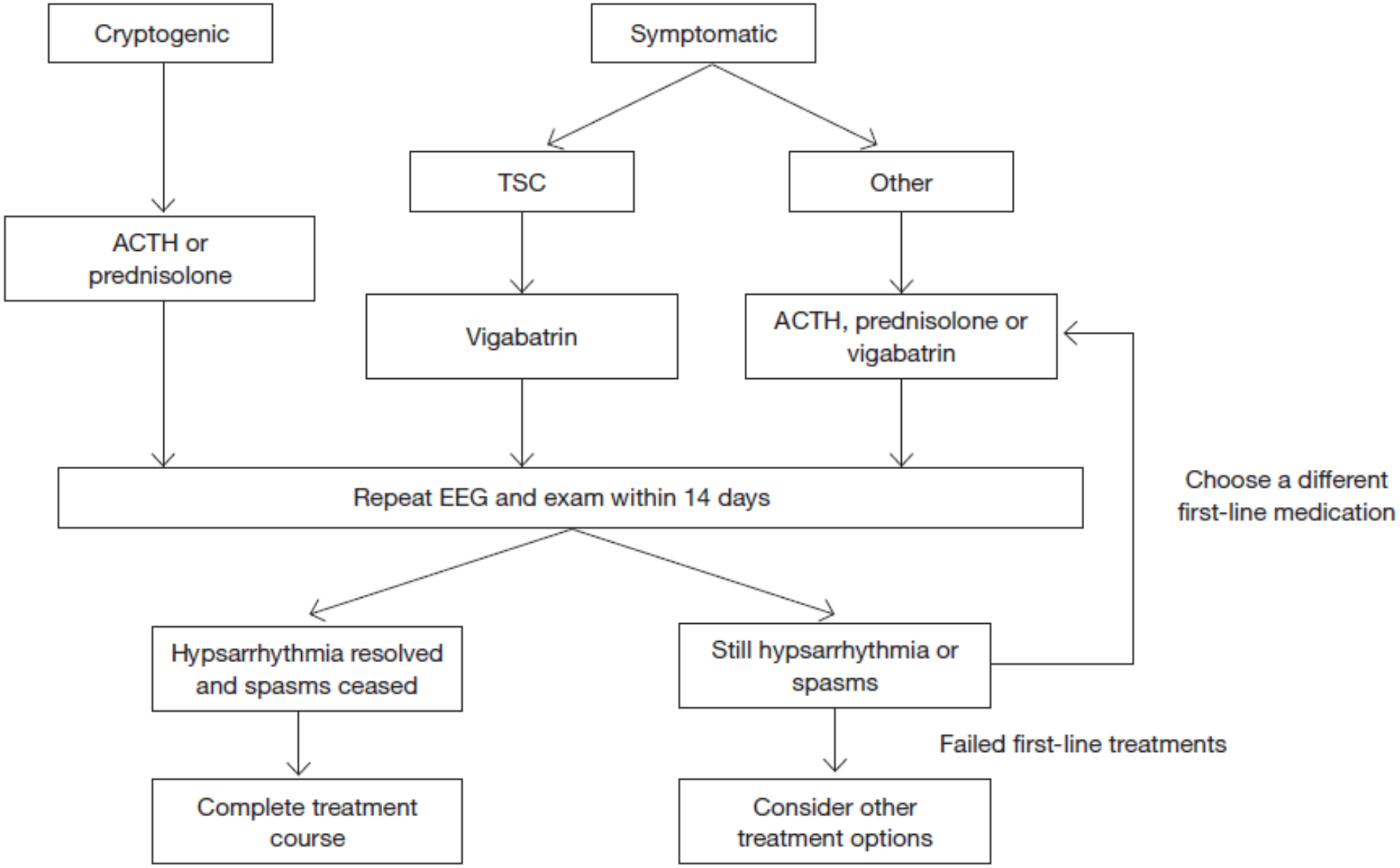
PROTOCOLLI D'USO dell'ACTH nella terapia della SINDROME di WEST e terapie alternative


Cryptogenic
Symptomatic
TSC
Other
ACTH or prednisolone
Vigabatrin
ACTH, prednisolone or vigabatrin
Repeat EEG and exam within 14 days
Choose a different first-line medication
Hypsarrhythmia resolved and spasms ceased
Still hypsarrhythmia or spasms
Failed first-line treatments
Complete treatment course
Consider other treatment options

Nelson, 2015

DIFFICOLTA' NEL CONFRONTO DIRETTO FRA STUDI E LIMITI METODOLOGICI

- Variabilità nel tipo di ACTH utilizzato (naturale – sintetico)
- Differenze nel calcolo della dose: mg/kg vs. UI/kg vs. UI/m^2

- Numerosità dei campioni
- Bias (randomizzazione, cieco, altre)

FORMULE DI CONVERSIONE PESO-m^2 SUPERFICIE CORPOREA

$m^2 = \sqrt{h(cm)} \times peso\ (kg)/3600$

$m^2 = 4 \times peso + 7/peso + 90$

EQUIVALENZA mg/kg – UI/kg (?)

1 UI = 0,025 mg
1 mg = 40 UI

1 UI = 0,0125 mg
1 mg = 80 UI
in Lux et al., 2004

EQUIVALENZA naturale – sintetico (?)

1 UI naturale=
0,025 di sintetico

there is […] uncertainty regarding the equivalence of biologic and synthetic preparations of ACTH.

Hussain et al., 2014

PROTOCOLLO ATTUALE

Piridossina (vitamina B6)
50 mg/kg/die per os 1 settimana

ACTH
0,0125 mg/kg/die i.m. 1°-2° settimana
0,0125 mg/kg i.m. a giorni alterni 3°-4° settimana
0,0125 mg/kg/i.m 2 volte/settimana 5°-6° settimana

Alla fine delle prime 4 settimane, in base a EEG e clinica se non responsivi:

GVG
30 mg/kg/die per os 3 giorni
60 mg/kg/die altri 3 giorni
90 mg/kg/die altri 3 giorni
120 mg/kg/die altri 2 giorni

ESEMPI DI ALTRI PROTOCOLLI

L'ESPERIENZA FINLANDESE

Alte dosi (120 UI) non superiori a basse dosi (40-60 UI)
(n= 54 vs. n= 97)
- per risoluzione spasmi
- scomparsa ipsaritmia
- recidive
- prognosi cognitiva (migliore nel gruppo con basse dosi)

Riikonen, 1982

Studio prospettico multicentrico (n= 30)
piridossina 150-200 mg 3-4 giorni
ACTH 3UI/kg/die
se risposta: scalato in 2 settimane
(**pz sintomatici: 2 settimane aggiuntive**)
no riposta: dose raddoppiata ogni 2 settimane fino a 12 UI/kg (sia criptogenici che sintomatici)
Scalato con dimezzamento della dose a intervalli settimanali
1 settimana prima di sospensione ACTH:
supplementazione cortisonica (schema: 1/0.75/0.50/0.25 mg/kg/d poi 0.25/0.125 a giorni alterni -ciascuna dose per 1 settimana), seguito da supplementazione cortisonica per 4-6 mesi in situazioni di stress.

100% spasmi criptogenici
1/3 spasmi sintomatici gestiti con basse dosi

11 pz hanno ricevuto alte dosi (4 la dose massima)

60% di risposta

Heiskala et al., 1996

Attuale protocollo:
piridossina
ACTH 0.03 mg/kg i.m. a gg alterni (2 settimane), riduzione progressiva nelle 2 settimane successive o se necessario altre 2 settimane a dose doppia (0.06/kg) e poi riduzione

Riikonen, 2009

PROTOCOLLI GIAPPONESI

Yanagaki et al., 1999

Protocollo:

•Piridossina 20-50 mg/kg/d per 7 giorni
•ACTH i.m. quotidianamente x 2 settimane
Basse dosi= **0,005 mg/kg/d** (**vs.** alte dosi= 0,025 mg/kg/d)
se efficace:
a giorni alterni x 1 settimana
2 volte/settimana la 2a settimana
se efficacia parziale (riduzione > 50%):
prosegue dosaggio pieno per 1-2 settimane
no risposta a basso dosaggio:
aumento a 0,025 mg/kg/d per 2 settimane
scalato in altre 2 settimane

A fine trattamento, se non in terapia AED, introducono VPA o CZP (≥ 2 aa)

Studio prospettico
26 pazienti (16 sintomatici, 10 criptogenici)
Assegnazione casuale al gruppo di trattamento, 50% vs 50%
1 C (gr. basse dosi) escluso per interruzione terapia (Rotavirus)

ELSEVIER

Brain & Development 000 (1999) 461–467

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

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Original article

A comparative study of high-dose and low-dose ACTH therapy for West syndrome

Shigeru Yanagaki[a], Hirokazu Oguni[a,*], Kitami Hayashi[a], Kaoru Imai[a], Makoto Funatuka[a], Teruyuki Tanaka[a], Masae Yanagaki[b], Makiko Osawa[a]

ACTH regimen	Cryptogenic		*P*-value	Symptomatic		*P*-value
	High-dose	Low-dose		High-dose	Low-dose	
N	5	4		8	8	
Responders/non-responders	5/0	3/1	0.44	6/2	6/2	0.99
Residual focal EEG spike in responders	2 (40%)	1 (33%)	0.99	3 (50%)	2 (33%)	0.99
Number of injections needed for seizure control	4.6 ± 3.6	2.7 ± 1.2	c > 0.13	9.0 ± 2.9	10.7 ± 2.3	0.62
Corresponding ACTH dose	39.2 ± 40.2	4.13 ± 1.29	0.001*	72.8 ± 67.4	20.1 ± 11.8	0.001*
(IU/kg)	4.6 ± 3.6	0.53 ± 0.23	0.11	9.0 ± 2.9	2.14 ± 0.46	0.044*
Total number of injections	19.4 ± 4.3	15.5 ± 1.7	0.13	18.8 ± 4.7	20.2 ± 6.1	0.63
Corresponding ACTH dose	150.8 ± 63.5	25.9 ± 4.6	0.006*	132.1 ± 51.9	38.1 ± 11.9	0.001*
(IU/kg)	19.4 ± 4.3	3.1 ± 0.34	0.001*	18.8 ± 4.7	4.04 ± 1.22	0.001*
Maximal serum cortisol levels (ng/ml)	3590.5 ± 1361.5	1713.8 ± 1692	0.13	1469.1 ± 1033.7	619.6 ± 197.6	0.039*

ACTH regimen	Cryptogenic		*P*-value	Symptomatic		*P*-value
	High-dose	Low-dose		High-dose	Low-dose	
Relapse/Responders	1/3	0/3	0.46	2/5	3/6	0.99
Follow-up period (months)	17.2 ± 11.3	28.3 ± 8.7	0.16	28.7 ± 23.5	42.8 ± 26.5	0.28
DQ at last follow-up	115.0 ± 5.7	100.5 ± 16.3	0.36	12.5 ± 3.5	18.7 ± 11.8	0.54

	High-dose	Low-dose	*P*-value
N	13	12	
Hypertension	0	0	0.99
Irritability (Mi/Mo/S)	2/6/5	4/4/4	0.99
Sleepiness[b] ($n = 22$)			
First 1 week period	1.077 ± 0.115 ($n = 12$)	0.983 ± 0.11 ($n = 10$)	0.048*
Second 1 week period	0.921 ± 0.114	0.873 ± 0.136	0.468
Weight change (%)	+8.6 ± 3.2	+9.4 ± 5.2	0.62
Elevated liver enzyme (*n*)	1	1	0.99
Hypokalemia (*n*)	1	0	0.99
Brain shrinkage (%)	12.4 ± 5.7	6.6 ± 4.6	0.023*

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Original article

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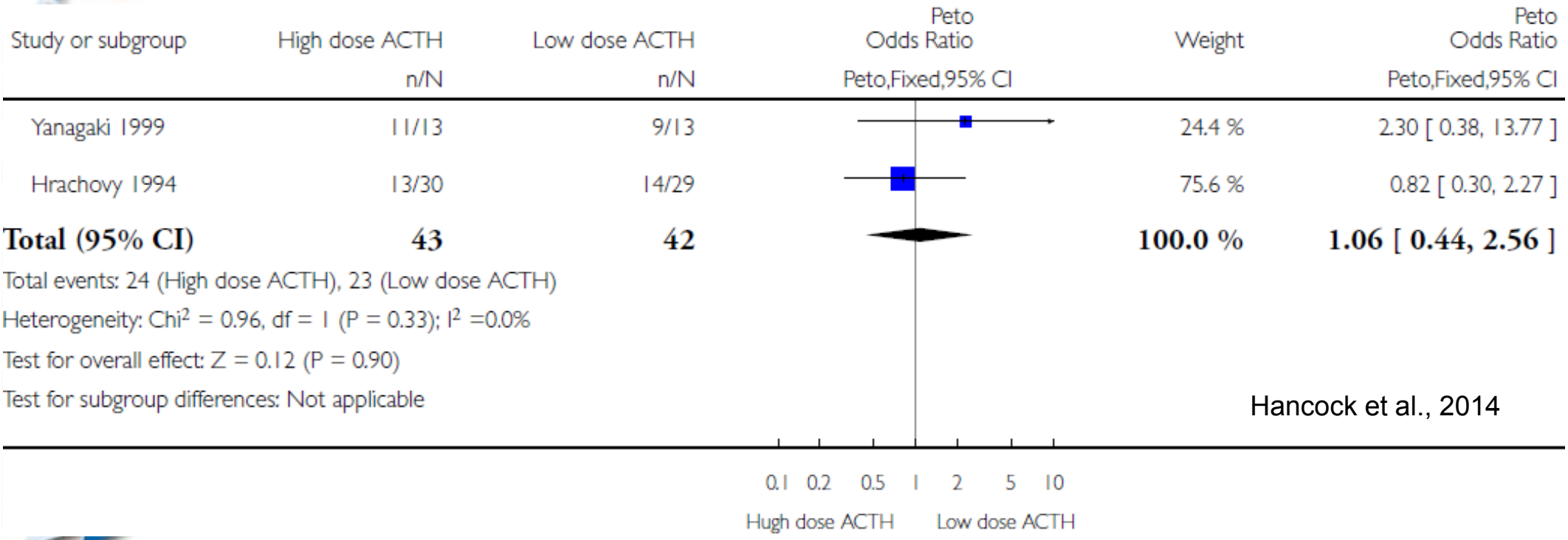


Hancock et al., 2014

Hrachovy (1994): 150 UI/m²/d 3 settimane scalate in 9 settimane (alta dose) vs. 20-30 UI/d (0,5-0,75 mg/d) per 2-6 settimane, scalate in 1 settimana (bassa dose) ACTH naturale

Analysis 4.2. Comparison 4 High-dose ACTH versus low-dose ACTH, Outcome 2 Relapse rates - number of patients who remain spasm free.

Review: Treatment of infantile spasms

Comparison: 4 High-dose ACTH versus low-dose ACTH

Outcome: 2 Relapse rates - number of patients who remain spasm free

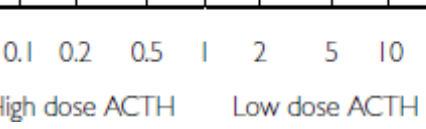
Study or subgroup	High-dose ACTH n/N	Low-dose ACTH n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Hrachovy 1994	11/30	12/29		70.0 %	0.82 [0.29, 2.32]
Yanagaki 1999	8/13	9/13		30.0 %	0.72 [0.15, 3.52]
Total (95% CI)	**43**	**42**		**100.0 %**	**0.79 [0.33, 1.88]**

Total events: 19 (High-dose ACTH), 21 (Low-dose ACTH)

Heterogeneity: $Chi^2 = 0.02$, df = 1 (P = 0.89); $I^2 = 0.0\%$

Test for overall effect: Z = 0.53 (P = 0.60)

Test for subgroup differences: Not applicable



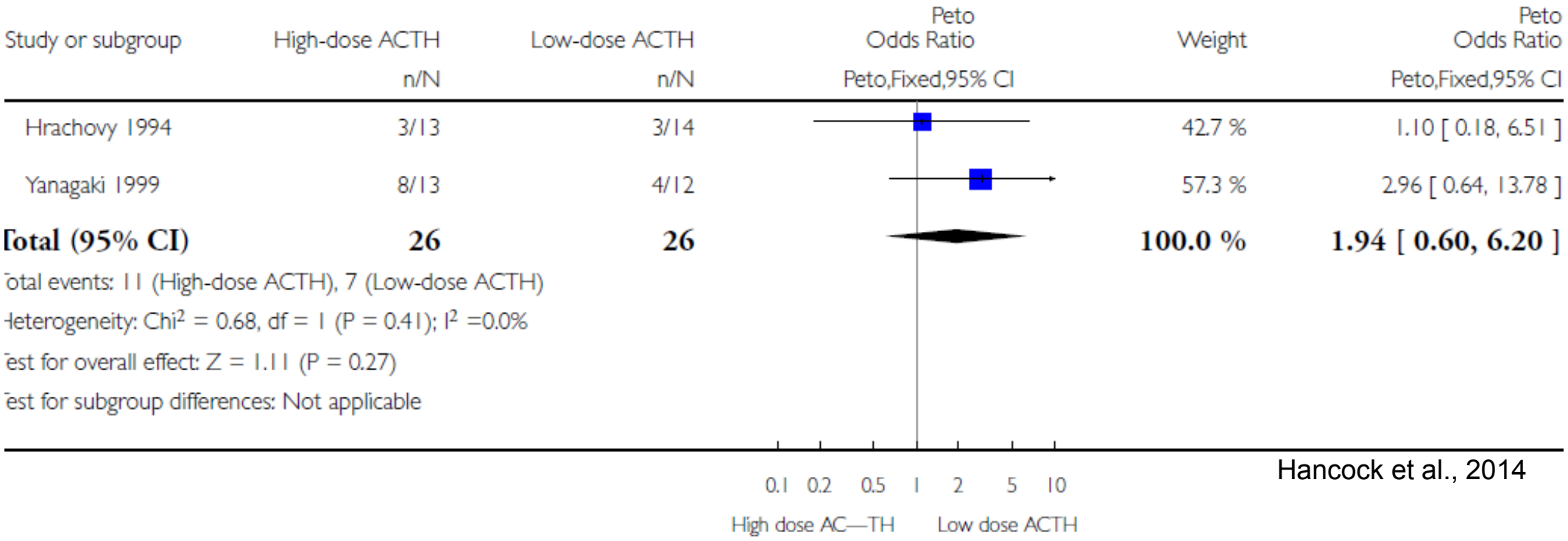
Hancock et al., 2014

Analysis 4.3. Comparison 4 High-dose ACTH versus low-dose ACTH, Outcome 3 Resolution of hypsarrhythmia.

Review: Treatment of infantile spasms

Comparison: 4 High-dose ACTH versus low-dose ACTH

Outcome: 3 Resolution of hypsarrhythmia



Hancock et al., 2014

CME

Low-dose ACTH therapy for West syndrome

Initial effects and term outcome

M. Ito, MD, PhD; H. Aiba, MD; K. Hashi i, MD, PhD; K. Tomiwa, MD, PhD; T. Okuno, MD; H. Hattori, MD, PhD; T. Go, M D, PhD; S. Dejima, MD; H. Ikeda, MD; M. Yoshioka, MD, PhD; O. Kanazawa, MD; J. Ochi, MD, PhD; N. Miki, MD; H. Noma, MD; K. Oguro, MD, PhD; N. Oza T. Matsubara, MD; T. Miyajima, MD; T. Fujii, MD, PhD; Y. Konishi and H. Hojo, MD, PhD

Abstract—*Background:* Most Japanes before using adrenocorticotropic hormone (ACTH) therapy for West s dose synthetic ACTH to avoid serious adverse effects. In this mu effects, adverse effects, and long-term outcome in patients tr he medical records of 138 patients with WS, who were tre the authors' institutions between 1989 and 1998, were a izures was noted in 106 of 138 (76%) patients, good e excellent in 53 of 138 (38%) patients, good in 76 -up, 51 of 99 (52%) patients were seizure-free f 98 (6%) patients, mild mental retardation tion in 50 (51%). The initial effects of 0.005 to 0.032 mg/kg, 0.2 to 1.28 II rrelated with total dosage of AC e and total dosage of ACTH, her doses used in previou possible to avoid serio

NEUROLOGY

Questionario a centri partecipanti
Analisi retrospettiva
n= 138

ACTH i.m. per 1-5 settimane
interrotto/ridotta frequenza iniezioni in ≤8 settimane
Risposta iniziale:
76% eccellente, buona 17%
73% S, 96% C liberi da crisi
n= 98 con follow-up ≥ 2 aa:
52% silenzio clinico

Factors	Seizure outcome			Mental outcome		
	Seizure-free	Persistent seizures	Total	Normal + mild	Moderate + severe	Total
Etiology						
Symptomatic	36 (46)	42 (54)	78	9 (12)	69 (88)	78
Cryptogenic	15 (71)*	6 (29)	21	7 (35)‡	13 (65)	20
Age at onset						
≤3 mo	4 (27)	11 (73)	15	3 (19)	13 (81)	16
>3 mo	47 (56)*	37 (44)	84	19 (23)	63 (77)	82
Treatment lag						
≤60 d	39 (63)†	23 (37)	62	17 (28)	44 (72)	61
>60 d	12 (32)	25 (68)	37	5 (14)	32 (86)	37
Initial effects of ACTH on seizure						
Excellent	47 (59)†	32 (41)	79	18 (23)	60 (77)	78
Good + poor	4 (20)	16 (80)	20	4 (20)	16 (80)	20
Initial effects of ACTH on EEG						
Excellent	24 (65)*	13 (35)	37	12 (33)*	24 (67)	36
Good + poor	27 (44)	35 (56)	62	10 (16)	52 (84)	62
Daily dosage of ACTH, mg/kg/d						
0.005–0.009	10 (48)	11 (52)	21	5 (24)	16 (76)	21
0.01–0.014	22 (67)	11 (33)	33	9 (27)	24 (73)	33
0.015–0.019	6 (35)	11 (65)	17	2 (12)	15 (88)	17
0.02–0.024	7 (39)	11 (61)	18	3 (18)	14 (82)	17
0.025–0.032	6 (60)	4 (40)	10	3 (30)	7 (70)	10
0.20–0.29	18 (53)	16 (47)	34	8 (24)	25 (76)	33
0.30–0.39	9 (53)	8 (47)	17	5 (28)	13 (72)	18
0.40–0.49	8 (47)	9 (53)	17	1 (6)	16 (94)	17
0.50–0.87	7 (41)	10 (59)	17	4 (25)	12 (75)	16
Brain volume loss on CT/MRI						
None + slight	31 (53)	28 (47)	59	13 (22)	46 (78)	59
Moderate + severe	8 (35)	15 (65)	23	2 (9)	20 (91)	22
Seizure outcome						
Seizure-free				20 (41)‡	29 (59)	49
Persistent seizures				2 (4)	46 (96)	48

Valutato immediatamente prima e dopo ACTH

STUDIO RETROSPETTIVO

Regime A: 0,015 mg/kg/dose in 18 (S= 11)
Regime B: 0,010 mg/kg/dose in 16 (S= 10)
ACTH i.m. ogni giorno x 2 settimane
Se spasmi o ipsaritmia dopo 2 settimane: ulteriori somministrazioni quotidiane/a giorni alterni per 1-2 settimane

	Total ($n=34$)		P value	Symptomatic ($n=21$)		P value	Cryptogenic ($n=13$)		P value
	Regimen A ($n=18$)	Regimen B ($n=16$)		Regimen A ($n=11$)	Regimen B ($n=10$)		Regimen A ($n=7$)	Regimen B ($n=6$)	
Cessation of spasms	17 (94%)	15 (94%)	ns	10 (91%)	9 (90%)	ns	7 (100%)	6 (100%)	ns
Number of injection[a]	5.2±3.1	9.0±6.4	<0.05	5.7±3.3	12.1±6.4	<0.05	4.4±3.1	4.3±2.3	ns
Total dose of ACTH (mg/kg)[a]	0.068±0.042	0.09±0.064	ns	0.069±0.041	0.121±0.064	<0.05	0.066±0.047	0.043±0.023	ns

Non differenze di efficacia o effetti collaterali.
N° iniezioni gruppo B > gruppo A
Dose totale di ACTH fino a cessazione spasmi non differisce
Sintomatici ricevono più iniezioni e dose totale maggiore di ACTH nel gruppo B.

CONCLUSIONI:

0,010 mg/kg/d adeguato per criptogenici
0,015 mg/kg/d raccomandato per sintomatici

Kondo et al., 2005

EFFETTI COLLATERALI RIPORTATI

Comparison of adverse effects between regimens A and B

	Total ($n=34$)		P value	Symptomatic ($n=21$)		P value	Cryptogenic ($n=13$)		P value
	Regimen A ($n=18$)	Regimen B ($n=16$)		Regimen A ($n=11$)	Regimen B ($n=10$)		Regimen A ($n=7$)	Regimen B ($n=6$)	
Hypertension	3 (17%)	1 (6%)	ns	3 (27%)	1 (10%)	ns	0	0	ns
Hypokalemia	1 (5.6)	0	ns	0	0	ns	1(8%)	0	ns
Glycosuria	0	0	ns	0	0	ns	0	0	ns
BW gain (%)	4.9±3.7	5.3±4.4	ns	4.8±4.1	4.1±2.6	ns	5.0±3.1	6.7±6.2	ns
BC gain (%)	3.8±4.1	4.7±4.3	ns	2.5±4.2	3.7±4.5	ns	6.1±2.8	6.7±3.4	ns
Infection	2 (11%)	1 (6%)	ns	1 (9%)	0	ns	1 (14%)	1 (17%)	ns
Irritability	17 (94%)	14 (88%)	ns	10 (90%)	9 (90%)	ns	7 (100%)	5 (83%)	ns
Somnolence	3 (17%)	8 (50%)	ns	2 (18%)	5 (50%)	ns	1 (14%)	3 (50%)	ns

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BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Extremely low-dose ACTH step-up protocol for West syndrome: Maximum therapeutic effect with minimal side effects

0,005 mg/kg/die ogni giorno per ≥ 2 settimane (massimo 3)
Controllo clinico ed EEG completo:
scalato in 1-2 settimane
In assenza di risposta:
incrementato a 0,025 mg/kg/die per 2 settimane
scalato in 2 settimane

Primo ciclo → Risposta completa (clinica + EEG): 17/31 (55%)
1 pz con buona risposta e 7/11 senza risposta → secondo ciclo
•Risposta completa: 2
•Risposta assente: 6 (9-18 somministrazioni aggiuntive, media 14)
4 che non hanno risposto al primo schema non hanno ricevuto il secondo

Risultato complessivo del protocollo (a breve termine): 19/31 (61%) risposta

Follow-up a lungo termine (>1 anno) n=27
13/27 in remissione all'ultimo follow-up (12/13 risposta al primo ciclo)

Unico fattore clinico predittivo di risposta completa: criptogenico vs. sintomatico.

ELSEVIER

Brain & Development 37 (2015) 449–454

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

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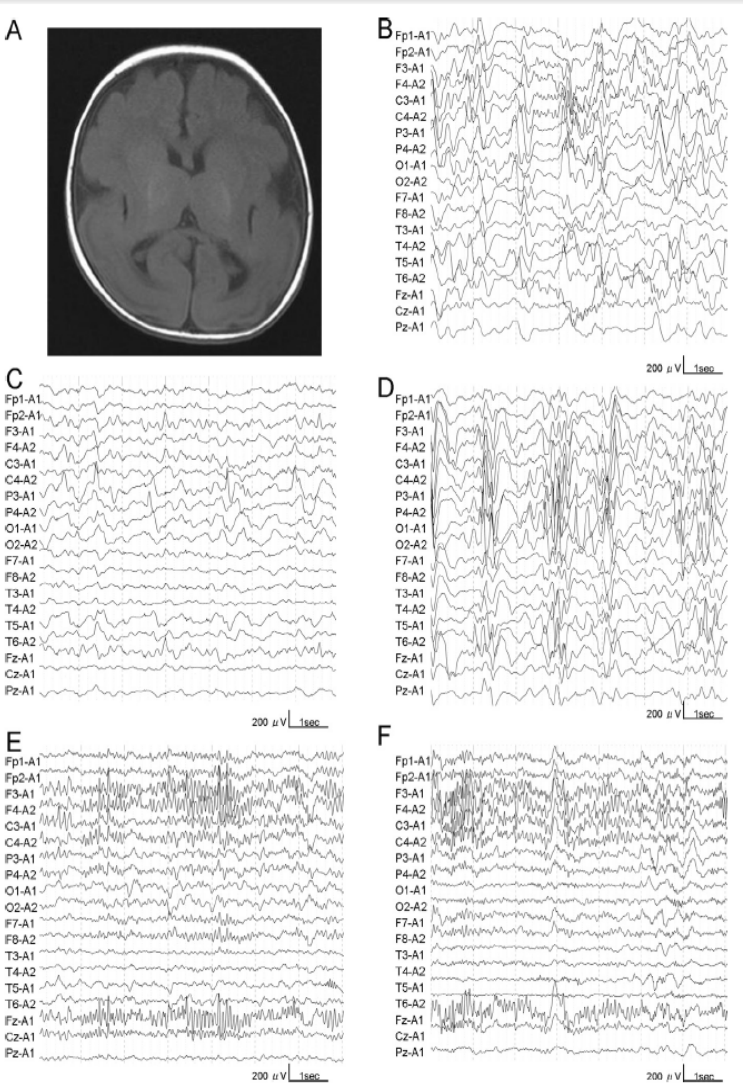
Case Report

Efficacy of long term weekly ACTH therapy for intractable epilepsy

Takehiko Inui [a,1,2], Tomoko Kobayashi [b,1], Satoru Kobayashi [a,c], Ryo Sato [a,b], Wakaba Endo [a,b], Atsuo Kikuchi [b], Tojo Nakayama [b], Mitsugu Uematsu [b], Masaru Takayanagi [d], Mitsuhiro Kato [e], Hirotomo Saitsu [f], Naomichi Matsumoto [f], Shigeo Kure [b], Kazuhiro Haginoya [a,b,*]

Case report
1 caso di spasmi infantili (lissencefalia)
A 3 mesi
Primo ciclo: 0,015 mg/kg/die per 2 settimane – scalato (0,015 mg/kg a gg alterni per 1 settimana, 0,0075 mg/kg a gg alterni per 1 settimana)
Risposta
Recidiva a 8 mesi

A 11 mesi (VPA + TPM + CZP)
Secondo ciclo:
protocollo iniziale (durata totale= 4 settimane)
poi
0,015 mg/kg 1 volta/settimana per 1 anno (esclusi episodi febbrili intercorrenti)
Follow-up di 1 anno: silenzio clinico
(VPA + TPM)



Inui et al., 2015

Reference	Design	Pts., N	Age at WS Onset (months)	Intervention	Primary End Point	Result/ Outcome, n (%)	Relapse Rate (%)
Low-dose vs high-dose ACTH							
Yanagaki (1999)[7]	P, R, C 4-6 weeks	25 (15 male) HD: 13 LD: 12	Mean (SD) HD cryptogenic: 4.4 (1.7) symptomatic: 5.2 (3.1) LD cryptogenic: 5 (1.4) symptomatic: 6.2 (4.6)	HD ACTH 0.025 mg/kg/day LD ACTH 0.005 mg/kg/day	Responder: cessation of spasms, resolution of hypsarrhythmia	Responders cryptogenic (n = 9) HD: 5/5 (100) LD: 3/4 (75), p = 0.44 symptomatic (n = 16) HD: 6/8 (75) LD: 6/8 (75), p = 0.99	1-year follow-up (n = 17): cryptogenic HD: 1/3, LD 0/3; symptomatic HD: 2/5, LD 3/6
Hrachovy (1994)[8]	P, R 12 weeks	50 HD: 24 LD: 26	NR	HD ACTH 150 IU/m²/day for 3 weeks; 80 IU/m²/day for 2 weeks; 80 IU/m²/day every other day for 3 weeks; 50 IU/m²/day every other day for 1 week; tapered to zero during a 3-week period LD ACTH 20-30 IU/day for 2-6 weeks	Responder: cessation of spasms, resolution of hypsarrhythmia	Cessation of spasms HD: 13/26 (50) LD: 14/24 (58) p value not significant Resolution of hypsarrhythmia HD: 6/26 (23) LD: 5/24 (21)	HD: 2/13 (15) LD: 3/14 (21) p > 0.05
Hamano (2006)[9]	RCR 2-4 weeks	135	Mean (SD) 5.8 (2.9)	ACTH, mg/kg/day 0.02, 0.015, 0.0125	Responder: cessation of spasms, resolution of hypsarrhythmia	Responders 0.02 mg/kg/day: 63/72 (88) 0.015 mg/kg/day: 11/13 (85) 0.0125 mg/kg/day: 39/50 (78)	1-year follow-up: 54/135 (40)
Low-dose regimens							
Ito (2002)[10]	RCR 1-5 weeks	138 (72 male)	Mean (range) 7.8 (1.5-60)	ACTH, mg/kg/day 0.005-0.032 for 1-5 weeks	Initial efficacy, ADR, long-term outcomes	Response: Excellent (total cessation of seizures) 106/138 (76) Good (50% decrease in seizure frequency) 23/138 (17) Poor (<50% decrease in seizure frequency) 9/138 (7)	2-year follow-up 48%
Kondo (2005)[11]	RCR 2 weeks + 1-2 additional weeks if symptoms persistent	34 (male: regimen A, 9; regimen B, 9)	Mean (SD) regimen A: 5.1 (2.7) regimen B: 5.8 (2.8)	ACTH, mg/kg/dose regimen A: 0.015 regimen B: 0.01	Cessation of spasms, resolution of hypsarrhythmia	Cessation of spasms regimen A: 17/18 (94) regimen B: 15/16 (94) p = 0.25	Regimen A: 10 (59) Regimen B: 5 (33)
Oguni (2006)[12]	RCR 2 weeks; 3-week maximum	31 (15 male)	Median (range) 7.5 (3-16)	ACTH First treatment course: 0.005 mg/kg/day for at least 2 weeks (3-week maximum) + 1- to 2-week taper Second treatment course (if response inadequate): step-up of 0.025 mg/kg/day for 2 weeks + 2-week taper	Short- and long-term therapeutic results; ADR	Short-term results 17 (55%) controlled with first treatment course 8 received second treatment course; only 2 had complete suppression of WS	1-year follow-up 14/27 (52)

Shumiloff et al., 2013

Three-Week Combination Treatment With ACTH + Magnesium Sulfate Versus ACTH Monotherapy for Infantile Spasms: A 24-Week, Randomized Follow-Up Study in China

Li-Ping Zou, MD, PhD[1,2]; Xu Wang, MD, and
Chun-Hong Chen, MD, MS[2]; Wei Zhao[3];

[1]Department of Pediatrics, Chinese PLA Gene
Beijing Children's Hospital, The Capital Uni
Electroencephalography, Department of N
Medical Sciences, Beijing, China; and [4]T
Neurology, Beijing Children's Hospital,

ABSTRACT

Back
and
f
gs. Adrenocorticot
en the treatment of choice for
associated with infection
ion is an N-methyl-
petitive antagonist
has antiepileptic
oprot
ctive: This
ficacy and
ility of ACTH
$MgSO_4$)

nd 10 (52.6%) in the control group. On EEG,
47.4%) in the ACTH + $MgSO_4$ group
recovery (normalized EEG), 5 (26.3%)
rovement (multifocal spike wave),
improvement (hypsarrhythmia
nia). At 4 weeks, in the control
gr
achieved complete recovery,
6 (31.
provement, and 8 (42.1%)
had no
12 patients who were
seizure fre
ACTH + $MgSO_4$ group,
11 (91.7%)
ery (normalized EEG);
this rate was
in the control group.
In the ACTH
he change from base-

Re
15 female
group). At 12
ceived ACTH + $MgSO_4$
control group were seizure free. At 24 weeks, seizure-free rates were 12 (63.2%) in the ACTH + $MgSO_4$

Nell'analisi statistic
•prove che i 2 grup
isticamente so
o riportate
•la regressione logi
i abbiamo solo in
relazion

Anche la Cochrane s
non è stato fatto il co
Troppo ottimistico che
ia la differenza?

Gli effetti sullo sviluppo p
riportati come cont
ei 2 singoli gruppi
fra *prima* e *dopo* il tratta

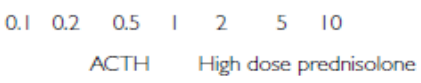
epted for publication January 7, 2010.
doi:10.1016/j.clinthera.2010.04.008
0149-2918/$ - see front matter

PREDNISOLONE AD ALTE DOSI

Comparison 10 ACTH versus high-dose prednisolone, Outcome 1 Cessation of infantile spasms.

Study or subgroup	ACTH n/N	High dose pred-nisolone n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Lux 2004	19/25	21/30		100.0 %	1.35 [0.41, 4.38]
Total (95% CI)	**25**	**30**		**100.0 %**	**1.35 [0.41, 4.38]**

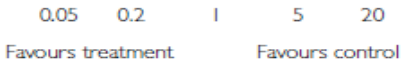
Total events: 19 (ACTH), 21 (High dose prednisolone)
Heterogeneity: not applicable
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable



Comparison 10 ACTH versus high-dose prednisolone, Outcome 2 Resolution of EEG.

Study or subgroup	ACTH n/N	High dose pred-nisolone n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Lux 2004	16/18	10/14		100.0 %	3.04 [0.52, 17.66]
Total (95% CI)	**18**	**14**		**100.0 %**	**3.04 [0.52, 17.66]**

Total events: 16 (ACTH), 10 (High dose prednisolone)
Heterogeneity: not applicable
Test for overall effect: Z = 1.24 (P = 0.22)
Test for subgroup differences: Not applicable



Risposta a 14 gg da inizio terapia:
70% prednisolone 76% ACTH (0.5/0.75 mg a gg alterni) vs 54% GVG (50/150 mg/kg/d)
Lux et al., 2004

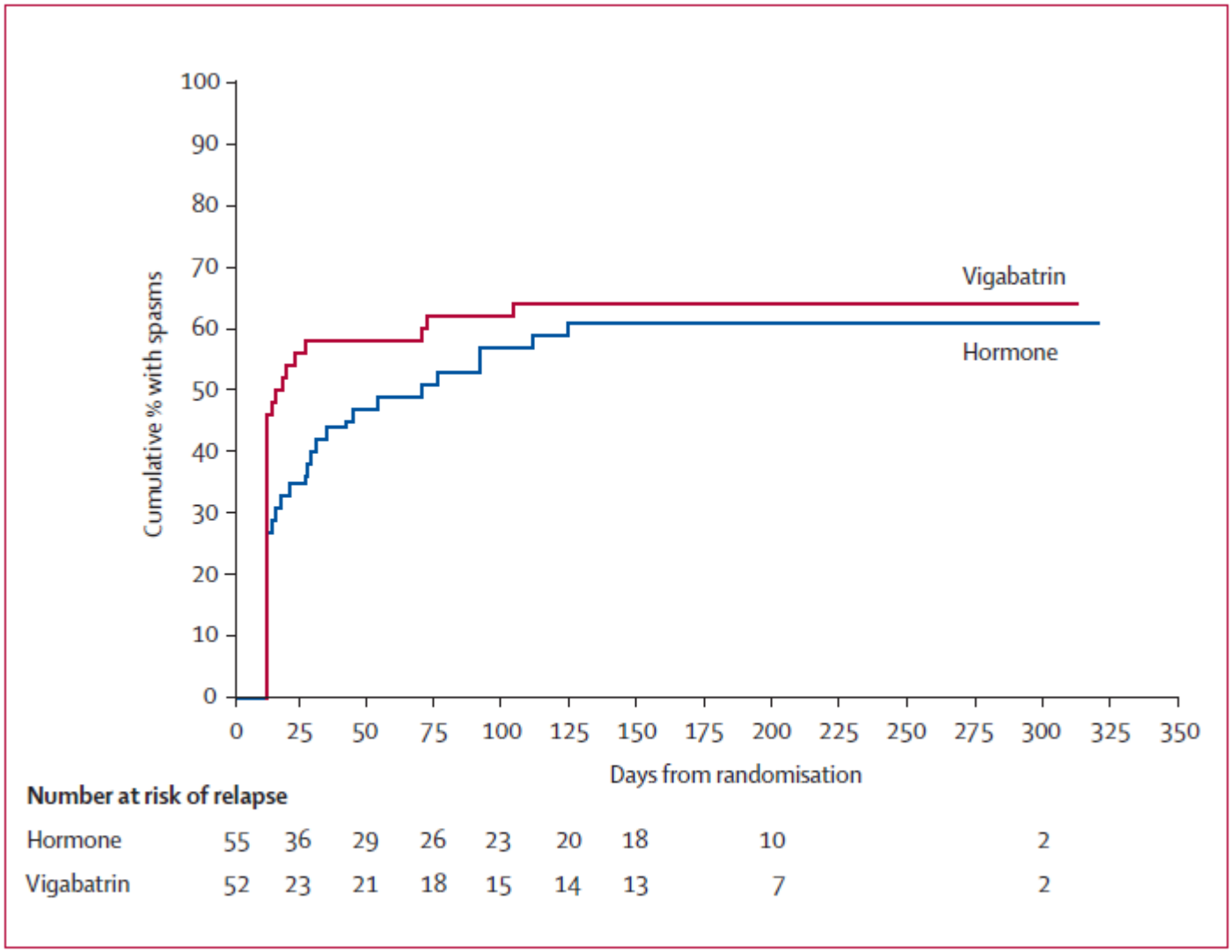


Figure 2: Actuarial curves showing cumulative percentages with spasms at any time after day 12

The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial

*Andrew L Lux, Stuart W Edwards, Eleanor Hancock, Anthony L Johnson, Colin R Kennedy, Richard W Newton, Finbar J K O'Callaghan, Christopher M Verity, John P Osborne, the trial steering committee on behalf of participating investigators**

	Prednisolone (n=30)	Tetracosactide (n=25)	Hormonal treatment subgroups (n=55)	Vigabatrin (n=52)
Number of infants with adverse events	19	11	30	28
Treatment unchanged	14	8*	22	19
Treatment not increased as protocol required	3	2*	5	7
Treatment reduced	1	1*	2	2
Treatment stopped	1	1*	2	0
Specific adverse events†				
Gastrointestinal	7	5	12	11
Irritability	12	7	19	2
Drowsiness	5	1	6	14
Infection‡	3	0	3	5
Increased appetite	4	3	7	1
Dermatological	1	3	4	2
Fluid and electrolyte (including high blood pressure)	3	2	5	0
Neuropsychiatric (including sleep disturbance)	1	0	1	4
Hypertonia	0	2	2	0
Treatment for varicella exposure	1	1	2	0
Other	3	4	7	5

*Treatment actions not mutually exclusive. †No adverse events reported in following categories: hypotonia, endocrine/metabolic (including excessive weight gain), ophthalmic (although visual field losses would be undetectable), musculoskeletal, varicella infection, and immunosuppression. ‡Fever, culture-positive disease. or treatment with antibiotics, but not varicella.

Table 4: Adverse events reported during first 14 days of study

Incidenza simile di effetti collaterali.
PA > 110/80 mmHg:
23% nel gr. prednisolone e 16% nel gr. ACTH.
PA > 120/90 mmHg:
13% nel gr. prednisolone e 16% nel gr. ACTH.

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Treatment of infantile spasms with very high dose prednisolone before high dose ACTH

Shaun A. Hussain, MD, MS[1], **Shlomo Shinnar, MD, PhD**[2], **Grace Kwong**[1], **Jason T. Lerner, MD**[1], **Joyce H. Matsumoto, MD**[1], **Joyce Y. Wu, MD**[1], **W. Donald Shields, MD**[1], and **Raman Sankar, MD, PhD**[1]

[1]Department of Pediatrics, Division of Neurology, Mattel Children's Hospital and David Geffen School of Medicine at UCLA, Los Angeles, California, USA

[2]Departments of Neurology, Pediatrics, and Epidemiology and Population Health, Montefiore Medical Center, Albert Einstein College of Medicine Bronx, New York, USA

Significance—Very high dose prednisolone demonstrated significantly higher efficacy than previously reported for lower doses in prior studies. High dose ACTH may be superior to very high dose prednisolone, and in lieu of a definitive clinical trial, the choice between prednisolone and ACTH for initial treatment of infantile spasms remains controversial.

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Brief Communication

High-dose oral prednisolone for infantile spasms: An effective and less expensive alternative to ACTH

Eric H. Kossoff*, Adam L. Hartman, James E. Rubenstein, Eileen P.G. Vining

The Johns Hopkins Medical Institutions, Baltimore, MD, USA

A B S T R A C T

The ideal treatment of infantile spasms is unclear, but many studies advocate hormonal treatment. In the United States, intramuscular ACTH is most widely used, despite the problematic financial cost and side effect profile. Since September 2007, we have replaced ACTH with high-dose oral prednisolone (40–60 mg/day) according to the 2004 United Kingdom Infantile Spasms Study (UKISS). Ten of 15 (67%) infants with new-onset and previously treated infantile spasms became spasm free within 2 weeks; 4 later recurred. More children with an idiopathic etiology for infantile spasms were spasm free than were symptomatic cases (88% vs 43%, $P = 0.10$). Spasm freedom was equivalent to our most recent 15 infants receiving ACTH, with 13 (87%) responding, $P = 0.16$. Oral prednisolone had fewer adverse effects (53% vs 80%, $P = 0.10$) and was less expensive ($200 vs approximately $70,000) than ACTH. We now routinely recommend oral prednisolone to all families of children with infantile spasms.

EFFETTI COLLATERALI

Gruppo prednisolone: 53% (irritabilità, edema, ipertensione, eccessivo incremento ponderale)

Gruppo ACTH: 80% (simili)

Wanigasinghe et al., 2015

PREDNISOLONE vs. ACTH

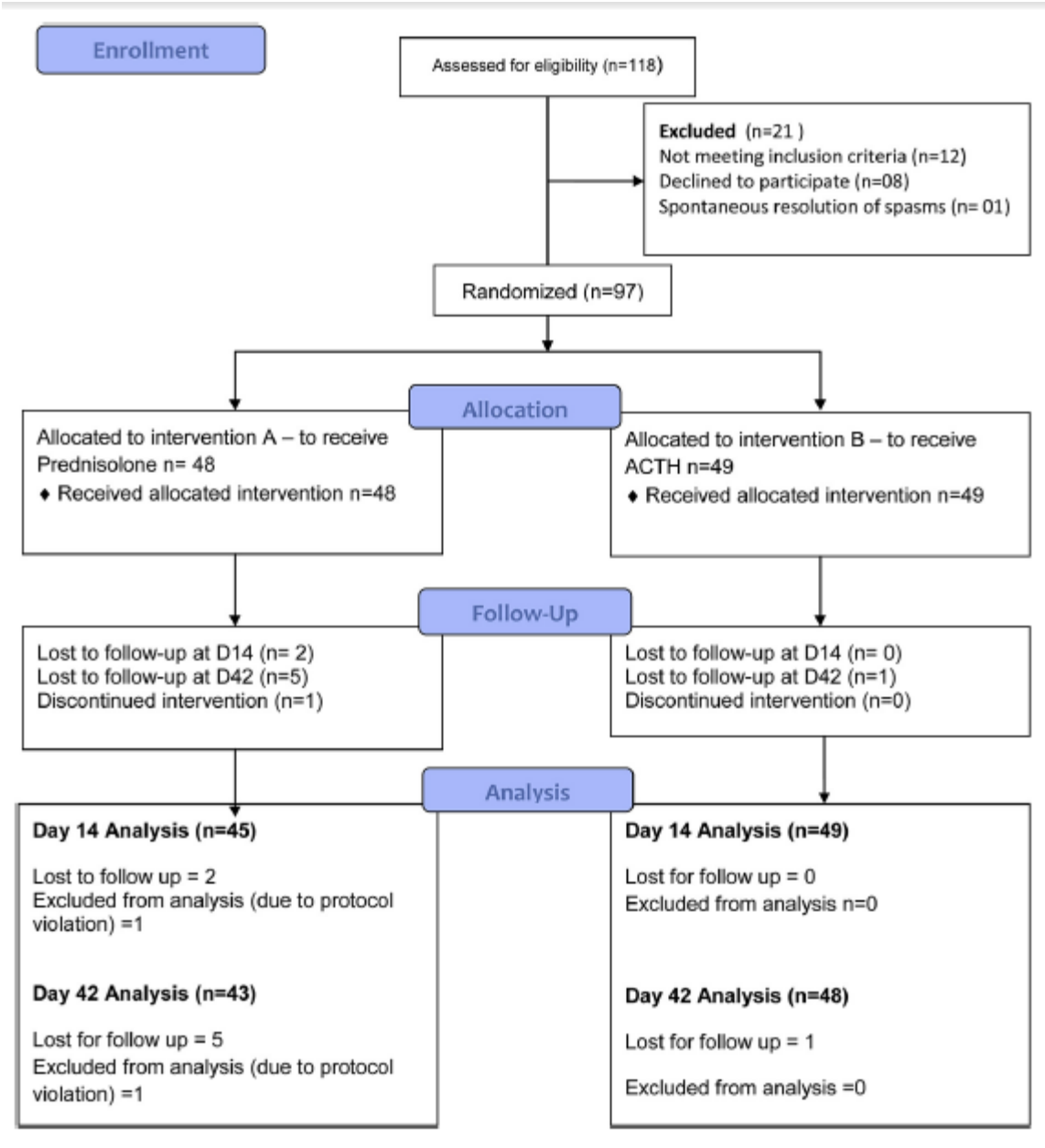
Singolo centro, singolo cieco, randomizzato.
•Prednisolone: 40-60 mg/die per os per 14 gg
•ACTH sintetico long-acting: 40-60 UI (0.5-0.75 mg) a gg alterni

n= 97
n= 48 prednisolone
n= 49 ACTH

Entro il 14° g:
•risposta clinica (28/48 58.3% vs 18/49 36.7%) (sig)
•risposta elettroclinica (EEG NREM) (21/48 43.7% vs 9/49 18.3%) (sig)

A 28 gg:
•Silenzio clinico (15 vs 6) (sig)

Giorni necessari per cessazione spasmi:
•3.85+/- 2,4 prednisolone
•8,65 +/- 3,7 ACTH (sig)



EFFETTI COLLATERALI

Side Effect	Prednisolone		ACTH		Level of Significance*
	No.	%	No.	%	
Increased appetite	28	73.7	19	43.2	0.005
Weight gain	19	50.0	14	31.8	0.09
Frequent crying spells	16	42.1	11	25.0	0.1
Drowsiness	4	10.5	7	15.9	0.48
Cushingoid features	8	21.1	9	20.5	0.95
Insomnolence	3	7.9	2	4.5	0.53
Lethargy	2	5.3	2	4.5	0.88
Reduction in social behavior	2	5.3	1	2.3	0.47
Abdominal distension	8	21.1	0	0	0.001*
Hypertension	1	2.6	1	2.3	0.92
Increased susceptibility to infection†	0	0.0	1	2.3	0.35
Irritability	8	21.1	5	11.4	0.23
Nausea	1	2.6	1	2.3	0.92
Vomiting	2	5.3	1	2.3	0.47
Diarrhea	2	5.3	3	6.8	0.77
Dyspepsia	2	5.3	2	4.5	0.88
Electrolyte imbalances	2	5.3	0	0.0	0.12

* Because of multiple comparisons, the level of significance was adjusted to $P < 0.00294$ by Bonferroni correction: $\alpha_{adjusted} = \alpha/c$, where α is the overall experiment-wise alpha (0.05); c is the number of comparisons made (17).

† Increased susceptibility to infection was assessed by history examination to look for presence of fever, any evidence of local or systemic infection.

Un soggetto ha sospeso terapia con prednisolone per ipertensione.

n = 63
4 mg/kg/d vs. 2 mg/kg/d
Cessazione spasmi in 14° giornata: 51,6% vs 25% (p = 0.03)
Come da valutazione genitoriale

Chellamuthu et al., 2014

n= 20 (3–53 m)
40 mg/d **prednisone** 2 settimane
Controlli T0, 2 e 7 settimane (fine trattamento)
Follow-up: 2–14 m.
16/20 (80%) risposta completa dopo 2 settimane 13/20 (65%) dopo 7 settimane
19/20 ipsaritmia o ipsaritmia modificata 12/19 risoluzione completa, 7/19 parziale (sia a 2 che a 7 settimane)
Periodo libero da crisi: 11 gg-14 m.
Recidive: 35.3%.

Yi et al., 2015

Revisione sistematica della letteratura (Arya et al., 2012):
Sulla base dei dati disponibili, efficacia corticosteroidi ad alte dosi simile ad ACTH a basse dosi e inferiore ad ACTH ad alte dose (attuale standard di trattamento).

Original Article

Outcomes in Treatment of Infantile Spasms With Pulse Methylprednisolone

Journal of Child Neurology
25(8) 948-953

DOI: 10.1177/0883073809356107
http://jcn.sagepub.com
SAGE

John R. Mytinger, MD,[1,2] Mark Quigg, MD, MS,[1] William C. Taft, MD, PhD,[1] Marcia L. Buck,[2] and Robert S. Rust, MA, MD[1,2]

20 mg/kg/d metilprednisolone ev per 3 giorni consecutivi
Seguito da 2 mesi di prednisolone orale progressivamente ridotto
Remissione spasmi in 2-6 giorni in 5/10 (50%)
Nel sottogruppo trattato ≤ 1 mese da esordio: 5/6 (83%) entro 6 giorni.

valutazione del risultato a 2 settimane (remissione, ricorrenza, persistenza)
basata su intervista telefonica

TABLE 1. Treatment Guidelines Recommended by PERC

Days	Dose
ACTH	
1–14	75U/m^2 IM twice daily
15–17	30U/m^2 IM in the morning
18–20	15U/m^2 IM in the morning
21–23	10U/m^2 IM in the morning
24–29	10U/m^2 IM every other morning (3 total doses)
Prednisolone	
1–14	10mg oral 4 times daily[a,b]
15–19	10mg oral 3 times daily[a]
20–24	10mg oral 2 times daily
25–29	10mg oral daily
Vigabatrin[b,c]	
1–3	50mg/kg/day divided 2 times daily
4–6	100mg/kg/day divided 2 times daily
>7	150mg/kg/day divided 2 times daily

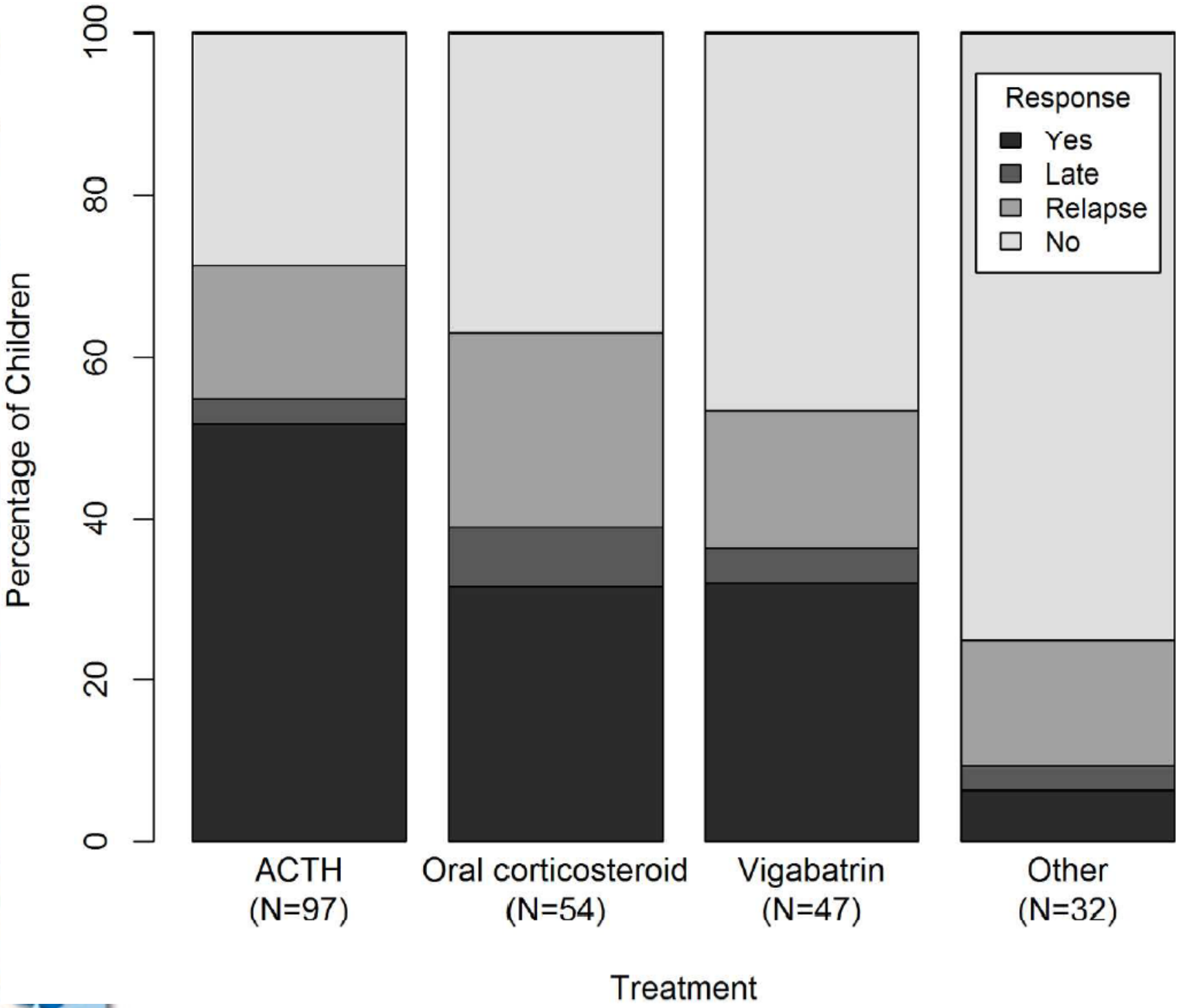
[a]If there is no clinical response after day 7 (ie, no 24-hour period free of infantile spasms), the dose can be increased to 20mg 3 times daily. If done, the taper schedule from days 15–19 would be 10mg 4 times daily, then proceeding as in the table beginning on day 20.
[b]If no clinical response by day 14, consider alternative treatment.
[c]Side effects (eg, sedation, hypotonia) may necessitate slower titration.
ACTH = adrenocorticotropic hormone; IM = intramuscular; PERC = Pediatric Epilepsy Research Consortium.

Response to Treatment in a Prospective National Infantile Spasms Cohort

Kelly G. Knupp, MD,[1] Jason Coryell, MD,[2] Katherine C. Nickels, MD,[3] Nicole Ryan, MD,[4] Erin Leister, MS,[5] Tobias Loddenkemper, MD,[6] Zachary Grinspan, MD, MS,[7] Adam L. Hartman, MD,[8] Eric H. Kossoff, MD,[8] William D. Gaillard, MD,[9] John R. Mytinger, MD,[10] Sucheta Joshi, MD,[11] Renée A. Shellhaas, MD, MS,[11] Joseph Sullivan, MD,[12] Dennis Dlugos, MD,[4] Lorie Hamikawa, MD,[13] Anne T. Berg, PhD,[14] John Millichap, MD,[14] Douglas R. Jr Nordli MD,[14] Elaine Wirrell, MD,[3] and the Pediatric Epilepsy Research Consortium

Characteristic			Response to treatment: Non-response N=136		Response N=94	P-value*
Prior seizures	Yes	55	(73)	20	(27)	0.002
	No	81	(52)	74	(48)	
History of AED use	Yes	58	(70)	25	(30)	0.013
	No	78	(53)	69	(47)	
Etiology	Genetic/metabolic/unknown abnormal	66	(62)	40	(38)	0.070
	Prior brain injury/MCD/other structural	56	(62)	34	(38)	
	Unknown normal	14	(41)	20	(59)	
Developmental issues	None/Mild	30	(47)	34	(53)	0.025
	Moderate/Severe	103	(63)	60	(37)	
Treatment	ACTH	44	(45)	53	(55)	<0.001
	Oral corticosteroid	33	(61)	21	(39)	
	Vigabatrin	30	(64)	17	(36)	
	Other	29	(91)	3	(9)	

Response To Treatment In A Prospective National Infantile Spasms Cohort.
Knupp et al., Ann Neurol. 2015 Dec 24.



Risposta= 2 sett
Tardiva= 3m

Durata F/U: 3m
n= 230
F/U completo

Dosaggi ACTH variabili (alti e bassi)
un unico gruppo per analisi statistica

Response To Treatment In A Prospective National Infantile Spasms Cohort.
Knupp et al., Ann Neurol. 2015 Dec 24.

Covariate		Crude Relative Risk (95% CI)	Adjusted* Relative Risk (95% CI)	Adjusted** Relative Risk (95% CI)
Treatment	ACTH	5.81 (4.10, 9.40)	5.50 (3.83, 9.18)	5.24 (3.59, 8.70)
	Oral corticosteroid	4.15 (2.78, 6.76)	4.11 (2.78, 6.52)	3.88 (2.63, 6.46)
	Vigabatrin	3.91 (2.60, 6.45)	3.92 (2.64, 6.50)	3.69 (2.55, 6.18)
	Other	Reference	Reference	Reference
Etiology	Genetic/metabolic/unknown abnormal	Reference	Reference	---
	Prior brain injury/MCD/other structural	1.00 (0.69, 1.43)	1.06 (0.98, 1.16)	---
	Unknown normal	1.56 (1.04, 2.22)	1.39 (0.89, 1.99)	---
Development	None/Mild	1.42 (1.04, 2.01)	---	1.23 (0.86, 1.72)
	Moderate/Severe	Reference	---	Reference

Relative risks, or relative probabilities, of treatment response between groups were estimated using the method of Kleinman and Norton applied logistic regression models; confidence intervals estimated via bootstrapping

*Model including treatment and etiology as covariates

**Model including treatment and development as covariates

Non discussi gli effetti collaterali

Terapia predice risposta anche correggendo per SPM ed eziologia.

Nei modelli aggiustati per tipo di terapia, effetto di SPM ed eziologia sono più deboli rispetto a modelli predittivi non corretti.

VIGABATRIN COME FARMACO DI PRIMA LINEA

n= 180
GVG prima linea
T0 valutazione SPM
Risposta n= 101 (56,9%) mediam. in 5 gg
Migliore se SPM all'esordio n.n.

Follow-up: 2.4-18.9 aa (media 10.64,DS 4.40)
Fra i responsivi:
38.1% deficit neurologici severi
42% epilessia
42.2% deficit cognitivo

Gruppo sintomatico + E.O.N. alterato all'esordio: P peggiore ed outcome più sfavorevole vs idiopatico
(85.1% e 81.6% vs 14.9% e 0%).
Pz idiopatici: tutti QI normale tranne un borderline cognitivo.

Djuric et al., 2014

	Primary outcome		
	Favorable	Unfavorable	
Etiology	Idiopathic	Symptomatic cryptogenic	$\chi^2(2) = 7.076$, $p = 0.029$
Type of spasms	Extensor	Flexor combined	$\chi^2(2) = 6.299$, $p = 0.043$
Psychomotor development before IS	Normal	Abnormal	OR = 4.2, 95% CI 2.1–8.3

n= 61
18/61 (30%) risposta EEG e clinica ≤4 settimane
2/18 (11%) recidiva spasmi
17/61 (27%) silenzio clinico a 15 m (+/- 6,6)
43 (70%) non risposta:
•28 risposta ad ACTH
•10 risposta a prednisolone
•5 ricevono altra T

•SPM n.n. predittivo di risposta al GVG
•Anamnesi perinatale positiva predittiva di mancata risposta

Jones et al., 2015

ALTRI FATTORI

- Età d'esordio degli spasmi

<3 m, < 4m ?

- Tempo trascorso prima dell'inizio del trattamento

anche aggiustando per eziologia, età di esordio e terapia

Andamento riduzione quoziente di sviluppo→ assenza soglia

O' Callaghan et al., 2011

Durata ipsaritmia → prognosi cognitiva

Rnere-Primec et al.,. 2006

Durata spasmi (TSC) → aumento R prognosi sfavorevole SPM

Goh et al., 2005

PUNTI DI DISCUSSIONE

ACTH:

•Schemi «step-up» da basse/bassissime dosi vs. tempi necessari per ottenere risposta clinica: prognosi cognitiva?

•Schemi differenziati in base a eziologia (C vs. S)? o in base a SPM?

•Oppure dosi differenziate?

PREDNISOLONE:

•Uso ad alte dosi? (o prove di efficacia ancora limitate?)

GVG:

•(sclerosi tuberosa a parte)
•idiopatici?
•lesionale focale?