SECONDARY OUTCOME: RESOLUTION OF CLINICAL SPASMS AND HYPSARRHYTHMIA

Evaluation of the literature. Providing an estimate of the secondary composite outcome (resolution of both clinical spasms and hypsarrhythmia) would require that this composite outcome is clearly quantifiable and similar between different studies. An evaluation of the existing literature on this topic showed that:

-Not all patients with infantile spasms had hypsarrhythmia in the pre-treatment electroencephalogram (EEG) [1-5], making it difficult to interpret the value of not having hypsarrhythmia in the follow-up EEG among patients who did not have hypsarrhythmia at baseline. Additionally, some patients with no hypsarrhythmia in the pre-treatment EEG had hypsarrhythmia in the follow-up EEG [4].

-Not all patients who had clinical resolution of spasms had a follow-up EEG [4, 6].

-There is an enormous variability in the time of the follow-up EEG from days to months after treatment initiation [7, 8]. Some studies performed follow-up EEG within a narrow time period, for example, days 12 to 19 after treatment initiation [4], within 2-4 weeks of treatment initiation [9], or at 1 month of treatment initiation [6]. Other studies considered EEG normalization within a wide range from 12 to 55 days after treatment initiation [10]. Some other studies performed EEGs frequently, twice per week [11], or after 10 and 20 days of spasms resolution [12]. Further, other studies evaluated resolution of hypsarrhythmia with a later EEG: 3 months after treatment initiation [3]. Importantly, many studies did not provide the time of the follow-up EEG [1, 2, 13].

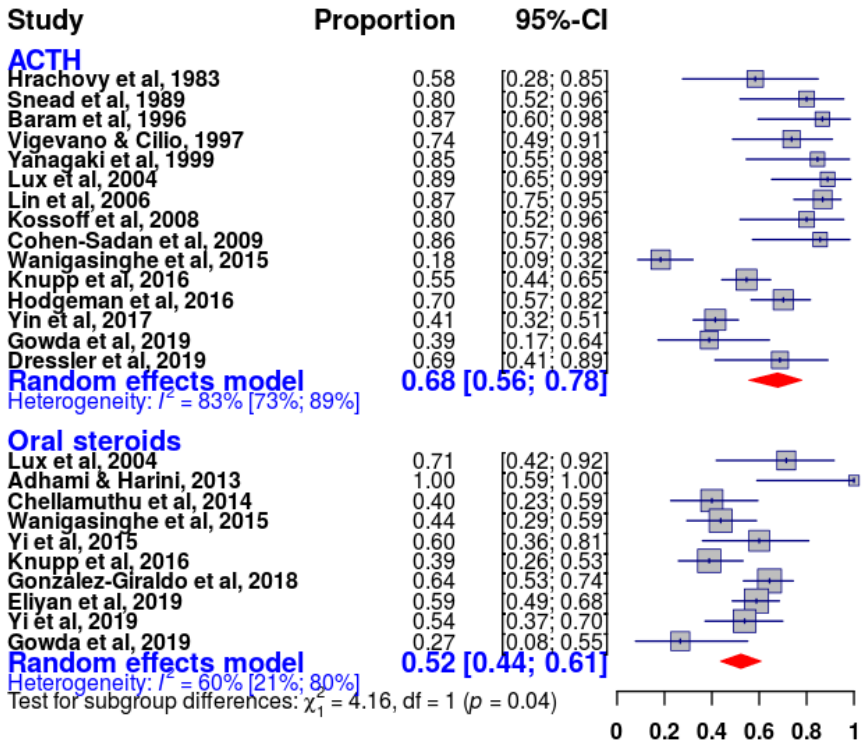
-The definition of resolution of hypsarrhythmia varied widely in the literature. Some studies had a strict definition that considered hypsarrhythmia resolved only if the EEG was completely normal [14] or only has focal epileptiform discharges [15]. Other studies had more lax definitions considering that

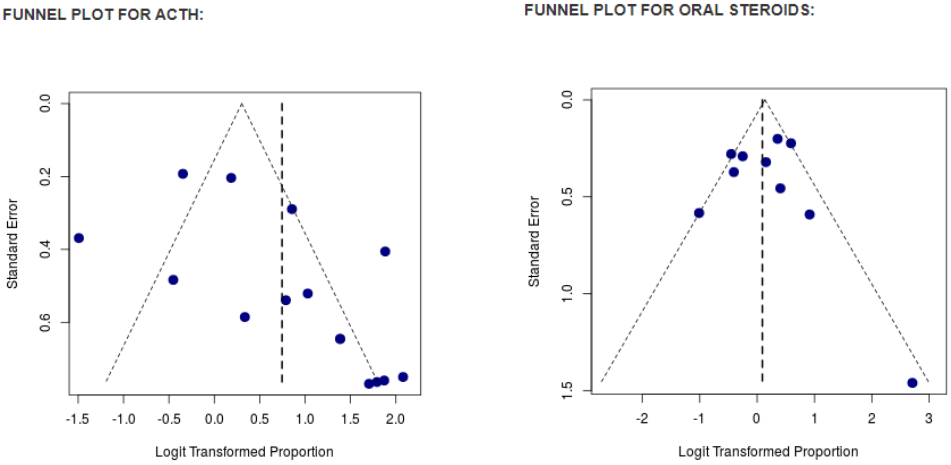
resolution of hypsarrhythmia during wakefulness (even if hypsarrhythmia was still present during sleep) was a partial remission [16, 17]. Importantly, many studies did not specify the criteria to determine resolution of hypsarrhythmia [1, 10, 11, 13, 18, 19]. In the context of subjectivity and low inter-rater concordance in the recognition of hypsarrhythmia [20], it appears that what has been defined as resolution of hypsarrhythmia in one study might not have been defined as such in a different study. We could only find one study with quantifiable and reproducible evaluations of the resolution of hypsarrhythmia [8, 21].

-Most studies did not specify whether hypsarrhythmia resolution occurred while the patient was still spasms free. Therefore, it could be that a patient had spasms resolution at day 14, but by the time the resolution of hypsarrhythmia was evaluated, the patient was not spasms free anymore. In some studies the number of patients with resolution of hypsarrhythmia is higher than the number of patients with resolution of clinical spasms [10].

For all the reasons above, we consider that evaluating the composite secondary outcome of resolution of both clinical spasms and hypsarrhythmia is at a very high risk of bias. We provide this composite secondary outcome as it was one of the study objectives, but caution the reader that no firm conclusions can be derived from it. However, trying to summarize the literature identifies the need for more homogeneous definitions of resolution of hypsarrhythmia.

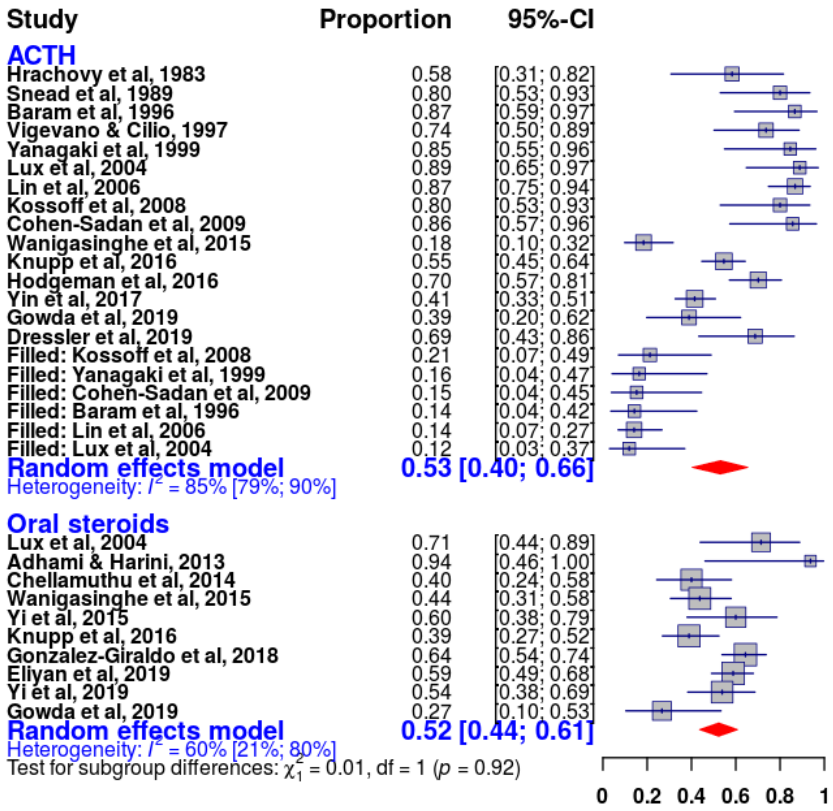
Meta-analysis on effectiveness. For this composite secondary outcome, we considered a very lax definition of resolution of clinical spasms at 14-28 days and EEG resolution of hypsarrhythmia (heterogeneously defined) in the corresponding follow-up EEG (performed at varying time periods). Entering these data (from Table e-1 at https://ivansanchezfernandez.github.io/CE_InfantileSpasms/Table_e1.pdf) in the meta-analysis App at https://bchis.shinyapps.io/metaanalysis_probability_spasmsresolution/ yields the following results:



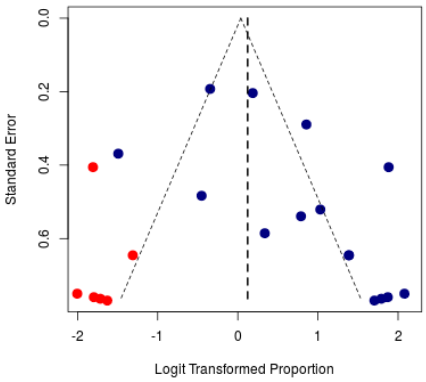


ACTH appears to be more effective (0.68, 95% CI: 0.56 to 0.78) than oral steroids (0.52, 95% CI: 0.44 to 0.61), but there is marked between-study variability, especially for ACTH, and there is substantial publication bias, especially for ACTH. These results should be considered with caution given that the only study with a quantifiable and reproducible way to evaluate resolution of hypsarrhythmia found that EEG resolution was better with prednisolone than with ACTH [8, 21].

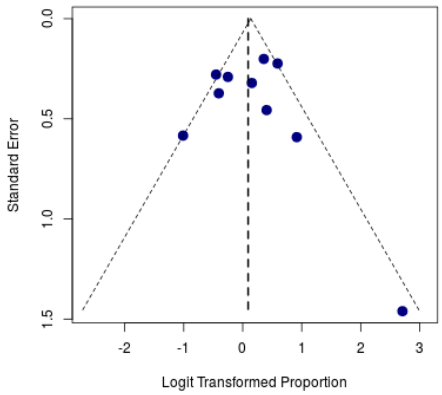
Further, adjusting for publication bias shows that the apparent superior effect of ACTH was likely due to publication bias:



FUNNEL PLOT FOR ACTH:



FUNNEL PLOT FOR ORAL STEROIDS:



Cost-effectiveness. Although we showed that these estimates are likely biased and not reliable, we present the cost-effectiveness analyses for illustration purposes.

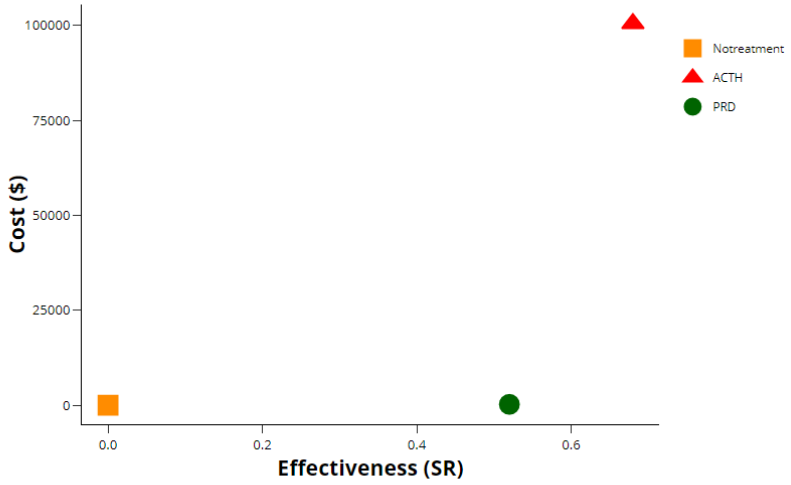
Entering the data from the unadjusted estimation of effectiveness (ACTH: 0.68 and prednisolone: 0.52) in the cost-effectiveness App at https://bchis.shinyapps.io/cost_effectiveness/ yielded the following results:

COST-EFFECTIVENESS TABLE

Names	Cost	Effectiveness	IE	IC	ICER
No treatment	0.00	0.00	0.00	0.00	NA
Prednisolone	210.00	0.52	0.52	210.00	403.85
ACTH	100464.00	0.68	0.16	100254.00	626587.50

***Strategies that are not cost-effective dissappear from the table**
Legend: IE: incremental effectiveness. IC: incremental cost. ICER: incremental cost-effectiveness ratio.

COST-EFFECTIVENESS PLOT



Legend: Notreatment: No treatment. ACTH: Intramuscular ACTH. PRD: Oral prednisolone. $: USA dollars. SR: Probability of spasms resolution.

The ICER for prednisolone was $404 per case of spasms resolved. The ICER for ACTH was $626,588 per case of spasms resolved.

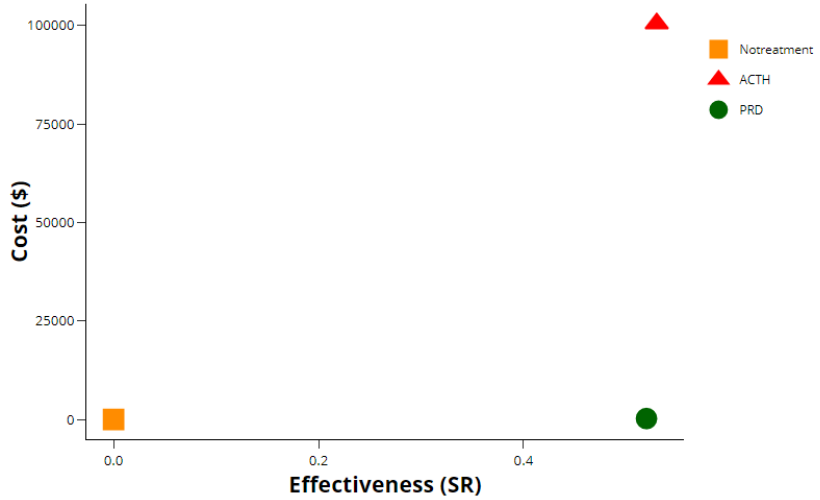
Entering the data from the estimation of effectiveness adjusted for publication bias (ACTH: 0.53 and prednisolone: 0.52) in the cost-effectiveness App at https://bchis.shinyapps.io/cost_effectiveness/ yielded the following results:

COST-EFFECTIVENESS TABLE

Names	Cost	Effectiveness	IE	IC	ICER
No treatment	0.00	0.00	0.00	0.00	NA
Prednisolone	210.00	0.52	0.52	210.00	403.85
ACTH	100464.00	0.53	0.01	100254.00	10025400.00

***Strategies that are not cost-effective dissappear from the table**
Legend: IE: incremental effectiveness. IC: incremental cost. ICER: incremental cost-effectiveness ratio.

COST-EFFECTIVENESS PLOT



Legend: Notreatment: No treatment. ACTH: Intramuscular ACTH. PRD: Oral prednisolone. $: USA dollars. SR: Probability of spasms resolution.

The ICER for prednisolone was $404 per case of spasms resolved. The ICER for ACTH was $10,025,400 per case of spasms resolved.

Conclusion. The main conclusion of this section is that the current literature does not allow a reliable estimate of the composite secondary outcome of resolution of both clinical spasms and hypsarrhythmia, and this estimation is at very high risk of bias. We provided this composite secondary outcome as it was one of the study objectives and for illustration purposes, but caution the reader that no firm conclusions can be derived from it. However, trying to systematically summarize the literature identified the need for more homogeneous definitions of resolution of hypsarrhythmia.

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