Epileptic Spasms: Evidence for oral corticosteroids and implications for low and middle income countries (Systematic Review)

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Table of Contents

Declaration

I, ……*Sharika Raga*……, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Implementation of international guidelines for the treatment of epileptic spasms, is challenging when access to adrenocorticotrophic hormone (ACTH) and vigabatrin is restricted, especially in Low and Middle Income Countries (LMIC). Oral corticosteroids are alternative interventions but evidence for the optimal agent, dose, duration, efficacy and long-term effects are lacking.

A systematic review of the literature was performed to assess the quality of evidence of prednisone and prednisolone (oral corticosteroids) for the management of epileptic spasms. There is level C recommendation based on class III evidence to support the efficacy of oral corticosteroids for the acute clinical control of epileptic spasms and EEG resolution. Efficacy of oral corticosteroids in comparison to the internationally recommended intervention of ACTH has class IV evidence supporting level U recommendation. Similarly, there is no data on the risk of relapse with oral corticosteroids (class IV, level U), compared to ACTH. There is class IV evidence supporting level U recommendation for the safety of oral corticosteroids and class II evidence for level B recommendation for ACTH. In terms of oral corticosteroids and effects on long-term development there is class IV evidence leading to level U recommendation, compared to class III evidence supporting level C recommendation for ACTH.

Randomized controlled studies are needed to compare oral corticosteroids with ACTH, the optimal dosage and regimen as well as the long-term neurodevelopmental outcomes. Based on the limited existing studies a treatment guideline for LMIC is proposed which could be used to standardize interventions permitting clarification of these unmet questions.

Acknowledgements and contributions

I gratefully acknowledge and thank my supervisor, Professor Jo Wilmshurst, for her guidance and support.

Contributions of authors

Sharika V Raga - wrote the protocol, performed the literature review, collated and analysed the data and wrote the main draft and were the lead author.

Jo M Wilmshurst - conceptualised the study theme, supervised the project development, critiqued the protocol content, supervised the data analysis and provided input the writing of the main draft contributing to revisions of the text.

Dedications

I dedicate this dissertation to my cat, Maximus, who literally sat beside me for virtually the entire duration of this project.

List of Tables

List of Figures

Abbreviations

ACTH: adrenocorticotrophic hormone
ES: epileptic spasms
UKISS: United Kingdom Infantile Spasms Study
TSC: Tuberous Sclerosis Complex
LMIC: low and middle income countries
AAN: American Academy of Neurology

Introduction

Access to hormonal and synthetic adrenocorticotrophic hormone (ACTH) is limited in many regions of the world [1]. This report explores the evidence to support use of oral corticosteroids, namely prednisolone or prednisone, in comparison to ACTH and other agents in the management of children with epileptic spasms (ES).

The incidence of childhood epilepsy is highest in the infantile period and epileptic spasms are the most common seizure type in this age period [2].

Epileptic spasms are characterized by a brief contraction followed by a sustained tonic contraction of the neck, trunk, upper and lower legs and may be flexor, extensor or mixed[3]. They tend to occur in clusters, usually while awakening or just before sleep[4]. Spasms are frequently misdiagnosed with conditions such as colic, gastrooesophageal reflux and constipation, which results in delayed intervention[5]. The diagnosis of epileptic spasms is based on the semiology of the seizure and the interictal pattern of hypsarrhythmia on the EEG [6]. Hypsarrhythmia is defined as random high voltage slow waves accompanied by focal, multifocal or generalized spikes [7]. Variations from classic hypsarrhythmia are called modified hypsarrhythmia and may include focality, burst suppression, slow waves without spikes and partial preservation of the background [5].

The incidence of epileptic spasms in high income countries range between 0.25 and 0.42 per 1000 live births per year, peak onset is between 4-6 months, with a slight male preponderance [8]. The term “epileptic spasms” replaced “infantile spasms”, as the seizure type may persist or have the potential to develop beyond the infantile period [9].

The United Kingdom Infantile Spasms Study (UKISS) found that the most common aetiologies for ES were hypoxic ischaemic encephalopathy (10%), chromosomal (8%), cerebral malformations (8%), cerebrovascular disease (8%), Tuberous Sclerosis Complex (TSC) (7%), periventricular leukomalacia or haemorrhage (5%) but in 33% no cause could be identified. [10] Data was collected from a high income resource equipped setting. Data is

limited on epilepsy in Africa in general, especially from sub-Saharan Africa, and even less so for this specific seizure type. A study based in rural Uganda in 1997, found that 7 out of 440 children with epilepsy, had a history suggestive of “infantile spasms”[11]. However, this may be an underestimation, since lack of resources, such as EEG, made it challenging to make a syndromic diagnosis[11].

Additional challenges facing Low and Middle Income Countries (LMIC) include greater numbers of aetiologies, such as perinatal asphyxia, which is associated with worse long term outcome [12].

Epileptic spasms are difficult to treat and associated with a high morbidity, with up to 90% of patients having intellectual disability [5, 13]. The persistence of hypsarrhythmia appears to be associated with ongoing epileptic encephalopathy, as such it is important to treat this finding until there is resolution on the EEG.[5] This differs from standard approaches in the management of epilepsy, where treatment of clinical events is promoted. For infants with epileptic spasms “normalization” of the EEG plays a critical role with regards to long-term developmental outcome. International evidence based recommendations support use of ACTH graded at level B and vigabatrin at level C, as graded according to the American Academy of Neurology Practice Parameters following systematic review [14, 15]. According to the Cochrane review by Hancock *et al* hormonal treatment resolves spasms in more infants than vigabatrin, and if prednisolone or vigabatrin are used, high dose is recommended [16].

The lag time refers to the time taken between ES onset and intervention with treatment. Early cessation of spasms and a shorter lag time to treatment result in a reduced total duration of epileptic encephalopathy and resultant developmental delay [17]. Prolonged lag time and acquired aetiologies (e.g. HIE, post-infectious) in LMICs result in lower rates of spasm freedom compared to high income countries. This is further compounded by lack of

health-seeking behaviour of parents, lack of awareness among health care professionals and inappropriate antiepileptic drug use [18].

A systematic review of the literature was undertaken to establish the quality of evidence relating to the use of oral prednisolone and prednisone in the management of children with epileptic spasms in comparison to agents such as ACTH and vigabatrin. This review was driven by the need to develop a recommendation to standardize a safe and effective regimen using this product over other agents, such as ACTH and vigabatrin in LMICs, where access to these internationally recommended agents is lacking.

Systematic review

Using the MeSH terms “infantile spasms” and “prednisolone” and keywords “epileptic spasms”, “treatment”, “management”, “prednisone” and “oral corticosteroids” in Pubmed, Web of Science, Scopus incl. Embase, Medline, Africa-Wide, Cinahl, Cochrane reviews and clinical trials.com a total of 114 studies were found between 1990-2017, n=96 were excluded as they did not address the study question. There were n=18 studies in total, n=14 addressing the intervention and immediate outcome and n=4 the long-term outcome [17, 19-21]. Search terms were broad to encompass any studies which utilised oral corticosteroids in the management of ES. Studies were critiqued for directness to the study question of “efficacy in the management of ES” and consistency in study methodology across studies to permit comparison of outcome data. Inclusion criteria included clinical human studies and articles in English. Review articles were checked for additional papers not captured by the search. Quality of data was graded according to the American Academy of Neurology (AAN) practice parameters [15]. In accordance with AAN practice parameters, level A evidence recommendations are established as effective, ineffective or harmful, level B probably effective, ineffective or harmful, level C possibly effective, ineffective or harmful and

level U data is inadequate or conflicting [15, 22]. Findings from the included studies are summarised in Table 1, based on expert opinion.

Management of epileptic spasms

Standardized management protocols for infants with epileptic spasms have resulted in an increase of affected patients receiving recommended first-line treatment, with improved remission rates three months after diagnosis [23]. For children whose spasms result from aetiologies, excluding TSC, ACTH is the preferred first line intervention (level B recommendation), at either low or high dose (level B recommendation)[14]. Evidence supports a level A recommendation that vigabatrin should be the first line treatment for epileptic spasms in children with TSC [24]. According to the meta-analysis in 2012, there is insufficient evidence to recommend the use of oral corticosteroids for the short-term treatment of epileptic spasms (level U recommendation). There is weak evidence that the use of ACTH or prednisolone, in children who were previously classified as having cryptogenic epilepsy may lead to an improved developmental outcome (level C recommendation) [14], but no data specifically addressing prednisone.

Oral corticosteroids, such as prednisone and prednisolone, are increasingly being used off-label for the treatment of epileptic spasms [1, 14, 25]. The product is less expensive, easy to administer and readily available worldwide[26]. Prednisolone is the active form of prednisone and should not be considered as equivalent treatments for infants, who have a reduced capacity to metabolise prednisone in the first 6 months of life [27]. Prednisone is not as effective as its active form[27]. In Africa, most institutions will have access to prednisone rather than prednisolone. The mechanism of action of prednisone/prednisolone and ACTH in epileptic spasms in not known. It has been proposed that ACTH may act via downstream cortisol effects as well as central melanocortin receptor signalling, therefore the potential superiority of ACTH is mechanistically plausible [28].

Access to ACTH is limited, especially in resource-poor settings, by high cost, discomfort from injections and duration of hospitalization [18]. In the US, after Questcor acquired the rights to ACTH the price increased dramatically and since then the company has maintained the monopoly. ACTH (natural gel) costs approximately US$150 000 per treatment course compared to US$200 for prednisolone[1]. In South Africa, a 10 day course of ACTH (synthetic) costs approximately ZAR200 000 (US$17 250) and 14 day course of prednisone ZAR17 (US$1,5). The National Essential Medicines List Committee, appointed by the Minister of Health in South Africa, is responsible for formulating and revising the National List of Essential Medicines, in order to guide rational use of these essential medicines [29]. Based on issues of cost and access to care in 2016 the South African Essential Drug committee removed ACTH and vigabatrin from the national code list [30]. In a setting where previously there was capacity for treatment of ES in line with international recommendations, this policy returned the country to the situation evident in most other sub-Saharan Africa settings, where the only viable agent is likely to be prednisone. As a result an urgent national and regional need arose to establish an alternate evidence based guideline for the management of ES using available agents.

Whilst there is a significant body of data for the management of ES with ACTH which supported its inclusion in guidelines and Cochrane review [14, 16], based on the systematic review (table 1) the same cannot be said for oral prednisone or prednisolone. Table 1 illustrates this in the summaries of the existing studies. Of the identified studies assessing the use of prednisolone, prednisone or methylprednisone there was marked variation evident in study methodologies, limiting comparison across studies. There was 1 class I study, 6 class II studies and 11 retrospective observational or uncontrolled comparative studies (class III). Six studies were based in LMICs.

Optimal cessation of spasms

Of the studies, the UKISS study was not powered enough to compare hormonal subgroups, however, prednisolone given at 40-60mg/day resulted in a remission rate of 70% and ACTH 76% at the final clinical assessment at 14 months[20]. The difference was not significant and neither was the risk of relapse between the groups [20]. A retrospective observational class III study, by Kossoff *et al* (n=15), found no statistical difference between ACTH and oral prednisolone, prescribed at a dose of 40-45mg/day, in the resolution of spasms after 2 weeks [31]. The study was underpowered to detect a significant difference between ACTH and prednisolone, although a large difference in favour of ACTH was reported. According to Arya *et al* 2mg/kg of prednisolone was less effective compared to ACTH [25] and Chellamuthu *et al* concluded that a significantly higher proportion of children had spasm cessation on day 14 who had received high dose prednisolone (4mg/kg/day) compared to those who received half the dose [18]. In the same year, Hussain *et al* demonstrated that very high dose prednisolone, 8mg/kg/day, had a significantly greater efficacy than lower doses reported from previous studies[32]. O'Callaghan *et al* in their 2017 report concluded that the combination of hormonal therapy and vigabatrin, was statistically more effective at stopping epileptic spasms than hormonal therapy alone. However, due to the lack of randomization of the hormonal group, it could not be determined if ACTH or prednisolone was more effective[33]. Furthermore, the diversity of ACTH formulations, such as natural versus synthetic, full-length ACTH vs n-terminal truncated ACTH, depot vs non-depot administration may influence efficacy and to some extent outcomes across studies.

The lack of consistency in study methodologies, directness in study questions and class I studies across reports limits forming a consensus on the evidence to support the use of prednisolone, especially as a replacement to ACTH. There was marked variation in the inclusion criteria, aetiologies of spasms from LMIC and HIC, drop-outs, treatment lag,

definition of response, proportion of low-risk/high risk, symptomatic patients, dose and duration of therapy and length of follow-up limiting comparison across studies. In addition, the optimal dose of prednisone and prednisolone still needs to be determined. For optimal care, combination therapy may be needed, as evidenced by ICISS study [33].

In terms of **other steroid formulations**, 57% of patients responded to dexamethasone in a retrospective observational study by Haberlandt *et al*, class III study, compared to 64% to ACTH. They concluded that pulsed dexamethasone is a suitable alternative to ACTH, however, relapse rate was not stated and long term outcomes not measured [34]. More recently, a small study by Yeh *et al*, n=14 class III study, concluded that short-term methylprednisolone pulsed therapy resulted in rapid resolution of epileptic spasms and hypsarrythmia without serious adverse effects [35]. There is insufficient evidence to recommend other therapies in the treatment of epileptic spasms such as valproic acid, nitrazepam, pyridoxine, zonisamide, thyrotropin-releasing hormone, topiramate, levetiracetam and ketogenic diet [14, 36].

Adverse effects of steroids are a concern, particularly the increased risk of infections, such as tuberculosis, in LMICs, and the complications from immunodeficiency in HIV-infected infants. Other side effects include increased appetite, weight gain, hypertension, cushingoid facies, irritability, glycosuria and cerebral atrophy [14, 18]. It is advisable that prior to starting treatment, for HIV status, chest x-ray, tuberculin skin test, baseline weight and blood pressure to be recorded[18].

Developmental Outcome

According to UKISS, there was no difference in the neurodevelopmental outcome in overall data on children with ES who received hormonal treatment or vigabatrin at 14 months and 4 years of age. However, there was significant improvement in developmental scores in those who received hormonal treatment without an identifiable aetiology. [20, 21] In the same

study, an increase in lag time to treatment was significantly associated with a lower developmental score at 4 years after adjusting for age of onset, aetiology and treatment [17]. Factors that result in a more favourable long term cognitive outcome include a shorter lag time to treatment with hormonal treatment or vigabatrin (level C) [14], shorter duration of hypsarrhythmia[37] and “cryptogenic” cause of epileptic spasms[38]. There are currently no studies assessing the long-term outcomes of children treated with prednisolone (level U recommendation).

In conclusion

Further randomised studies are needed to compare oral corticosteroids to ACTH and to determine the optimal dose, comparison efficacy, as well as long-term studies looking at the neurodevelopmental outcomes of these groups. High dose oral prednisolone appears to be evolving as a strong alternate candidate for infants with epileptic spasms, especially in settings where access to ACTH is not viable. In children with epileptic spasms and TSC vigabatrin remains the first line recommended agent. In settings where oral corticosteroids are used, standardized protocols should be in place and outcomes audited. Based on the accumulated data a recommendation has been compiled (Figure 1) for settings without reliable access to ACTH and vigabatrin.

Whilst there appears to be efficacy using oral corticosteroids for children with ES (level C recommendation), the optimal dose has not been defined beyond limited case series promoting higher doses. Of concern it remains unclear whether these children have a disadvantage with regard to their relapse rate, subsequent epilepsy syndrome development and neurodevelopmental outcome.

In summary, there is class III evidence supporting a level C recommendation for the efficacy of oral corticosteroids for the acute clinical control of epileptic spasms and EEG resolution. Use of oral corticosteroids in comparison to the internationally recommended intervention of ACTH has class IV evidence resulting in a level U recommendation. Similarly, the risk of relapse with oral corticosteroids has class IV evidence and level U recommendation, and compared to ACTH, class IV evidence with level U recommendation. There is class IV evidence resulting in level U recommendation for the safety of oral corticosteroids and class II evidence supporting level B recommendation for ACTH. In terms of oral corticosteroids and effects on long-term development evidence is class IV evidence leading to level U recommendation, compared to ACTH which has class III evidence supporting level C recommendation.

Table I: Overview of the studies which included oral corticosteroids in the management of epileptic spasms.

Author, year Add country / region	Study Design	Class	Sample Size	Treatment	Directness to study question	Consistency across studies	Efficacy	Outcomes Short Term	Outcomes Long Term
Demarest et al 2017 USA [39]	Prospective, observational study, multicenter	Class II	447 total; 366 with hypsarrhythmia, 81 without hypsarrhythmia	196 ACTH 75IU/m^2 twice/day for 2 weeks followed by gradual tapering over 2 weeks, 85 prednisolone 10mg 4 times daily for 2 weeks followed by weaning by 10mg/day every week, 66 vigabatrin 50-150mg/kg/day divided into 2 doses	Yes	Yes	Prednisolone more effective than vigabatrin but less effective than ACTH in the treatment of epileptic spasms. Actual percentage response rate not given	Vigabatrin odds ratio (OR) 5.2, prednisolone OR 8, ACTH OR 10.2 cessation of spasms and resolution of hypsarrhythmia and no relapse within 3 months	
Yeh et al 2017 Korea [40]	Prospective open-label, uncontrolled, multicenter (2 tertiary hospitals)	Class III	14	Methylprednisone 30mg/kg/day for 3 days followed by tapering doses of prednisolone 1mg/kg 2 doses, rapidly reduced each week for 2-4 weeks	Yes	Consistent with doses compared to UKISS and Hussain et al, only sleep EEG's performed, follow up till 3 months	Yes, based on electroclinical response after 3 weeks. Overall response to steroids comparable to other studies	64.3% responded after 3 weeks with resolution of hypsarrythmia on EEG. Relapse rate for spasms 45.5%	55.5% remained seizure free after discontinuing steroids at 3 months. Developmental outcomes not assessed

Tang-Wai et al 2017 Canada [41]	Retrospective observational study, single center	Class III	26 IVIG vs 25 prednisone	IVIG 1g/kg every 3 weeks and prednisone 2mg/kg/day (max 60mg/day) for 2 weeks followed by 6-8 week taper OR prednisone 1-2mg/kg/day (max 60mg/day) for 2-4 weeks followed by 4-6 week taper	Yes	Only study comparing IVIG with prednisone. Only 1 other study (Bara, et al) with same dose of Prednisone. Follow up EEG's not consistent in IVIG group.	84.6% responded to IVIG, mean seizure reduction 77.3% after mean 9.8 weeks, 24% responded to prednisone with mean seizure reduction of 95%, 2.7 weeks mean time to max response	Percentage of seizure reduction higher for IVIG compared to prednisone (p=0.001)	Long term and cognitive outcomes not assessed
O'Callaghan et al 2017 (ICISS) Australlia, Germany, New Zealand, Switzerland, UK [33]	Randomised, multi centre, open label	Class I	186 vigabatrin and hormonal therapy vs. 191 on hormonal therapy	Vigabatrin (50-150mg/kg/day) and hormonal treatment, 51 ACTH (40IU alternate days for 2 weeks), 134 prednisolone (10mg 4 times/day) for 2 weeks, tapered by 10mg every 5 days vs. hormonal treatment (60 ACTH, 131 prednisolone)	Yes	Consistent with doses of prednisolone in Wanigasinghe et al, Ware et al, Mohamed et al and follow up. Parents allowed to choose type of hormonal therapy	Yes, hormonal treatment with vigabatrin significantly more effective at stopping spasms than hormonal therapy alone, similar to primary clinical response in UKISS BUT different definitions for "cessation of spasms".	Cessation of spasms in 89% on combination therapy vs. 69% on hormonal therapy (p<0.001) on days 13 & 14, 19% relapsed by day 42 (33 on combination and 24 on hormonal treatment).	Day 14-42, no spasms in 72% combination therapy vs. 57% on hormonal therapy (p=0.002). Electroclinical response 66% combination therapy vs. 55% hormonal therapy (p=0.023).

Knupp et al 2016 USA [13]	Prospective, observational, multi center	Class II	230 total – ACTH 97, 54 prednisolone, 47 vigabatrin, 32 non-standard therapy	ACTH 75IU/m^2 twice/day for 2 weeks followed by gradual weaning over 2 weeks, prednisolone 10mg 4 times daily for 2 weeks followed by weaning by 10mg/day every week, vigabatrin 50-150mg/kg/day divided into 2 doses	Yes	Consistent with doses in ICISS, Ware et al, Mohammed et al and follow up in the short and long term. All patients received EEG's. Treatment not randomized, providers allowed to choose medication therefore biased based on aetiology and development status.	ACTH associated with higher response rate than vigabatrin (p=0.038) and oral corticosteroids (p-0.06)	After 2 weeks, 55% responded to ACTH, 39% to prednisolone, 36% to vigabatrin electroclinically. Relapse rate highest for oral corticosteroids, 24%.	After 3 months, sustained response to ACTH significantly higher than vigabatrin and marginally higher than oral corticosteroids. Long term developmental outcomes not assessed.
Wanigasinghe et al 2015 Sri Lanka [12, 42]	Randomised control trial, single center, single blinded	Class II	48 prednisolone vs. 49 ACTH	Prednisolone 10mg 4 times/day for 2 weeks followed by tapering by 10mg/day per week over 3 weeks or ACTH 40IU alt days for 2 weeks	Yes	Consistent with doses in ICISS, Ware et al, Mohammed et al and follow up in the short and long term. EEG recording	Cessation of spasms at 14 days 58.3% prednisolone vs. 36.7% ACTH (p=0.03). Electroclinical remission on day 14 in 43.75% prednisolone	Significantly better control of spasms with prednisolone at 14 days and 28 days. 6 relapsed in prednisolone group and 8 from ACTH group.	Follow up study at 3 months showed significantly better spasm control if treated with prednisolone 64.6% than ACTH 38.8% p=0.01. Spasm control at 6 months, 58.3% prednisolone and 44.9% ACTH p=0.19.

				followed by taper over the next 3 weeks		limited to 30 mins and not done at every visit due to resource constraints. Spasm-free periods determined by parental reports from preceding week at each testing period	and 18.4% on ACTH (p=0.007). On day 42 cessation of spasms in 66.7% on prednisolone vs. 38.7% on ACTH (p=0.079). After 28 days electroclinical response 31.2% prednisolone and 12.22% ACTH (p=0.008).		At 12 months spasm cessation 56.2% prednisolone and 40.8% ACTH p=0.13. After 12 months no difference in relapse between groups. Cognitive outcomes not assessed
Jones et al 2015 Canada [43]	Retrospective observational study, single center	Class III	15 ACTH vs 5 Prednisolone	ACTH 1.9mg/m^2 alt days followed by a tapering schedule from week 2-12 vs Prednisolone 4-4.5mg/kg/day for 1-2 weeks, followed by 3mg/kg/day for 1 week, then 1.5mg/kg/day for 1 week	Yes	Second line treatment after failed course of vigabatrin	No, prednisolone not effective, hormonal treatment used a second line agents if no response to vigabatrin	80% electroclinical response to ACTH vs. 20% response to prednisolone (p=0.03) after 2 weeks	58% relapsed on ACTH, 100% relapse, follow up between 6-38 months from spasm onset (p=0.26). Cognitive outcomes not assessed
Yi et al 2015 China [44]	Observational study, single center	Class III	20 prednisolone	Prednisolone 10mg 4 times/day for 2 weeks reduced weekly	Yes	Consistent with doses of prednisolone with	Yes, higher response rate to prednisolone	80% cessation of spasms after 2 weeks prednisolone	Median follow up time 10.5 months, 47.1% relapse. Neuroodevelopmenta

				to complete a 7 weeks course		Wanigasinghe et al, Ware et al, Mohamed et al, UKISS consistent with EEG's	after 2 weeks compared to Wanigasinghe et al, Ware et al, Mohamed et al, UKISS studies		l outcome, lower developmental quotient after treatment but not significant (p=0.098)
Chellamuthu et al 2014 India [18]	Randomised control trial, single center, not blinded	Class II	32 low dose prednisolone vs. 31 high dose prednisolone	Prednisolone 2mg/kg/day vs. 4mg/kg/day in 3 divided doses for 2 weeks followed by tapering over 2 weeks	Yes	Dose consistent with Kossoff et al, follow up only for 6 months, EEG recorded for 1 hour. Relying on parental reporting of spasm frequency	High dose prednisolone (51.6%) significantly more effective than low dose prednisolone (25%) for spasm resolution after 14 days (p=0.03). Electroclinical response high dose prednisolone 38.7% vs. 21.9% low dose prednisolone, not significant (p=0.15).	Response rate lower than HMIC (UKISS, Kossoff et al), comparable to ACTH in LMIC	At 6 months, 4 children relapsed in the usual dose group and 5 in the high dose group. Cognitive outcomes not measured
Hussain et al 2014 USA [32]	Retrospective observational study, single center	Class III	27	Response to prednisolone at 8mg/kg/day (max 60mg/day) divided in 3 doses for 2 weeks	Yes	Only study that used prednisolone at this dose, video EEG response to	Very high dose prednisolone significantly higher efficacy than lower doses from	63% responded completely (video-EEG response) to prednisolone after 2 weeks	2 patients relapsed at 2 and 5 months respectively. Cognitive outcomes not measured

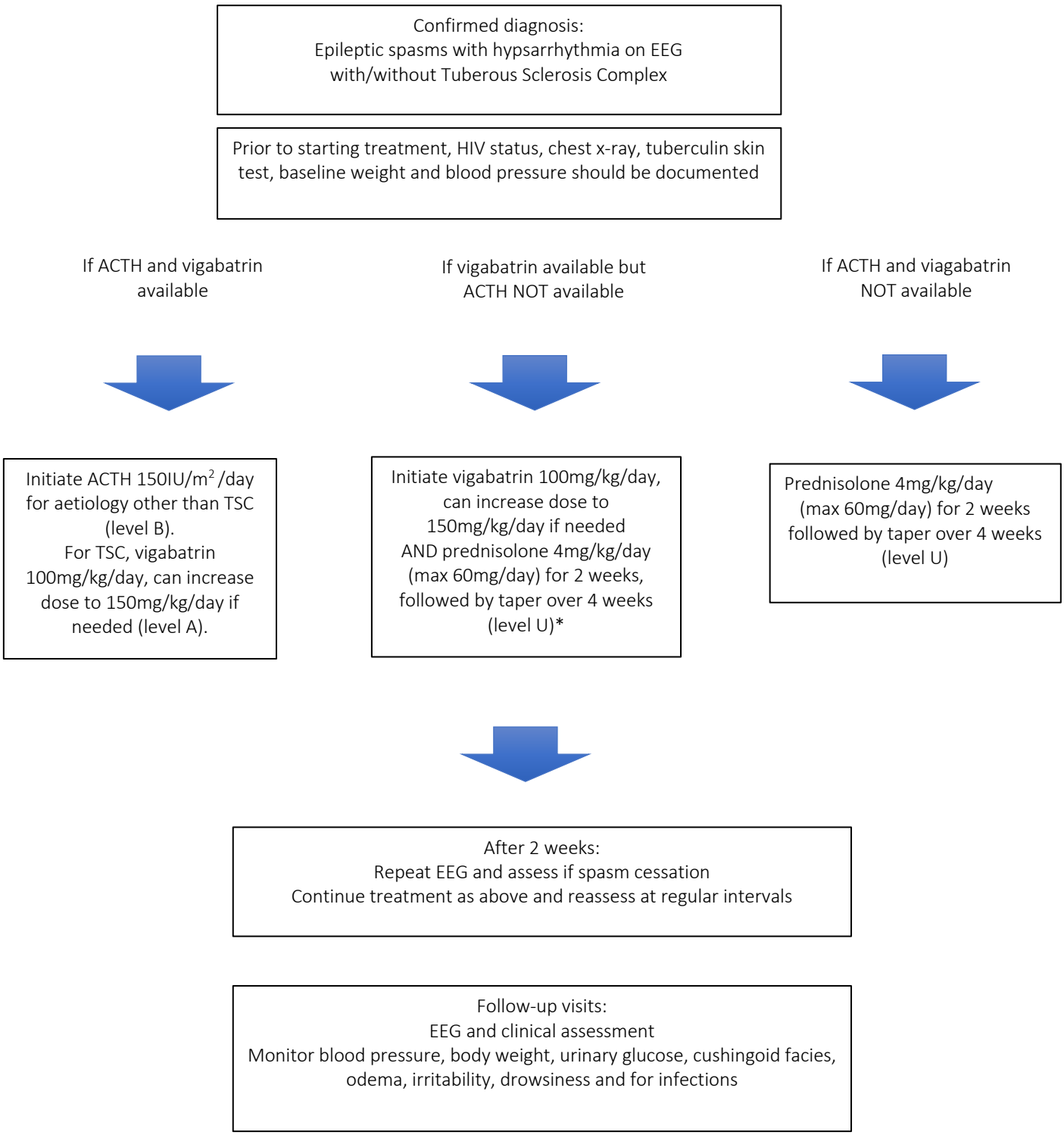
				followed by tapering over 2 weeks		treatment, limited follow up time	prior studies (Baram et al)		
Ware et al 2012 Australia [45]	Retrospective observational study, single center	Class III	17 Prednisolone vs. 6 vigabatrin, 5 not treated as per protocol	Prednisolone 10mg 4 times/day for 2 weeks followed by tapering by 10mg every 5 days and vigabatrin 50-150mg/kg/day	Yes	Consistent with doses in ICISS, Wanigasinghe et al and Mohamed et al, TSC patients not excluded in this study. Follow up EEG findings not documented	Yes, response to prednisolone higher than UKISS, Wanigasinghe et al and Mohammed et al, TSC patients not excluded	Initial response to spasm cessation on day 14 76% prednisolone and 17% vigabatrin	Follow up 21 months, none who received prednisolone with cryptogenic aetiology relapsed and 10 with symptomatic aetiology relapsed (not specified how many received prednisolone or not treated with protocol), 4 of the 6 with TSC who received vigabatrin relapsed. Cognitive outcomes not measured
Mohamed et al 2011 (UK) [46]	Retrospective observational study, single center	Class III	54 Vigabatrin vs. Steroids in 18 (17 Prednisolone, 1 ACTH)	Prednisolone 2-4mg/kg/day prior to UKISS, after UKISS 40mg daily for 2 weeks followed by tapering by 10mg every 5 days, Vigabatrin 25-50mg/kg/day increased up to 150mg/kg/day	Yes	Inconsistent with prednisolone doses – different doses used before and after UKISS, after UKISS doses consistent with UKISS, consistent with EEG's, inconsistent	Prednisolone and vigabatrin similar efficacy, responsiveness to steroids less than UKISS, vigabatrin comparable other studies (Elterman et al, Appelton et al, Aicardi et al).	61.1% response to steroids, 3 relapsed. 42.5% response to vigabatrin, 7 relapsed	1 relapsed on steroids after 11 months and 1 relapsed on vigabatrin. Neurodevelopmental outcomes not specified

						with follow up	Steroids more effective in children with cryptogenic aetiology. Faster response to steroid therapy		
Mytinger et al 2010 (USA) [47]	Prospective, not randomised, single center	Class III	10	Methylprednisone 20mg/kg for 3 days followed by prednisolone 4mg/kg/day for 2 weeks, followed by tapering over 6 weeks	Yes	Lower dose pulse Methypred compared to Yeh et al. Relied on parent reporting of spasms at 2 weeks. Follow up not consistent	Lower response rate than high dose prednisolone used by Yeh et al. Results complicated by use of ineffective antiseizure drugs prior to starting treatment	50% remission confirmed on video EEG between 2-6 days. 80% of primary responders relapsed	60% had relapse or continuation of spasms at follow up. Cognitive outcomes not measured
Noureen et al 2010 Pakistan [48]	Retrospective, observational study, single center	Class III	50	Response to prednisolone 2mg/kg/day in 3 divided doses for 4 weeks followed by tapering over 2 weeks	Yes	Lower dose of prednisolone given compared to ICISS, Wanigasinghe et al, Cochrane review	Lower response to steroids compared to ICISS and Wanigasinghe et al BUT lower dose of prednisolone used. Also lower response to Azam et al	Cessation of spasms or >50% reduction in spasms noted in 54% after 2 weeks. Relapse in 8%.	Long term data and cognitive outcomes not measured

							(low dose prednisone)		
Kossoff et al 2009 USA [31]	Retrospective observational study, single center	Class III	15	Response to prednisolone at 40-45mg/kg/day in 3 divided doses for 2 weeks followed by tapering over 2 weeks	Yes	Consistent with dose in 2008 Cochrane review	Yes, prednisolone response rate similar to UKISS, 10/15 (67%) responded to prednisolone vs. 13/15 (87%) to ACTH at same center p=0.16 Results not statistically significant but comparison to ACTH from previous data.	67% spasm free within 2 weeks, 40% relapse after initial response	No long term data available
Azam et al 2005 Pakistan [49]	Retrospective comparative study, single center	Class III	23 ACTH, 72 prednisolone	ACTH 20-40IU/day for 4 weeks and tapered over 2 weeks vs. Prednisolone 2-3mg/kg/day in 2 divided doses total duration incl. tapering 6-8 weeks	Yes	Lower dose of prednisolone compared to ICISS, UKISS, Wanigasinghe et al, no 24 hour EEG monitoring or follow up EEG's, parents chose ACTH or prednisolone	Response to treatment defined as spasm cessation OR >50% reduction in spasms. Response to prednisolone comparable to studies mentioned but different definitions used	82% responded to ACTH and 71% to prednisolone, difference not significant (p=0.41)	Follow up variable 6-10 months. 33% ACTH remained spasm free, 24% prednisolone spasm free. No long term data re: relapse rate or cognitive outcomes

Lux et al 2005 (UKISS) UK [17, 20, 21]	Randomised control trial, multicenter, not blinded	Class II	30 prednisolone, 25 ACTH	Prednisolone 10mg 4 times/day for 2 weeks followed by tapering by 10mg every 5 days vs. ACTH 40-60IU alt days for 2 weeks followed by tapering every 5 days	Yes	Prednisolone dose not consistent-lower than ICISS, Wanigasinghe et al, Ware et al. Consistent with follow up.	Cessation of spasms at 14 days-hormonal treatment more effective than vigabatrin, no difference at 12-14 months of age. No significant difference prednisolone and ACTH.	70% responded to prednisolone and 76% to ACTH – no significant difference (p=0.61)	No difference in spasm control at 12-14 months. No identified aetiology led to better developmental outcomes at 14 months and 4 years of age
Baram et al 1996 USA [50]	Randomised, prospective, single blinded, single center	Class II	15 ACTH vs 14 prednisone	ACTH 150IU/m^2/day for 2 weeks followed by tapering over 2 weeks vs. Prednisone 2mg/kg/day in 2 divided doses for 2 weeks followed by tapering over 2 weeks	Yes	Prednisone given instead of prednisolone, low dose prednisone only consistent with Azam et al consistent with EEG's	ACTH significantly more effective than prednisone	86.6% responded clinically and EEG to ACTH, 28.6% to prednisone (p=0.002) after 2 weeks. Relapse rate not reported	Long term data not available

Figure 1: Recommended Low and Middle Income Country treatment guideline based on existing evidence



- Infants with TSC are recommended to receive vigabatrin as first line intervention and the role for additional homonal therapy has not been reported.

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Appendices

Appendix A: Instructions to authors for European Journal of Epilepsy

Appendix B: Reviewer comments

Appendix A: Instructions to authors for European Journal of Epilepsy

SEIZURE - EUROPEAN JOURNAL OF EPILEPSY

AUTHOR INFORMATION PACK

TABLE OF CONTENTS

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Seizure focuses especially on clinical and psychosocial aspects, but will publish papers on the basic sciences related to the condition itself, the differential diagnosis, natural history and epidemiology of seizures , as well as the investigation and practical management of seizure disorders (including drug treatment, neurosurgery and non-medical or behavioural treatments).

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Observational Studies - STROBE - Strengthening the Reporting of Observational studies in Epidemiology

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[2] Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. Heliyon. 2018;19:e00205. https://doi.org/10.1016/j.heliyon.2018.e00205
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Reference to a website:
[5] Cancer Research UK. Cancer statistics reports for the UK, http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/; 2003 [accessed 13 March 2003].
Reference to a dataset:
[dataset] [6] Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. https://doi.org/10.17632/xwj98nb39r.1.
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Appendix B: Reviewer comments

Comments from the editors and reviewers:
-Reviewer 1

-

This is a concise review.

I have some minor suggestions:

When there is no firm conclusion from the literature with regard to the dose and duration of oral therapy with prednisolone, the authors should clarify that the content and the guideline in Figure 1 is their expert opinion.

Figure 1. the title should be more informative of the content.

Figure 1. the layout has a problem in the file, please recheck!

Table 1. should have a column on duration of the maintenance dose and tapering of the therapy.

-Reviewer 2

-

This an an important novel review. The review was driven by the need to develop a recommendation to standardize a safe and effective regimen using oral steroids over other agents, such as ACTH and vigabatrin in low and middle income countries, where acess to internationally recommended agents are lacking. Oral steroids are there used because of the lower price. Also in other parts of the world predniolone is increasingly used because of its efficacy and easiness to administer (orally).

The authors review carefully already a large existing literature. Eighteen studies (14 addressing the intervention and immediate outcome) were found between 1990-2017 (Table 1).

However, it can be seen that there are still many unmet questions concerning the use of (prednisone) and prednisolone: optimal dose, duration of the therapy, efficacy, relapse rate and long-term effects. Furthermore comparison with other 1-line drugs ACTH and vigabatrin are insufficiently studied. The studies are inhomogenous and difficult to compare. Randomized controlled studies are needed.

Systematic review, P. 6: 4th line n=4: ”long-term outcome” (give the follow-up time). Did the author mean Waningshire et al, Y et al , Lux et al, Ware et al with long-term studies ???

At the end of the Systematic review the authors present the Practice parameters of AAN. They should also give the Class ranking used in Table 1.

Management of epileptic spasms Page 7 (middle chapter). The authors give a very important statement which might distinguish prednisone from prednisolone. They are refering Reference 24. This reference mentions it, but no original reference is included.

Prednisone has no glucocorticoid effect. It has to be metabolized to prednisolone to have any effect. The same mechanism is happening: inactive cortisone has to be changed to cortisol (via 11beta-hydroxisteroiddehydrogenase type 1). These conversions might indeed be defective at the age of less than 6 months. This is very crucial finding and might partly explain why prednisone is ”ineffective” in treatment of infantile spasms reported in litterature. Add original reference if possible. (The diffrent dose might, of course, be also important).

Page 8: At bottom of last prgh; Add the bolded to the text. Of the identified studies assessing the use of prednisone, or methylprednisone there was marked variation evident in study methologies **(inclusion criteria, drop-outs,treatment lag, definion of response, proportion of low-risk/high-risk, cryptogenic/symptomatic patients, dose and duration of therapy and length of follow-up**), limiting the comparison across the studies.

Some studies have selection bias of low-risk patients where the effect of therapy is high (Baram et al 1996,Lux et al 2004, O`Callaghan et al 2017); some others give the therapy to all consequent patients (Knupp et al 2016) and the therapeutic response seems to be less. The studies with large numbers of low-risk patients could be marked by asterix and foot-note in Table 1.

Page 9, 2nd prgh: last sentence ”For optimal **short-term** care, combination therapy may be needed as evidenced by ICISS study (29). ---- Relapses andl long-term cognitive outcome is not known in ICISS study. The patients have adverse effects of both drugs (personal opinion, not to be added to the review (Riikonen The Lancet Neurology 2015).

P 10: Adverse effects. 2nd sentence ”other side effects include increased appetite, weight gain, hypertension, **hypertrophic cardiomyopathy**, cushingoid faces, irritabilty, glucosuria, cerebral atrophy, **hypopituitary-adrenal axis insufficiency and immunosuppression**.

The followind sentence should be deleted starting ”Kossoff… ….”

In the Kossoff et al study irritability, edema, hypertension and excessive weight gain were seen in 12/15 patients in ACTH treatment and 8/15 in prednisolone. The a.m. adverse effects are difficult to measure, and the difference was not significant.

P 11 ”cryptogenic” cause (patients with normal development before onset of infantile spasms and no known etiology, MRI normal).

In Conclusion

I agree with the following conclusion

Page 12: ”In summary, there is level C evidence to support the efficacy of oral corticosteroids for the acute control of epileptic spasms and EEG resolution, Use of oral corticosteroids in comparison to interenationally recommended intervention of ACTH is lecvel U.”

Figure 1 is excellent.

Table 1

Demarest Short-term Vigabatrin or 5.2 prednisolone or 8, ACTH 10,2 What are these numbers?

Knupp 7th column: last word : ..and ..??

Mohammed et al 2011 (GOSH, UK) …. What is GOSH ???

References are largely lacking. In Table 1 there are many authors without references. The references should be added to Reference list.

Demarest et al 2017, Tang-Wai et al. 2017, Bara et al ?? (Baram?), Ware et al,. 2012, Appleton et al .Elterman, Aicardi, Noureen et al 2012, Azam et al 2005 . Authors of Reference 15 should be Gronseth G, French F