalopathy likely plays a role. This study was not designed to evaluate longitudinal development; however, the results indicate that there is a high percentage of infants with spasms who will respond to a second treatment, and it is important to identify if this subgroup similarly shows improved development relative to the refractory population and if this benefit is seen independent of etiology.

One limitation of this project is a nonrandomized study design. As such, bias in the initial medication choice based on baseline developmental status as well as etiology at the

Table 3. Relative probability (relative risk) of response to treatment

Characteristic	Total N	Responders N (%)	p-Value ^a	Crude risk ratio (95% CI)	Adjusted ^b risk ratio (95% CI)	Adjusted ^c risk ratio (95% CI)
Treatment sequence						
Standard–standard, mechanism change	49	27 (55)	<0.001	2.26 (1.60, 3.22)	2.01 (1.46, 3.08)	2.25 (1.64, 3.35)
All other sequences	69	17 (25)		REF	REF	REF
Development						
None/mild/moderate	49	23 (47)	0.06	1.59 (0.97, 2.78)	1.31 (0.79, 2.10)	–
Severe	67	20 (30)		REF	REF	–
Time to first treatment						
Within 4 weeks	82	36 (44)	0.040	1.90 (1.05, 4.62)	–	1.82 (1.08, 4.10)
>4 weeks	34	8 (24)		REF	–	REF

REF, reference group.

Relative risks estimated via logistic regression models using the method of Kleinman and Norton.³²

^aChi-square test.

^bModel including treatment sequence and development as covariates.

^cModel including treatment sequence and time to first treatment as covariates.

Table 4. Characteristics by response to second spasm treatment

Characteristic	Response to second treatment		p-Value ^a
	Response N = 44	Non-response N = 74	
Sex			
Female	18 (33)	36 (67)	0.42
Male	26 (41)	38 (59)	
Race			
Black	5 (29)	12 (71)	0.58
White	31 (40)	47 (60)	
Other	4 (29)	10 (71)	
Ethnicity			
Hispanic	3 (23)	10 (77)	0.20
Non-Hispanic	37 (42)	52 (58)	
Gestational age			
<37 weeks	9 (35)	17 (65)	0.80
At least 37 weeks	34 (37)	57 (63)	
Age at spasm onset			
<12 months	40 (39)	63 (61)	0.87
At least 12 months	4 (36)	7 (64)	
First treatment to second treatment			
Within 4 weeks	21 (30)	48 (70)	0.12
4–8 weeks	17 (52)	16 (49)	
>8 weeks	6 (38)	10 (63)	
First spasm to second treatment			
Within 3 weeks	5 (29)	12 (71)	0.17
3–6 weeks	19 (50)	19 (50)	
>6 weeks	20 (33)	41 (67)	
Prior seizures			
Yes	18 (39)	28 (61)	0.74
No	26 (36)	46 (64)	
History of AED use			
Yes	18 (37)	31 (63)	0.92
No	26 (38)	43 (62)	
Etiology			
Genetic/metabolic/unknown abnormal	17 (30)	39 (70)	0.16
Prior brain injury/MCD/other structural	19 (40)	29 (60)	
Unknown normal	8 (57)	6 (43)	

MCD, malformation of cortical development.
 Values are N (row %).
^aChi-square test.
 The following variables had missing values: race (9), ethnicity (16), gestational age (1), age at spasm onset (4), time between first spasm and treatment start (2), time between first spasm and second treatment start (2), and development (2).

time of medication initiation is present. We attempted to minimize the impact of prescribing bias by fitting multivariable logistic regression models. However, we were limited by our sample size in the number of variables for which we were able to adjust in a single model, and our study is likely underpowered to detect differences in response by certain clinical characteristics. In addition, the developmental measure used in this study is a subjective measure. Given that this was not a randomized trial, the dosing regimens and

intervals between medication changes were not uniform. A high utilization of NISC dosing guidelines among subjects helped to minimize this variability. Furthermore, for the purposes of this study, nonstandard treatments were grouped together, as there were insufficient numbers to analyze each individually. Treatments with more published evidence such as ketogenic diet, valproate, and topiramate may have had superior benefit as second therapies theoretically than others (e.g., oxcarbazepine, pyridoxine, and phenobarbital). Larger cohorts are needed to evaluate efficacy of these specific nonstandard treatment options.

More than one third of children who require a second medication for treatment of IS will achieve resolution of clinical spasms and hypsarhythmia. Use of a standard medication improves outcome, and the evidence of benefit for nonstandard treatments, as a group, is relatively weak. Although rapid initiation of medications did not affect response to first medication, response to second therapy is improved in those who were treated early. Other factors such as development and etiology did not appear to influence overall resolution of IS.

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DISCLOSURE OF CONFLICT OF INTEREST

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APPENDIX: ADDITIONAL CONTRIBUTORS

The named authors participated in the conception and design of the study, and in the data analysis and editing. The members of the Pediatric Epilepsy Research Consortium contributed data and participated in editing of the manuscript. They and their academic affiliations are included in the table.

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