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RESEARCH ARTICLE

Association of Time to Clinical Remission With Sustained Resolution in Children With New-Onset Infantile Spasms

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Abstract

Background and Objectives

Standard therapies (adrenocorticotropic hormone [ACTH], oral steroids, or vigabatrin) fail to control infantile spasms in almost half of children. Early identification of nonresponders could enable rapid initiation of sequential therapy. We aimed to determine the time to clinical remission after appropriate infantile spasms treatment initiation and identify predictors of the time to infantile spasms treatment response.

Methods

The National Infantile Spasms Consortium prospectively followed children aged 2–24 months with new-onset infantile spasms at 23 US centers (2012–2018). We included children treated with standard therapy (ACTH, oral steroids, or vigabatrin). Sustained treatment response was defined as having the last clinically recognized infantile spasms on or before treatment day 14, absence of hypsarrhythmia on EEG 2–4 weeks after treatment, and persistence of remission to day 30. We analyzed the time to treatment response and assessed clinical characteristics to predict sustained treatment response.

Results

Among 395 infants, clinical infantile spasms remission occurred in 43% (n = 171) within the first 2 weeks of treatment, of which 81% (138/171) responded within the first week of treatment. There was no difference in the median time to response across standard therapies (ACTH: median 4 days, interquartile range [IQR] 3–7; oral steroids: median 3 days, IQR 2–5; vigabatrin: median 3 days, IQR 1–6). Individuals without hypsarrhythmia on the pretreatment EEG (i.e., abnormal but not hypsarrhythmia) were more likely to have early treatment response than infants with hypsarrhythmia at infantile spasms onset (hazard ratio 2.23, 95% CI 1.39–3.57). No other clinical factors predicted early responders to therapy.

Discussion

Remission after first infantile spasms treatment can be identified by treatment day 7 in most children. Given the importance of early and effective treatment, these data suggest that children who do not respond to standard infantile spasms therapy within 1 week should be reassessed immediately for additional standard treatment. This approach could optimize outcomes by facilitating early sequential therapy for children with infantile spasms.

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Pediatric Epilepsy Research Consortium coinvestigators are listed in the appendix at the end of the article.

Glossary

ACTH = adrenocorticotropic hormone; **AUC** = area under the curve; **FDR** = false discovery rate; **IQR** = interquartile range; **NISC** = National Infantile Spasms Consortium; **ROC** = receiver operating characteristic; **TSC** = tuberous sclerosis complex.

Children with infantile spasms are at high risk of persistent epilepsy and neurodevelopmental disorders.[1,2] Adrenocorticotropic hormone (ACTH), oral steroids, and vigabatrin are standard therapies for the treatment of infantile spasms.[3-6] Although etiology plays an important role in prognosis, early and effective infantile spasms treatment is independently associated with both earlier clinical remission and improved long-term developmental outcomes.[7]

Recently, the combination of vigabatrin and hormonal therapy (ACTH or prednisolone) demonstrated superior early remission rates compared with hormonal therapy alone.[8] However, there are concerns regarding the possible side effects and the costs of dual therapy.[9] Moreover, dual therapy was not associated with improved developmental or epilepsy outcomes at 18 months.[10]

Sequential treatment with standard treatments has shown efficacy,[11] with assessment for treatment response at 2 weeks, as per expert opinion and retrospective studies.[12,13] Sequential treatment with vigabatrin followed by combination therapy (vigabatrin with high-dose oral steroids) after failure of monotherapy at 14 days resulted in a rate of clinical infantile spasms remission of 72.7%.[14] Traditional dosing regimens call for reassessment of an infant on day 14 of infantile spasms treatment.[12,15] Yet, studies have demonstrated a mean time to clinical remission of less than 6 days with high-dose natural ACTH,[13] oral steroids,[16,17] and vigabatrin.[18] However, no large-scale prospective study has directly compared the time to response across all 3 standard therapies for infantile spasms.

The goal of this study was to identify the time to response for standard medications to inform and facilitate treatment modifications (addition of a second medication or switch to a different medication) as efficiently as possible. To address our hypothesis that infantile spasms remission can be accurately predicted earlier in the treatment course, we analyzed the time to last clinically apparent infantile spasms and evaluated the influence of clinical variables on the time to response after initial standard monotherapy among children enrolled in the prospective multicenter National Infantile Spasms Consortium (NISC) established by the Pediatric Epilepsy Research Consortium.

Methods

Study Design and Inclusion and Exclusion Criteria

The NISC prospective multicenter observational cohort study of children with infantile spasms was conducted primarily through chart review. The details of investigations and treatment response to medication for children with infantile spasms in the NISC cohort were previously published.[5,6,11,19,20] In brief, infants aged 2–24 months with new-onset infantile spasms (defined by the occurrence of epileptic spasms) with and without hypsarrhythmia on EEG were enrolled from 2012 to 2018 across 23 US pediatric epilepsy centers. Data were collected at diagnosis and at 1 follow-up (typically at 3 months). Infants with missing or incongruent data (e.g., date of the last infantile spasm before the day of initial treatment or date of last spasms after 2 weeks but coded as 2-week responder), those with less than 30 days of follow-up, and those who never received standard therapy for infantile spasms were excluded from this analysis.

Standardized dosing regimens were suggested by the NISC investigators for natural ACTH, oral steroids, and vigabatrin,[6] but the final treatment decisions were made by the treating clinicians. Data collected included demographics, clinician assessment of developmental delay at infantile spasms onset (defined as no delay, probable delay, or definite delay), antiseizure medications prescribed for infantile spasms and for other seizure types (if the child had preexisting epilepsy before the infantile spasms diagnosis), lead time (time from infantile spasms onset to first treatment), treatment response, date of last infantile spasms, and etiology. For this study, we grouped etiology into 6 categories: genetic/metabolic, tuberous sclerosis complex (TSC), structural acquired, structural congenital, infectious, and unknown cause, similar to a recent study.[5]

The NISC dataset did not include central review of EEGs. As with all the NISC studies,[5,6,11,20] hypsarrhythmia was defined as random or chaotic high-voltage (>200 μV) slow waves with intermixed multifocal spikes. Hypsarrhythmia variants and resolution were determined by the referring epileptologist at each site. Modified hypsarrhythmia and hypsarrhythmia were grouped, given the poor interrater reliability in determining hypsarrhythmia and modified hypsarrhythmia.[21] Children enrolled in the NISC were assessed at day 14 and 30 after treatment initiation along with posttreatment follow-up EEGs that were interpreted by the clinical team. If the child had responded, the day of last clinically recognized infantile spasms was documented. For this analysis, infants who met all the following 3 criteria were considered "treatment responders": (1) resolution of clinical infantile spasms by day 14 of treatment, (2) sustained infantile spasms freedom at day 30 without introduction of new medication, and (3) resolution or continued absence of hypsarrhythmia on posttreatment EEG 2–4 weeks after medication initiation. For all treatment responders, the time to clinical response was calculated as the number of days between the initiation date of first therapy and

the date of last observed clinical infantile spasms. Infants who met any of the following criteria were categorized as "nonresponders": (1) late resolution of infantile spasms with initial therapy (response noted only after day 14 of treatment), (2) resolution of infantile spasms within 14 days of initial therapy but relapse between days 14–30, or (3) no infantile spasms resolution with initial therapy.

Standard Protocol Approvals, Registrations, and Patient Consents

The institutional review board at each institution approved the study. Written informed consent was obtained from a parent or guardian for each enrolled child. The IRB at Boston Children's Hospital waived the need for additional approval for this secondary analysis of the NISC dataset. The study was only observational and not entered into the public trials registry. There are no recognizable persons in this publication.

Statistical Methods

The primary analysis of the time to response among the 3 standard monotherapy treatment groups was performed using Kaplan-Meier estimates, the log-rank test, and univariate Cox proportional hazard analysis. The multivariate Cox proportional hazard model with stepwise selection was performed for the time to treatment response to adjust for covariates. We evaluated whether the treatment response before day 14 resulted in persistent resolution of infantile spasms at the 30-day endpoint. The predictive values (sensitivity, specificity, positive predictive value, and negative predictive value) and receiver operating characteristic (ROC) curve and its area under the curve (AUC) were calculated for clinical remission at each day before day 14 as a predictor of sustained infantile spasms remission. For each day after treatment, true positives were "treatment responders" as defined above with sustained clinical infantile spasms resolution. Late responders (i.e., false negatives) were defined as children who did not respond by the day evaluated but responded later, were not treated with additional medication, and had sustained electroclinical response for at least 30 days. False positives were children with clinical infantile spasms resolution by the day evaluated who had infantile spasms relapse within the first month after treatment. True negatives were the nonresponders, that is, the children who continued to have infantile spasms on day 14 or relapsed clinically or on EEG before 1-month follow-up. Summary statistics were performed with counts and percentages for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. Multiple-group comparison was conducted with the Pearson χ^2 test or Fisher exact test for categorical variables and the Mann-Whitney U test or Kruskal-Wallis test for continues variables. To adjust for multiplicity and control the false discovery rate (FDR) in pairwise log-rank tests, we applied the Benjamini-Hochberg procedure with an FDR of 0.1. All statistical analyses were conducted using SAS software, version 9.4.

Data Availability

Anonymized data will be shared by request from any qualified investigator.

Results

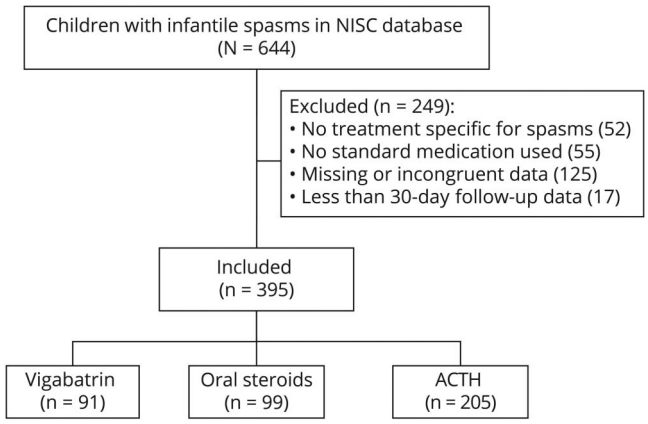
Sample Size and Baseline Demographics

Among the 644 children enrolled in the NISC from 2012 to 2018, 395 were included in the present analysis (Figure 1). The other 249 were excluded because there was no identified treatment for infantile spasms (n = 67), nonstandard therapies prescribed as first infantile spasms treatment (i.e., any treatment other than ACTH, oral steroids, or vigabatrin) (n = 55), incongruent or missing data (n = 125), and lack of at least 30 days of follow-up data (n = 17).

Among the included 395 children, 205 received ACTH, 99 received oral steroids, and 91 received vigabatrin as their first infantile spasms treatment (Table 1). There were no differences across treatments with respect to sex, lead time (days from first infantile spasms to first treatment), age at infantile spasms onset, or days to last follow-up (Table 1). Vigabatrin was less likely than ACTH or oral steroids to be prescribed for infants with hypsarrhythmia on initial EEG and more likely to be prescribed for infants with structural etiology, prior seizures, and developmental delays before infantile spasms onset (this pattern was previously reported).[20]

Sustained resolution of infantile spasms to standard treatment by day 14 was observed in 48% (99/205) on ACTH, 41% (41/99) on oral steroids, and 34% (31/91) on vigabatrin (Fisher exact test across treatments, $p = 0.068$), with a cumulative response rate of 57% (171/395) (Table 1). The day 14 response in the ACTH group was significantly higher than that in the vigabatrin group (Fisher exact test, $p = 0.03$), but not different from the oral steroids group (Fisher exact test, $p = 0.27$). There was no significant difference in the day 14 response between oral steroids and vigabatrin (Fisher exact test, $p = 0.37$).

Figure 1 Flow Diagram of the Participants



ACTH = adrenocorticotropic hormone; NISC = National Infantile Spasms Consortium.

Table 1 Baseline Characteristics of 395 Children With New-Onset Infantile Spasms, Categorized by the First Prescribed Treatment

Characteristic	ACTH, n (%) (N = 205)	Oral steroids, n (%) (N = 99)	Vigabatrin, n (%) (N = 91)	Total, n (%) (N = 395)	*p* Value
Sex (male)	111 (54%)	55 (56%)	53 (58%)	219 (55%)	0.81
Prematurity (<37 wk of gestation)	33 (16%)	25 (25%)	19 (21%)	77 (19%)	0.16
Previous ASM	29 (14%)	32 (32%)	30 (33%)	91 (23%)	**<0.0001**
Age at infantile spasms onset (mo, IQR)	6 (4.7, 8.0)	7 (5.5, 8.7)	6 (4.5, 8.2)	6.2 (4.7, 8.0)	0.16
EEG at infantile spasms onset					
Hyps/modified hyps	173 (84%)	74 (75%)	56 (62%)	303 (77%)	**0.0007**
Abnormal (not hyps)	22 (11%)	16 (16%)	25 (27%)	63 (16%)	
Unknown	10 (5%)	9 (9%)	10 (11%)	29 (7%)	
Development at infantile spasms onset					
Normal	74 (36%)	18 (18%)	15 (16%)	107 (27%)	**0.001**
Minor abnormalities	35 (17%)	18 (18%)	23 (25%)	76 (19%)	
Definite delays	92 (45%)	59 (60%)	48 (53%)	199 (50%)	
Unknown	4 (2%)	4 (4%)	5 (5%)	13 (3%)	
Infantile spasms etiology					
Unknown	106 (52%)	47 (47%)	16 (18%)	169 (43%)	**<0.0001**
Acquired	43 (21%)	27 (27%)	20 (22%)	90 (23%)	
TSC	4 (2%)	1 (1%)	22 (24%)	27 (7%)	
Genetic	30 (15%)	12 (12%)	12 (13%)	54 (14%)	
Developmental brain abnormality	17 (8%)	9 (9%)	14 (15%)	40 (10%)	
Others	5 (2%)	3 (3%)	7 (8%)	15 (4%)	
Days to the first infantile spasms treatment (median, IQR)	11.0 (5.0, 28.0)	14.0 (5.0, 27.0)	14.0 (6.0, 26.0)	13.0 (5.0, 27.0)	0.55
Days to the last follow-up (median, IQR)	99.0 (83.0,152.0)	108.0 (89.0,144.0)	97.0 (86.0,125.0)	100.0 (84.5,138.0)	0.54
Responders to the first infantile spasms treatment (compared with nonresponders)	99 (48%)	41 (41%)	31 (34%)	171 (43%)	0.068
Days to treatment response (median, IQR)	4.0 (3.0, 7.0)	3.0 (2.0, 5.0)	3.0 (1.0, 6.0)	4.0 (2.0, 6.0)	0.26

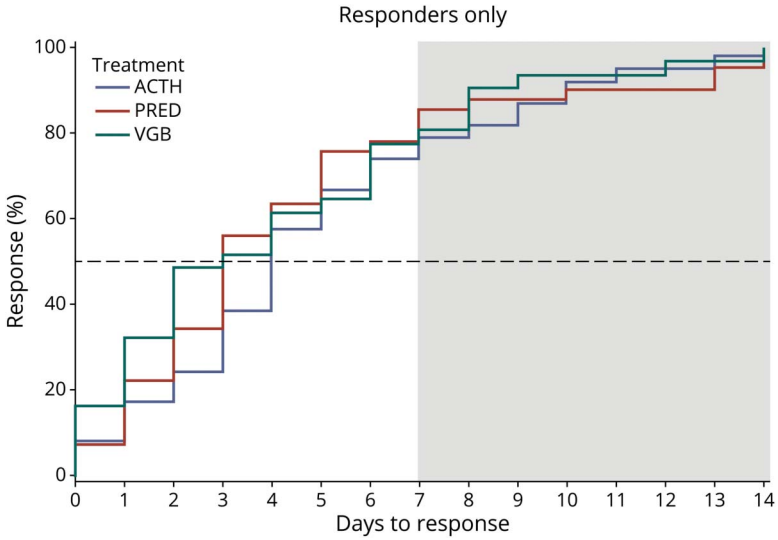
Abbreviations: ACTH = adrenocorticotropic hormone; ASM = antiseizure medication; Hyps = hypsarrhythmia; IQR = interquartile range; TSC = tuberous sclerosis complex.
p Values calculated by the Fisher exact test or Pearson χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables.
Bold indicates significant *p* values.

Time to Infantile Spasms Treatment Response

We evaluated the time to clinical infantile spasms remission among the 3 standard treatments. The time to response was not statistically significantly different across all 3 treatments or between treatments after adjusting for multiple comparisons (log-rank test, $p = 0.61$) (Figure 2). The time to response remained not statistically significantly different across all 3 treatments after adjusting for other covariates in Cox proportional hazards analysis (eTables 1 and 2, links.lww.com/WNL/C300) (oral steroids vs ACTH, hazard ratio [HR] = 1.09, 95% CI: 0.76–1.57, $p = 0.643$; vigabatrin vs ACTH, HR = 1.18, CI: 0.79–1.77, $p = 0.415$). Among responders, the median time to treatment response was 4 days (IQR: 2–6) and did not differ across the treatment groups (Table 1; Figure 2).

We calculated the sensitivity and specificity for the treatment response at each day after treatment initiation to predict sustained infantile spasms response (Table 2). Over the first week (day 7), a steep increase in the treatment response was noted. The improvement in treatment response decreased after the first week, as evaluated by the ROC curve (eFigure 1, links.lww.com/WNL/C300) that integrates sensitivity and

Figure 2 Kaplan-Meier Survival Curves of the Time to Response for First-Line Standard Infantile Spasms Medications for the Responders to Initial Standard Medication With ACTH, Oral Steroids (PRED), or Vigabatrin (VGB)



The clinical infantile spasms response occurred by day 4 in a majority (dashed line = 50% of response). By day 7, over 75% responded across all treatments (shaded area differentiates the first- and second-week posttreatment). No difference in the survival pattern of the rate of response was found among the 3 treatment groups (log-rank test, p = 0.61). ACTH = adrenocorticotropic hormone; PRED = oral steroids (e.g. prednisolone or prednisone); VGB = vigabatrin.

specificity data with different thresholds. Across all 3 medication options, the day 7 clinical response to predict sustained infantile spasms response at 1 month had a sensitivity of 81% (CI: 74%–86%) and a specificity of 98% (CI: 95%–99%), with an AUC of 0.983 (eTable 3, eFigure 1). Clinical response to ACTH on day 7 predicted infantile spasms resolution with a sensitivity of 79% (CI: 69%–86%) and a specificity of 100% (CI: 97%–100%). Clinical response to oral steroids on day 7 predicted infantile spasms resolution with a sensitivity of 85% (CI: 71%–94%) and a specificity of 95% (CI: 86%–99%). Clinical response to vigabatrin on day 7 predicted infantile spasms resolution with a sensitivity of 81% (CI: 63%–93%) and a specificity of 97% (CI: 89%–100%).

Predictors of Early Infantile Spasms Treatment Response

We assessed whether clinical factors influenced the time to treatment response by conducting survival analysis on time to response by univariate and multivariate Cox proportional hazards models. The analysis results from univariate analysis showed that the time to treatment response was unaffected by sex, gestational age, age at spasms onset, history of prior antiseizure medication, etiology, infantile spasms treatment selection, and treatment lag. Compared with those without developmental delay at infantile spasms onset, there was a significantly decreased hazard rate of early response for those with definite delays at infantile spasms onset (HR = 0.68, CI: 0.47–0.98, p = 0.039). Individuals without hypsarrhythmia on the pretreatment EEG (i.e., abnormal but not hypsarrhythmia) were more likely to have early treatment response (96%, 26/27 responding within 7 days) compared with those with hypsarrhythmia at infantile spasms onset (77%, 106/138 responding within 7 days; HR = 1.93, CI: 1.27–2.94, p = 0.0021) (eTable 1, links.lww.com/WNL/C300). Along with marginally significant developmental delay and pretreatment EEG in univariate analysis, age at infantile spasms onset was identified as significant on initial multivariate Cox proportion analysis with all covariates (eTable 2). However, stepwise variable selection in multivariate Cox proportional hazards regression analysis showed that only the pretreatment EEG without hypsarrhythmia remained in the final model and significant (HR = 1.93, CI: 1.27–2.94, p = 0.002).

We further evaluated how the pretreatment EEG results were associated with the time to response (Table 3). Individuals with a pretreatment EEG without hypsarrhythmia had a significantly earlier time to treatment response (median 2 days, IQR 1–4) compared with those with hypsarrhythmia on the initial EEG (median 4 days, IQR 2.3–7) (p = 0.0055). Although we found a difference in the *time* to response, the overall likelihood of response to treatment between those with and without hypsarrhythmia on the initial EEG was similar (hypsarrhythmia: 46%, 138/303; no hypsarrhythmia: 43%, 27/63; p = 0.6965). In the subgroup analysis, we identified that children with an abnormal pretreatment EEG without hypsarrhythmia were more likely to have TSC (16%, 10/63) compared with having hypsarrhythmia (4%, 12/303) (p = 0.0003). The time to response for TSC was 3.5 days (IQR 1–6.5), which was not significantly different among those with and without hypsarrhythmia (p = 0.1763). Overall, etiology did not have a significant influence on the time to treatment response regardless of the pretreatment EEG (all p > 0.07, eTable 2, links.lww.com/WNL/C300).

Discussion

In this prospective multicenter study of infants with a variety of infantile spasms etiologies, we demonstrate that a robust

Table 2 Early Treatment Response (By 0–14 Days of Treatment) Predicts Ongoing Remission of Infantile Spasms Evidenced by Sensitivities and Specificities (and CIs) Derived From 14 Different Days of Treatment

Day of treatment	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive Predictive Value % (95% CI)	Negative Predictive Value % (95% CI)
0	9.4 (5.4, 14.8)	100.0 (98.4, 100.0)	100.0 (79.4, 100.0)	59.1 (54.0, 64.1)
1	21.1 (15.2, 27.9)	99.6 (97.5, 100.0)	97.3 (85.8, 99.9)	62.3 (57.1, 67.3)
2	31.0 (24.2, 38.5)	98.7 (96.1, 99.7)	94.6 (85.1, 98.9)	65.2 (59.9, 70.3)
3	45.0 (37.4, 52.8)	98.2 (95.5, 99.5)	95.1 (87.8, 98.6)	70.1 (64.7, 75.1)
4	59.7 (51.9, 67.1)	98.2 (95.5, 99.5)	96.2 (90.6, 99.0)	76.1 (70.8, 80.9)
5	68.4 (60.9, 75.3)	98.2 (95.5, 99.5)	96.7 (91.8, 99.1)	80.3 (75.1, 84.8)
6	75.4 (68.3, 81.7)	97.8 (94.9, 99.3)	96.3 (91.5, 98.8)	83.9 (78.9, 88.2)
7	80.7 (74.0, 86.3)	97.8 (94.9, 99.3)	96.5 (92.0, 98.9)	86.9 (82.1, 90.8)
8	84.8 (78.5, 89.8)	97.8 (94.9, 99.3)	96.7 (92.4, 98.9)	89.4 (84.8, 93.0)
9	88.3 (82.5, 92.7)	96.9 (93.7, 98.7)	95.6 (91.1, 98.2)	91.6 (87.3, 94.8)
10	91.8 (86.6, 95.5)	96.4 (93.1, 98.5)	95.2 (90.7, 97.9)	93.9 (90.0, 96.6)
11	93.6 (88.8, 96.8)	96.0 (92.5, 98.2)	94.7 (90.1, 97.5)	95.1 (91.5, 97.6)
12	94.2 (89.5, 97.2)	95.5 (91.9, 97.8)	94.2 (89.5, 97.2)	95.5 (91.9, 97.8)
13	97.1 (93.3, 99.0)	95.1 (91.4, 97.5)	93.8 (89.2, 96.9)	97.7 (94.7, 99.3)
14	100.0 (97.9, 100.0)	94.6 (90.8, 97.2)	93.4 (88.8, 96.6)	100.0 (98.3, 100.0)

initial response and sustained clinical remission after standard therapies occur within 7 days in most responders. Our data provide support for an earlier (i.e., 1 week vs the traditional 2 weeks) assessment for infantile spasms treatment response and raise the possibility that alteration in therapy (whether this be an add-on or switch to a different therapy) for initial nonresponders could reasonably be implemented after 7 days of first treatment. Initial monotherapy with early add-on therapy may also allow responders to avoid the side effects and cost associated with a uniform initiation of combination therapy.

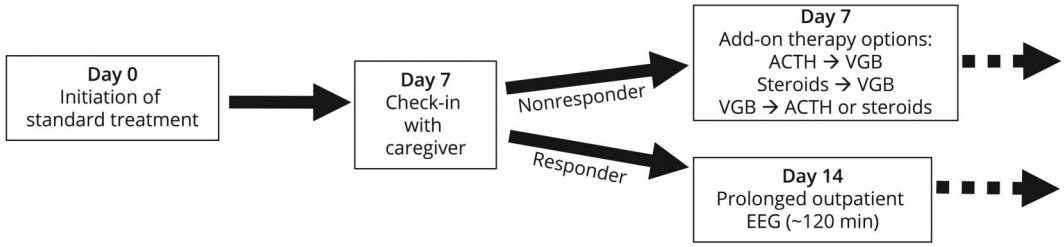
Our results highlight that the response to standard therapies occurs early in the treatment course for most children. The majority of the responders did so within 1 week of infantile spasms treatment initiation. Our findings are in line with published data that suggest the time to clinical remission is less than 6 days for ACTH,[13] oral steroids,[16,17] and

Table 3 Evaluation of the Pretreatment EEG, Etiology, and Treatment Response

	Pretreatment EEG at infantile spasms onset					
	Abnormal without hypsarrhythmia			Hypsarrhythmia		
Etiology	Responder, n (%)	Days to response for responders (median, IQR)	Nonresponder, n (%)	Responder, n (%)	Days to response for responders (median, IQR)	Nonresponder, n (%)
Unknown	8 (30%)	2.5 (2–4.5)	13 (36%)	62 (45%)	4 (1.75–7)	73 (44%)
Acquired	6 (22%)	1 (0.8–6.3)	7 (19%)	33 (24%)	5 (3.5–8)	40 (24%)
Genetic	1 (4%)	4 (—)	6 (17%)	20 (14%)	4 (2.3–4.8)	24 (15%)
Developmental brain anomaly	3 (11%)	4 (1–4)	5 (14%)	9 (7%)	5 (2.5–8.5)	20 (12%)
TSC	7 (26%)	2 (1–6)	3 (8%)	7 (5%)	6 (3–9)	5 (3%)
Others	2 (7%)	1.5 (1–2)	2 (6%)	7 (5%)	3 (1–6)	3 (2%)
Total	27 (100%)	2 (1–4)	36 (100%)	138 (100%)	4 (2.3–7)	165 (100%)

Abbreviations: IQR = interquartile range; TSC = tuberous sclerosis complex.
Percentages are calculated from the total within each column.

Figure 3 Flowchart of Early Add-on Treatment for Infantile Spasms



Clinical staff check-in with the child's caregiver to assess clinical treatment response. (i) Nonresponders are individuals with ongoing clinical infantile spasms, even if there is a decrease in infantile spasms frequency or severity. All nonresponders are eligible for add-on therapy, ideally with a medication that has an alternative mechanism of action. Once an additional medication is added, the clinical and electrographic response should be evaluated 14 days from the date of add-on therapy initiation. (ii) Responders are individuals with a clear resolution of clinical infantile spasms not just a decrease in infantile spasms frequency or severity. If the child is a clear responder by day 7, then proceed with day 14 EEG for electrographic confirmation of infantile spasms resolution. ACTH = adrenocorticotropic hormone; VGB = vigabatrin.

vigabatrin.[18] Our analyses suggest that using treatment day 7 is a rational threshold to assess treatment response. At the end of the first week of treatment, ~80% of children will be correctly identified as responders or nonresponders, thus enabling early alteration in therapy for nonresponders.

Aside from hypsarrhythmia on initial diagnostic EEG, no other clinical variable, including lead time or etiology, was predictive of the time to treatment response among responders. We found that children without hypsarrhythmia (but with an abnormal EEG) more often experienced clinical remission within 1 week. Yet, the presence or absence of pretreatment hypsarrhythmia had no association with the response to treatment when all responders were considered together. Therefore, the pretreatment EEG was associated with the *time* to treatment response but was not a predictor of *overall* response. One explanation for the time to response difference was that children without hypsarrhythmia were also more likely to be treated with vigabatrin and have TSC as the etiology. The clinical EEG is a reliable biomarker for epilepsy in TSC[22]; thus, many of these infants may have had prehypsarrhythmia on their EEG and early treatment initiation because of close observation (although these children were enrolled before the recent EPISTOP[23] and PREVENT trials, NCT02849457). Despite these differences, most children responded to standard therapy by day 7 regardless of the pretreatment EEG results or other clinical factors.

Our study is timely given the recent data supporting the use of combination therapy.[8] In a randomized clinical trial, combination therapy (vigabatrin with either synthetic ACTH or oral steroids) compared with monotherapy (synthetic ACTH or oral steroids) led to superior early electroclinical outcome, but the follow-up at 18 months failed to demonstrate improved development or epilepsy outcomes.[10] Concerns exist about the risk/benefit ratio of combination therapy in infants with moderate to severe developmental delays, especially because this subgroup of children did not benefit from the combination approach even in the short term.[9] In addition, concurrent use of hormonal therapy with vigabatrin may exacerbate symptomatic vigabatrin-associated MRI changes.[24] The price of vigabatrin can be over $20,000 US for a 6-month course.[25] Recent cost-effectiveness analysis supports prednisolone over ACTH in the United States.[26] Although a formal cost-effectiveness analysis was beyond the scope of this study, the economic impact of an aggressive induction therapy should be weighed against benefits of such therapy.

We estimate the impact of treatment assessment at day 7 vs day 14. In our cohort, 57% (n = 224) had an incomplete response to initial treatment by day 14. Standard therapy as second line yields a response rate of up to 55%.[11] Our data suggest that in our cohort, 123 children may have benefitted from earlier infantile spasms resolution with second-line therapy given by day 7. Data suggest that the sooner the infantile spasms are controlled, the better the outcome is.[7] By contrast, only 33 children in our study responded after the first week of therapy and would potentially be exposed to additional medication if a change was made on day 7. Clinicians can use our data to evaluate other timing for treatment response after the first medication is initiated. Ultimately, these results may be used for clinical counseling of families on the risks and potential benefits of earlier secondary treatment initiation if the first treatment fails. Taken together, sequential therapy with early add-on of the second drug may be advantageous by providing efficient therapy escalation when needed, while minimizing potential adverse effects and costs from multiple agents in early responders.

Limitations of our study include the lack of treatment randomization or standardized dosing. We relied on the clinical remission of infantile spasms as the outcome measure because it is practical across a range of clinical settings, but we recognize that a clinical trial may well require EEG confirmation of electroclinical remission. Given the poor interrater reliability of assessing hypsarrhythmia,[21] future studies should incorporate a central review or a standard scoring method for hypsarrhythmia. A number of patients had missing data and were excluded; this could introduce potential selection bias. However, strengths of our study include the large sample size

for this rare disease, participation from many US epilepsy centers, and the prospective data collection (including the time to clinical infantile spasms remission). A limitation with the proposed add-on therapy approach is that children with infantile spasms remission beginning between day 7 and 14 of treatment would potentially have an unnecessary alteration of therapy if their treatment was changed after only 1 week (as would be the case for 10% (21/99), 6% (6/41), and 7% (6/31) of children who received ACTH, oral steroids, or vigabatrin, respectively). Therefore, earlier recognition, evaluation, and treatment may prevent delays and could potentially lead to improved outcomes.

We propose a change in clinical practice such that the first routine evaluation after infantile spasms treatment initiation occurs by the end of the first week of treatment (Figure 3). A phone call or virtual visit with the neurologist may be sufficient to determine whether clinical infantile spasms have resolved. Lack of complete infantile spasms resolution would prompt a change in the treatment course and motivate prescription of an additional/alternate medication with a different mechanism of action on day 7.[11] If the child appeared to have responded to treatment by day 7, we would continue to advocate for follow-up prolonged video EEG to confirm remission at day 14.[27]

In conclusion, nearly 80% of children who respond to first-line infantile spasms therapy experience clinical remission by day 7 of treatment. This finding is widely applicable to clinical practice because neither infantile spasms etiology nor other clinical characteristics appeared to influence the time to response to the first infantile spasms medication. We provide rationale for early add-on or alternative therapy for infantile spasms refractory to initial monotherapy. Future work should assess the impact of such efficient treatment escalation on long-term outcomes.

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Elissa G. Yozawitz, MD	Department of Neurology, Montefiore Medical Center, Bronx, NY	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Cynthia G. Keator, MD	Jane and John Justin Neurosciences, Cook Children's Hospital, Fort Worth, TX	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data

Continued

Appendix 1 *(continued)*

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Appendix 2 *(continued)*

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