Published in final edited form as:

J Clin Neurophysiol. 2015 December ; 32(6): 486–494. doi:10.1097/WNP.0000000000000198.

Could EEG monitoring in critically ill children be a cost-effective neuroprotective strategy?

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Abstract

Objectives—Electrographic status epilepticus (ESE) is associated with unfavorable functional outcomes but identifying candidates for ESE management requires resource-intensive continuous EEG monitoring. We performed a cost-effectiveness analysis to estimate how much ESE identification and management would need to improve patient outcomes to make EEG monitoring strategies a good value.

Methods—We created a decision tree to examine the relationships among variables important to deciding whether or not to perform EEG monitoring. We estimated variable costs from their component parts, estimated outcomes in quality-adjusted life years (QALYs), and calculated incremental cost-effectiveness ratios to compare the relative values using four alternative EEG monitoring strategies that varied by monitoring duration.

Results—Forty-eight hours of EEG monitoring would be worth its cost if ESE identification and management improved patient outcomes by 7%. If ESE identification and management improved patient outcomes by 3–6%, then either 24 or 48 hours of EEG monitoring would be worth the cost depending on how much decision makers were willing to pay per QALY gained. If ESE identification and management improved outcomes by as little as 3%, then 24 hours of EEG monitoring would be worth the cost.

Conclusions—Continuous EEG monitoring has the potential to be cost effective if ESE identification and management improves patient outcomes by as little as 3%.

Keywords

EEG Monitoring; Seizure; Status Epilepticus; Pediatric; Non-Convulsive Seizure; Cost-Effectiveness

Introduction

Electrographic seizures are reported in 10–40% of children with acute encephalopathy who undergo continuous EEG monitoring.(Abend, et al. 2013, Abend and Dlugos 2007, Abend, et al. 2011, Abend, et al. 2009, Abend, et al. 2013, Arango, et al. 2012, Arndt, et al. 2013, Gold, et al. 2014, Greiner, et al. 2012, Hosain, et al. 2005, Jette, et al. 2006, Kirkham, et al. 2012, McCoy, et al. 2011, Payne, et al. 2014, Piantino, et al. 2013, Schreiber, et al. 2012, Shahwan, et al., Tay, et al. 2006, Williams, et al. 2011) EEG monitoring is required for identification since most electrographic seizures in critically ill children have no clinical correlate.(Abend, Arndt, Carpenter, et al. 2013, Abend, Gutierrez-Colina, Topjian, et al. 2011, Gold, Crawford, Glaser, et al. 2014, Greiner, Holland, Leach, et al. 2012, Jette, Claassen, Emerson, et al. 2006, Kirkham, Wade, McElduff, et al. 2012, McCoy, Sharma, Ochi, et al. 2011, Piantino, Wainwright, Grimason, et al. 2013, Schreiber, Zelleke, Gaillard, et al. 2012, Shahwan, Bailey, Shekerdemian, et al. 2010, Williams, Jarrar and Buchhalter 2011) About one-third of children with electrographic seizures have a sufficiently high seizure burden to be categorized as experiencing electrographic status epilepticus (ESE), although the exact definitions of ESE have varied across studies.(Abend, Arndt, Carpenter, et al. 2013, Abend and Dlugos 2007, Abend, Gutierrez-Colina, Topjian, et al. 2011, Abend, Topjian, Ichord, et al. 2009, Abend, Wusthoff, Goldberg, et al. 2013, Arango, Deibert, Brown, et al. 2012, Arndt, Lerner, Matsumoto, et al. 2013, Gold, Crawford, Glaser, et al. 2014, Greiner, Holland, Leach, et al. 2012, Hosain, Solomon and Kobylarz 2005, Jette, Claassen, Emerson, et al. 2006, Kirkham, Wade, McElduff, et al. 2012, McCoy, Sharma, Ochi, et al. 2011, Payne, Zhao, Frndova, et al. 2014, Piantino, Wainwright, Grimason, et al. 2013, Schreiber, Zelleke, Gaillard, et al. 2012, Shahwan, Bailey, Shekerdemian, et al., Tay, Hirsch, Leary, et al. 2006, Williams, Jarrar and Buchhalter 2011) Outcome studies adjusting for the etiology and severity of acute encephalopathy have demonstrated that high electrographic seizure exposures, often categorized as ESE, are associated with worse outcomes.(Abend, Arndt, Carpenter, et al. 2013, Kirkham, Wade, McElduff, et al. 2012, Payne, Zhao, Frndova, et al. 2014, Topjian, et al. 2013, Wagenman, et al. 2014) Additionally, there is some evidence that existing anti-seizure medications terminate electrographic seizures in many patients.(Abend, et al. 2013) Although studies have not evaluated whether electrographic seizure identification and intervention improves neurodevelopmental outcomes, recent guidelines have emphasized the importance of EEG monitoring to identify and manage electrographic seizures in many critically ill children, (Brophy, et al. 2012, Herman, et al. 2015, Herman, et al. 2015) and surveys regarding EEG monitoring use within pediatric intensive care units have described rapid increases in the number of children undergoing EEG monitoring.(Sanchez, et al. 2013)

Identification and management of ESE could serve as a neuroprotective strategy by reducing seizure-induced secondary brain injury. However, EEG monitoring is resource intense since it involves expensive equipment and a substantial amount of work by technologists and physicians. Small utilization changes may have substantial impacts on equipment and personnel needs.(Gutierrez-Colina, et al. 2012) In a prior study we estimated the cost of identifying a critically ill child experiencing electrographic seizures using four EEG monitoring strategies (none, 1 hour EEG, 24 hours of EEG, or 48 hours of EEG) and

concluded that the preferred monitoring strategy was dependent on how much the decision maker was willing to pay.(Abend, et al. In press.) However, the prior study assumed a decision had been made to perform EEG monitoring since identification and management of electrographic seizures would be beneficial to the patient. Thus, it did not provide direct evidence about whether monitoring should or should not be done. Further, it identified the cost to identify a seizing patient, but did not assess the cost to increase quality adjusted life years (QALY), a more patient centered outcome assessment.

If identifying and managing ESE improves neurodevelopmental outcome, then EEG monitoring could be good value despite the resource intense nature of EEG monitoring. However, if minimal improvements in outcome are achieved by ESE identification and management, then widespread implementation of EEG monitoring may not be a cost effective strategy. We modelled four EEG monitoring strategies differing by monitoring duration and evaluated their relative cost-effectiveness when applied to critically ill children. We aimed to determine how much ESE identification and management would need to improve patient neurodevelopmental outcome for EEG monitoring to be a good value and thus a desirable strategy.

Methods

Model Structure

We constructed a decision tree to evaluate the costs and QALY of a pediatric intensive care unit taking care of patients with acute encephalopathy undergoing four EEG monitoring strategies. The strategies were: (1) no EEG, (2) 1 hour of EEG monitoring, (3) 24 hours of EEG monitoring, or (4) 48 hours of EEG monitoring (Figure 1). The analysis was conducted using a societal perspective with a life time horizon. Costs and effects were discounted at 3% per year.

We did not include any potentially harmful effects of EEG monitoring strategies in our model since these were considered to be negligible. For example, skin breakdown is very rare even with prolonged electrode placement, and it has not been reported as a complication in any of the studies of clinically indicated EEG monitoring. Additionally, any benefit from ruling out electrographic seizures was not included. For example, benefit might occur when continuous EEG monitoring determined that events considered seizures by critical care practitioners were not seizures, thereby leading to avoidance or withdrawal of unnecessary anti-seizure medications.(Abend, et al. 2011, Gold, Crawford, Glaser, et al. 2014)

Model Inputs: ESE Prevalence

Our methods for estimating electrographic seizure prevalence were described previously. (Abend, Topjian and Williams In press.) Briefly, we conducted a systematic literature review using PubMed to identify articles published in English related to EEG monitoring in critically ill children and also reviewed the reference lists from available publications. As previously described, (Abend, Topjian and Williams In press.) we pooled data from published studies of critically ill children undergoing EEG monitoring and found that 740 of 2,247 (0.33) children who underwent EEG monitoring experienced electrographic seizures

(Supplemental Table 1). Children with electrographic seizures could experience a low seizure exposure or a high seizure exposure, referred to as ESE. Several studies have suggested that only high seizure exposures are associated with worse outcomes.(Abend, Arndt, Carpenter, et al. 2013, Payne, Zhao, Frndova, et al. 2014, Topjian, Gutierrez-Colina, Sanchez, et al. 2013, Wagenman, Blake, Sanchez, et al. 2014) Thus, identifying and managing patients with high seizure exposure is key if EEG monitoring is to improve outcomes. We pooled data from published studies containing data regarding electrographic seizure exposure and found that 257 of 597 (0.43) children with electrographic seizures experienced ESE (Supplemental Table 1). Electrographic seizures could begin at different time points after the initiation of EEG monitoring, and seizures would be more likely identified with longer EEG monitoring duration. As previously described, (Abend, Topjian and Williams In press.) we pooled data from some of the same studies to obtain the probabilities of seizure identification with each EEG monitoring strategy: 0.55 with 1 hour of EEG monitoring; 0.85 with 24 hours of EEG monitoring; and 0.89 with 48 hours of EEG monitoring (Supplemental Table 2).

Model Inputs: EEG Costs

We have previously described our micro-costing approach to estimate the direct medical costs of performing EEG monitoring.(Abend, Topjian and Williams In press.) Briefly, we identified the components used to conduct EEG monitoring (equipment, technologists, and encephalographers), estimated how much of each component is used, and assigned a cost to each unit of use. We did not include fixed costs, which do not change when the EEG monitoring strategy changes. Costs were converted to 2013 dollars using a consumer price index data inflation calculator. To calculate personnel costs, we multiplied salaries by 1.3 to account for benefits. We divided yearly salaries by 1920 hours (assuming 40 hours of work per week for 48 weeks per year) to obtain an hourly cost. The interquartile ranges for costs were used to generate standard errors. The detailed tables summarizing physician, technologist, EEG machine, and electrode costs were reported previously, (Abend, Topjian and Williams In press.) and the final cost estimates for each EEG strategy are provided in Table 1.

Model Inputs: ESE Management Effectiveness

Strategies to identify and manage ESE might improve outcomes by reducing seizure-induced secondary brain injury, but the effectiveness of such strategies is unknown. Our primary aim was to establish the impact EEG monitoring strategies would need to have on outcome to make EEG monitoring cost-effective. In our model, the probability of management effectiveness refers to the probability that a composite strategy including ESE identification and anti-seizure medication would reduce secondary brain injury and lead to improved patient neurodevelopmental outcomes. The probability of outcome improvement was modeled from 0.01 (very small improvement in outcome compared to no identification and management of ESE) to 1.00 (outcome as if ESE had not occurred). As shown in the results section, the key range impacting conclusions was between 0.03 and 0.07 so most of our results are from this range.

Model Inputs: Outcomes

We used published data regarding survival to discharge from the pediatric intensive care unit. In a study of short-term outcomes among children with acute encephalopathy who underwent continuous EEG monitoring, mortality was 30% among those with ESE and 15% among those without seizures or with only electrographic seizures.(Topjian, Gutierrez-Colina, Sanchez, et al. 2013) In our model, survivors could have favorable or unfavorable outcomes. In a study of long-term outcome among critically ill children with acute encephalopathy who had undergone EEG monitoring while in the pediatric intensive care unit, (Wagenman, Blake, Sanchez, et al. 2014) outcome was assessed using the pediatric version of the Glasgow Outcome Score extended (GOS-E-Peds), (Beers, et al. 2012) and survivors were grouped into those with a favorable outcome (GOS-E-Peds 1–4) or an unfavorable outcome (GOS-E-Peds 5–7).(Wagenman, Blake, Sanchez, et al. 2014) Although the GOS-E-Peds scores represent functional outcomes and not only mental retardation scores, utility values for these functional outcome categories are not available. Therefore, we estimated health utility values for each of these functional outcome states using a study of parent preferences which included utility values for mental retardation.(Carroll and Downs 2009) The utility value for perfect health was 1.0 and the mean utility values for mild, moderate, and severe mental retardation were 0.84, 0.79, and 0.59, respectively. For the current analysis which required outcome dichotomization to link to prior data, (Wagenman, Blake, Sanchez, et al. 2014) we estimated a favorable outcome to have a utility of 0.9 and unfavorable outcome to have a utility of 0.6.

By combining the frequencies of subjects having favorable and unfavorable outcomes with the utility values, we calculated utility values for patients exposed or not exposed to ESE. For patients with ESE that is unidentified and untreated, 64% have an unfavorable outcome (utility 0.6) while 36% have a favorable outcome (utility 0.9), yielding an average utility of 0.70. For subjects without ESE, 26% have an unfavorable outcome while 74% have a favorable outcome, yielding an average utility of 0.82. Subjects with ESE that is identified and managed might have some improvement in their outcomes if secondary brain injury is mitigated, yielding utility values between 0.70 to 0.82, depending on the effectiveness of the EEG monitoring based management strategy. If management were perfectly effective in mitigating ESE-induced secondary brain injury, then the outcome would be like the outcome of patients without ESE (utility 0.82). If management was entirely ineffective in mitigating ESE-induced secondary brain injury then the outcome would be the same as the outcome of patients with unmanaged ESE (utility 0.70).

We calculated QALYs by multiplying the utility value times the number of years the patient would spend in a given health state. Patients with more severe neurologic problems are at increased risk for death. We used literature review (Katz 2003) and expert opinion to estimate a life expectancy of 70 years for patients with a favorable discharge outcome and 59 years for patients with an unfavorable discharge outcome. We discounted QALYs by 3% each year.

Analyses

We performed all analyses were performed using TreeAge Pro software (TreeAge Software Inc., 2014, Williamstown, MA, USA). We created a decision tree model to examine the relationships among variables important to the decision about whether or not to perform EEG monitoring. In addition, we estimated variable costs from their component parts, estimated outcomes in QALYs, calculated incremental cost effectiveness ratios to compare the relative values of alternative strategies (Table 2), and estimated how many QALYs would have to be saved at what cost using four different EEG monitoring strategies for each strategy to be good value.

The primary outcome for this analysis was the incremental cost effectiveness ratios, defined as the incremental cost of each strategy divided by the number of QALY gained for each strategy. We calculated the increase in cost and the increase in the number of identified children by ranking the strategies in order of effectiveness and comparing each strategy to the closest strategy with a lower effectiveness. We did not compare each strategy to the least-effective strategy because this would understate the cost required to produce additional benefits since with each increase in the duration of monitoring the amount of benefit gained decreases relative to the cost of additional monitoring.

We performed two types of sensitivity analyses. First, we performed a deterministic sensitivity analysis (one way factor analysis evaluating a single factor) in which we varied the probability of outcome improvement from 0.01 to 1.0. Results are shown only for the range 0.01 to 0.07 since the 48 hour EEG monitoring strategy dominates other strategies when the probabilities are above 0.07. Importantly, the “intervention” comprises an overall management strategy including seizure identification strategies and management approaches. These sensitivity analyses identify the probability of outcome improvement above which EEG monitoring is a cost effective neuroprotective strategy and below which it is not.

Second, we performed a probabilistic sensitivity analysis using a second-order Monte Carlo simulation with 10,000 replications in which the values for all model inputs were randomly sampled from probability distributions (Table 2). To display the results of the probabilistic sensitivity analysis, we created a cost-effectiveness acceptability curve. This curve plots the relative frequency that the incremental cost effectiveness ratios for each EEG monitoring strategy was cost-effective on the y-axis against increasing willingness-to-pay values on the x-axis. A willingness-to-pay value is the amount a decision maker is willing to pay to achieve one increased QALY in a critically ill child. An incremental cost-effectiveness value is cost effective when it is equal to or less than the willingness-to-pay value. There is no single accepted willingness-to-pay threshold, although \$50,000 per QALY is a commonly used estimate, with recent proposals that \$100,000 per QALY may be more appropriate in the United States.(Neumann, et al. 2014)

Results

Table 3 provides our deterministic sensitivity analysis (one way factor analysis evaluating a single factor) for the probability that management improves outcome. The data describe how

the incremental cost effectiveness ratios for the four EEG monitoring strategies change as the probability that management strategies will improve outcome increases from 0.01 to 0.07. At all probabilities that management improved outcome, the 24 and 48 hour EEG monitoring strategies dominated the no EEG and 1 hour EEG strategies, meaning those strategies had higher cost and were less effective. Thus, the no EEG and 1 hour EEG strategies would never be chosen. If management improved outcome by a probability of 0.03, then one would choose the 24 hour EEG monitoring strategy for willingness-to-pay values below \$136,286 per QALY and the 48 hour EEG monitoring strategy for higher willingness-to-pay values. If management improved outcome by a probability of 0.05, then one would choose the 24 hour EEG monitoring strategy for willingness-to-pay values below \$35,674 per QALY and the 48 hour EEG monitoring strategy for higher willingness-to-pay values. If management improved outcome by a probability of 0.07%, then the 24 hour strategy would be dominated by the 48 hour strategy. If management improved outcome by more than a probability of 0.07 then the 48 hour EEG monitoring strategy would continue to dominate, so higher probabilities are not shown.

Based on the values in Table 1, Figure 2 displays incremental cost effectiveness ratios for 48 hours of EEG monitoring as the probability that management improved outcome increased from 0.02 to 0.07. As the probability that management improves outcome increased, the incremental cost effectiveness ratio decreased. At commonly accepted willingness-to-pay values of \$50,000 and \$100,000, 48 hours of EEG monitoring would be selected when the probability that management improves outcome was about 0.035 and 0.045, respectively. If management improved outcome by more than a probability of 0.07, then the 48 hour EEG monitoring strategy dominated the 24 hour EEG monitoring strategy so the incremental cost effectiveness ratio equaled zero. The no EEG and 1 hour EEG strategies are not displayed since they had negative incremental cost effectiveness ratios at all probabilities that management would improve outcomes, indicating those strategies would never be selected.

To help determine the confidence a decision maker could have in these results, we performed probabilistic sensitivity analyses at each probability that management improved outcomes for willingness-to-pay values ranging from \$0 to \$100,000 per QALY. The no EEG and 1 hour EEG were never selected. This is consistent with Table 1 which indicates the no EEG and 1 hour EEG strategies were always dominated by the 24 and 48 hour EEG monitoring strategies. Decisions between the 24 and 48 hour EEG monitoring strategies varied based on the probability that management improved outcome and decision makers' willingness-to-pay. At low probabilities that management would improve outcome and low willingness-to-pay values the 24 hour strategy was selected in about 70–90% of trials. At high probabilities that management would improve outcome and high willingness-to-pay values the 48 hour strategy was selected in about 50–70% of trials. Figure 3 shows a representative cost effectiveness curve at a probability that management would improve outcome of 0.05. At willingness-to-pay values below about \$30,000 more trials selected the 24 hour strategy and at willingness-to-pay values about \$30,000 more trials selected the 48 hour strategy. However, even at very low (\$10,000) or high (\$100,000) willingness-to-pay values, either strategy was only selected by about 30–60% of trials. These results suggest levels of confidence (or uncertainty) about which strategy should be selected.

Discussion

Identification and management of ESE could serve as a neuroprotective strategy by reducing ESE-induced secondary brain injury, but performing the EEG monitoring required for ESE identification is resource intense. To date, studies have not determined whether combined ESE identification and management strategies improves outcome. Our “what if” analysis sought to determine whether identifying and managing ESE could be a cost-effective neuroprotective strategy. We estimated how much improvement in outcome would need to be achieved by ESE identification and management for EEG monitoring to be a cost-effective neuroprotective strategy. Even with low estimations for improvement in outcome based on ESE identification and management, EEG monitoring for 24 or 48 hours could be cost-effective at willingness-to-pay values of about \$50,000 per QALY gained. Our results indicate that EEG monitoring for 48 hours would be worth its cost if ESE identification and management improved outcomes by 7%. If ESE identification and management improved outcomes by 3–6%, then either 24 or 48 hours EEG monitoring strategies would be worth their costs depending on how much decision makers were willing to pay per each QALY gained. If ESE identification and management improved outcomes by as little as 3%, then 24 hours of EEG monitoring still would be worth the cost. These data suggest that despite the acute costs associated with 24 or 48 hours of EEG monitoring, these monitoring strategies would be good values from a societal perspective if even small improvements in outcome could be achieved by identifying and managing ESE.

These results also suggest that further investigations are warranted to optimize ESE identification and management and to determine whether these approaches improve patient neurodevelopmental outcomes. Further, such investigations may need to be designed to detect small improvements in outcomes. In our prior study of long-term outcome study, ESE, but not electrographic seizures, was associated with worse functional outcomes. (Wagenman, Blake, Sanchez, et al. 2014) Thus, for the purposes of this analysis, we only considered patients with ESE to have an exposure worth identifying and managing. In our prior study, unfavorable outcome occurred among 9 of 14 children exposed to ESE (incidence 0.64) and among 12 of 46 children not exposed to ESE (incidence 0.26). (Wagenman, Blake, Sanchez, et al. 2014) Thus, the percentage of attributable risk related to ESE exposure was 59%. Additionally, there is some evidence that existing anti-seizure medications may terminate electrographic seizures and ESE. (Abend, Sanchez, Berg, et al. 2013) While these studies were small and preliminary, they suggest that achieving a small improvement in outcome by ESE identification and management might be achievable. Small improvements in outcome may be necessary targets for two main reasons. First, even with development and implementation of optimal management strategies for ESE, patients would still have brain injury related to the underlying cause of the ESE. Second, no anti-seizure medication has been perfectly effective for seizure or ESE management in any context, ranging from acute symptomatic seizure management in critically ill patients to outpatient epilepsy management. Therefore, even very rapid and accurate seizure identification and intervention might not terminate ESE in all patients rapidly and completely.

This study has several limitations. First, we estimated the probability of electrographic seizures and ESE primarily from studies of clinically indicated EEG monitoring, and we

grouped together studies addressing heterogeneous acute encephalopathy etiologies. Patients selected to undergo EEG monitoring by clinicians may be at higher risk for experiencing ESE, and thus our seizure probability estimates may be biased towards a high estimate. However, this estimate also reflects current clinical practice which is driven by physician decisions regarding EEG monitoring implementation. Second, our model did not account for any potential injury or outcome worsening that might occur as a result of attempts at ESE management. If attempts to manage seizures lead to adverse effects then outcome could be worsened. However, most clinicians consider use of standard anti-seizure medications to be safe, particularly in a highly monitored intensive care unit environment. Third, few data are available regarding utility values for neurologic conditions, (Carroll and Downs 2009) post intensive care unit quality of life, life expectancy, (Katz 2003) and care costs. Thus, many of these values in our model were drawn from limited data or expert opinion. This limitation is common to studies that address the cost-effectiveness of neuroprotective strategies in children and neonates.(Bickford, et al. 2013) Further study regarding long-term outcome following neurocritical care illness in children is needed to fix this problem. Finally, we considered our data in the context of willingness-to-pay values of \$50,000-\$100,000 per QALY. While this is a commonly used and recommended range, (Neumann, Cohen and Weinstein 2014) there is substantial variability across studies, and generally higher values are placed on life extending than quality improving interventions.(Hirth, et al. 2000, Ryen and Svensson 2014) Our study cannot establish exactly what decision makers should set as a reasonable willingness-to-pay per QALY as such decisions must occur in the context of overall healthcare and societal resources and needs.

Conclusions

Healthcare costs are rising yet societal resources are limited. Thus, it is increasingly important for physicians to consider medical care in terms of patient outcomes and cost-effectiveness.(Holloway and Ringel 2011) We evaluated the cost-effectiveness of four EEG monitoring strategies (no monitoring and monitoring for 1 hour, 24 hours, or 48 hours) while varying the probability that an EEG monitoring based management strategies would improve outcome. Our results indicated that if even small neurodevelopmental outcome improvements are achieved, then EEG monitoring could be a cost-effective neuroprotective approach. At willingness-to-pay values of about \$50,000 per QALY gained, if ESE identification and management improved neurodevelopmental outcomes by as little as 3% then 24 hours of EEG monitoring would be cost-effective. If larger outcome improvements were achieved, then 48 hours of EEG monitoring could also be cost-effective. Further study is needed to evaluate whether strategies to identify and manage ESE actually improve neurodevelopmental outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

Abend NS, Arndt DH, Carpenter JL, et al. Electrographic seizures in pediatric ICU patients: Cohort study of risk factors and mortality. *Neurology*. 2013; 81:383–391. [PubMed: 23794680]

- Abend NS, Dlugos DJ. Nonconvulsive status epilepticus in a pediatric intensive care unit. *Pediatr Neurol.* 2007; 37:165–170. [PubMed: 17765803]
- Abend NS, Gutierrez-Colina AM, Topjian AA, et al. Nonconvulsive seizures are common in critically ill children. *Neurology.* 2011; 76:1071–1077. [PubMed: 21307352]
- Abend NS, Sanchez SM, Berg RA, Dlugos DJ, Topjian AA. Treatment of electrographic seizures and status epilepticus in critically ill children: A single center experience. *Seizure.* 2013; 22:467–471. [PubMed: 23601851]
- Abend NS, Topjian A, Ichord R, et al. Electroencephalographic monitoring during hypothermia after pediatric cardiac arrest. *Neurology.* 2009; 72:1931–1940. [PubMed: 19487651]
- Abend NS, Topjian AA, Gutierrez-Colina AM, Donnelly M, Clancy RR, Dlugos DJ. Impact of continuous EEG monitoring on clinical management in critically ill children. *Neurocrit Care.* 2011; 15:70–75. [PubMed: 20499208]
- Abend NS, Topjian AA, Williams S. How much does it cost to identify a critically ill child experiencing electrographic seizures? *Journal of Clinical Neurophysiology.* In press.
- Abend NS, Wusthoff CJ, Goldberg EM, Dlugos DJ. Electrographic seizures and status epilepticus in critically ill children and neonates with encephalopathy. *Lancet Neurol.* 2013; 12:1170–1179. [PubMed: 24229615]
- Arango JI, Deibert CP, Brown D, Bell M, Dvorchik I, Adelson PD. Posttraumatic seizures in children with severe traumatic brain injury. *Childs Nerv Syst.* 2012; 28:1925–1929. [PubMed: 22843174]
- Arndt DH, Lerner JT, Matsumoto JH, et al. Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort. *Epilepsia.* 2013; 54:1780–1788. [PubMed: 24032982]
- Beers SR, Wisniewski SR, Garcia-Filion P, et al. Validity of a pediatric version of the Glasgow Outcome Scale-Extended. *J Neurotrauma.* 2012; 29:1126–1139. [PubMed: 22220819]
- Bickford CD, Magee LA, Mitton C, et al. Magnesium sulphate for fetal neuroprotection: a cost-effectiveness analysis. *BMC Health Serv Res.* 2013; 13:527. [PubMed: 24350635]
- Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care.* 2012; 17:3–23. [PubMed: 22528274]
- Carroll AE, Downs SM. Improving decision analyses: parent preferences (utility values) for pediatric health outcomes. *J Pediatr.* 2009; 155:21–25. 25 e21–25. [PubMed: 19394030]
- Gold JJ, Crawford JR, Glaser C, Sheriff H, Wang S, Nespeca M. The role of continuous electroencephalography in childhood encephalitis. *Pediatr Neurol.* 2014; 50:318–323. [PubMed: 24507696]
- Greiner HM, Holland K, Leach JL, Horn PS, Hershey AD, Rose DF. Nonconvulsive status epilepticus: the encephalopathic pediatric patient. *Pediatrics.* 2012; 129:e748–755. [PubMed: 22331332]
- Gutierrez-Colina AM, Topjian AA, Dlugos DJ, Abend NS. EEG Monitoring in Critically Ill Children: Indications and Strategies. *Pediatric Neurology.* 2012; 46:158–161. [PubMed: 22353290]
- Gwer S, Idro R, Fegan G, et al. Continuous EEG monitoring in Kenyan children with non-traumatic coma. *Arch Dis Child.* 2012; 97:343–349. [PubMed: 22328741]
- Hasbani DM, Topjian AA, Friess SH, et al. Nonconvulsive electrographic seizures are common in children with abusive head trauma*. *Pediatr Crit Care Med.* 2013; 14:709–715. [PubMed: 23842589]
- Herman ST, Abend NS, Bleck TP, et al. Consensus statement on continuous EEG in critically ill adults and children, part I: indications. *J Clin Neurophysiol.* 2015; 32:87–95. [PubMed: 25626778]
- Herman ST, Abend NS, Bleck TP, et al. Consensus Statement on Continuous EEG in Critically Ill Adults and Children, Part II: Personnel, Technical Specifications, and Clinical Practice. *J Clin Neurophysiol.* 2015; 32:96–108. [PubMed: 25626777]
- Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard. *Med Decis Making.* 2000; 20:332–342. [PubMed: 10929856]
- Holloway RG, Ringel SP. Getting to value in neurological care: a roadmap for academic neurology. *Ann Neurol.* 2011; 69:909–918. [PubMed: 21681794]

- Hosain SA, Solomon GE, Kobylarz EJ. Electroencephalographic patterns in unresponsive pediatric patients. *Pediatr Neurol.* 2005; 32:162–165. [PubMed: 15730895]
- Jette N, Claassen J, Emerson RG, Hirsch LJ. Frequency and predictors of nonconvulsive seizures during continuous electroencephalographic monitoring in critically ill children. *Arch Neurol.* 2006; 63:1750–1755. [PubMed: 17172615]
- Katz RT. Life expectancy for children with cerebral palsy and mental retardation: implications for life care planning. *NeuroRehabilitation.* 2003; 18:261–270. [PubMed: 14530591]
- Kirkham FJ, Wade AM, McElduff F, et al. Seizures in 204 comatose children: incidence and outcome. *Intensive Care Med.* 2012; 38:853–862. [PubMed: 22491938]
- McCoy B, Sharma R, Ochi A, et al. Predictors of nonconvulsive seizures among critically ill children. *Epilepsia.* 2011; 52:1973–1978. [PubMed: 22003955]
- Neumann PJ, Cohen JT, Weinstein MC. Updating Cost-Effectiveness - The Curious Resilience of the \$50,000-per-QALY Threshold. *N Engl J Med.* 2014; 371:796–797. [PubMed: 25162885]
- Payne ET, Zhao XY, Frndova H, et al. Seizure burden is independently associated with short term outcome in critically ill children. *Brain.* 2014; 137:1429–1438. [PubMed: 24595203]
- Piantino JA, Wainwright MS, Grimson M, et al. Nonconvulsive Seizures Are Common in Children Treated With Extracorporeal Cardiac Life Support. *Pediatr Crit Care Med.* 2013; 14:601–609. [PubMed: 23823196]
- Ryen L, Svensson M. The Willingness to Pay for a Quality Adjusted Life Year: A Review of the Empirical Literature. *Health Econ.* 2014
- Saengpatrachai M, Sharma R, Hunjan A, et al. Nonconvulsive seizures in the pediatric intensive care unit: etiology, EEG, and brain imaging findings. *Epilepsia.* 2006; 47:1510–1518. [PubMed: 16981868]
- Sanchez SM, Carpenter J, Chapman KE, et al. Pediatric ICU EEG Monitoring: Current Resources and Practice in the United States and Canada. *Journal of Clinical Neurophysiology.* 2013; 30:156–160. [PubMed: 23545766]
- Schreiber JM, Zelleke T, Gaillard WD, Kaulas H, Dean N, Carpenter JL. Continuous video EEG for patients with acute encephalopathy in a pediatric intensive care unit. *Neurocrit Care.* 2012; 17:31–38. [PubMed: 22565632]
- Shahwan A, Bailey C, Shekerdemian L, Harvey AS. The prevalence of seizures in comatose children in the pediatric intensive care unit: A prospective video-EEG study. *Epilepsia.* 2010; 51:1198–1204. [PubMed: 20163439]
- Tay SK, Hirsch LJ, Leary L, Jette N, Wittman J, Akman CI. Nonconvulsive status epilepticus in children: clinical and EEG characteristics. *Epilepsia.* 2006; 47:1504–1509. [PubMed: 16981867]
- Topjian AA, Gutierrez-Colina AM, Sanchez SM, et al. Electrographic Status Epilepticus is Associated with Mortality and Worse Short-Term Outcome in Critically Ill Children. *Critical Care Medicine.* 2013; 31:215–223. [PubMed: 23164815]
- Wagenman KL, Blake TP, Sanchez SM, et al. Electrographic status epilepticus and long-term outcome in critically ill children. *Neurology.* 2014; 82:396–404. [PubMed: 24384638]
- Williams K, Jarrar R, Buchhalter J. Continuous video-EEG monitoring in pediatric intensive care units. *Epilepsia.* 2011; 52:1130–1136. [PubMed: 21671924]

Figure 1.

Decision Tree and Markov Model. (Top) This analysis aims to evaluate four different EEG strategies (none, 1 hour EEG, 24 hours EEG, and 48 hours EEG). (Middle) For each EEG strategy, the patient may or may not be exposed to electrographic status epilepticus. If the patient experiences electrographic status epilepticus, it may or may not be identified by the selected EEG strategy. If electrographic status epilepticus is identified, it may or may not be managed effectively. The probability that management was effective was varied in a sensitivity analysis as this study's primary outcome. (Bottom) The patient may or may not survive to intensive care unit discharge. For surviving patients, a Markov model (M in figure) assesses the probability of surviving each subsequent year. The square signifies the choose node, circles signify chance nodes, and triangles signify terminal nodes.

Figure 2.

Change in the incremental cost-effectiveness ratio of the 48 hour EEG monitoring strategy as the probability that management improves outcome varies from 0.02 to 0.07. As the probability that management improves outcome increases, the incremental cost effectiveness of the 48 hour EEG strategy becomes smaller. When the probability that management improves outcome equals or exceeds 0.07, the 48 hour EEG monitoring strategy dominates all other strategies so the incremental cost effectiveness ratio equals zero. When the curve intersects values of incremental cost effectiveness ratios that are also commonly accepted willingness-to-pay values of \$50,000 or \$100,000 (dotted lines), 48 hours of EEG monitoring would be selected when the probability that management improves outcome is about 0.035 and 0.045, respectively.

Figure 3.

Example cost effectiveness curve from probabilistic analysis demonstrating the relative frequency that the incremental cost-effectiveness ratios from the probabilistic sensitivity analysis (y-axis) meet increasing willingness-to-pay value (x-axis). The example is derived from a probability of management improving outcome of 0.05. Our willingness-to-pay (above or below about \$30,000 per QALY) would determine whether the 24 or 48 hour EEG monitoring strategy would be selected. At higher or lower willingness-to-pay values, an increasing number of trials would favor the 48 or 24 hour strategies, respectively.

Table 1

Estimated costs of 1 hour, 24 hour, and 48 hour EEG monitoring strategies

Cost Component	1 hour EEG	24 hours EEG	48 hours EEG
EEG Technologist	\$48.03	\$96.06	\$192.12
Physician	\$31.40	\$125.60	\$251.20
Systems Analyst	\$0.70	\$4.23	\$8.46
EEG Machine	\$4.01	\$24.04	\$48.08
Electrodes	\$0.55	\$0.55	\$1.10
Total Cost	\$84.69	\$250.48	\$500.96

Table 2

Variables, base case values, and distribution characteristics.

Variable	Base Case Value	Distribution Type	Distribution Parameter 1	Distribution Parameter 2
Probability of Electrographic Seizures	0.33	Beta	740	1507
Probability of ESE (among those experiencing electrographic seizures)	0.43	Beta	257	340
Probability of ESE Identification with a 1 hour EEG	0.55	Beta	148	120
Probability of ESE Identification with 24 hours of EEG monitoring	0.85	Beta	229	39
Probability of ESE Identification with of 48 Hours EEG monitoring	0.89	Beta	238	30
Probability of Survival at ICU Discharge if ESE	0.7	Beta	30	13
Probability of Survival at ICU Discharge if no ESE	0.85	Beta	134	23
Probability of Survival Yearly if Favorable ICU Outcome	0.987 (70 years)	Beta	987	13
Probability of Survival Yearly if Unfavorable ICU Outcome	0.984 (59 years)	Beta	984	16
QALY if ESE	0.7	Normal	0.7	0.01
QALY if no ESE	0.82	Normal	0.82	0.01
Cost of EEG for 1 hour	\$84.69	Normal	\$84.69	\$9.37
Cost of EEG for 24 hours	\$250.48	Normal	\$250.48	\$31.29
Cost of EEG for 48 hours	\$500.96	Normal	\$500.96	\$62.58
Yearly Cost if Unfavorable Outcome	\$50,000	Normal	50000	10000
Yearly Cost if Favorable Outcome	\$5,000	Normal	5000	1000

EEG, electroencephalogram; ESE, electrographic status epilepticus; ICU, intensive care unit; QALY, quality adjusted life years

* For beta distributions, parameter 1 is alpha (number with seizures) and parameter 2 is beta (number without seizures). For normal distributions, parameter 1 is mean and parameter 2 is standard error.

Table 3

Deterministic sensitivity analysis (one way factor analysis evaluating a single factor) varying the probability that management would improve outcome.

Probability Management Improves Outcome	Strategy	Cost (\$)	Incremental Cost (\$)	Effect	Incremental Effect	Incremental Cost Effectiveness Ratio	Dominated
0.01	No EEG	195,525	425	15.723	-0.0073	-	Dominated ^a
	1 hour EEG	195,073	149	15.728	-0.0025	-	Dominated ^a
	24 hours EEG	194,924	0	15.730	0	0	
	48 hours EEG	195,100	176	15.730	0.0003	639,344 ^b	
0.02	No EEG	195,525	1,265	15.723	-0.0146	-	Dominated ^a
	1 hour EEG	194,549	290	15.732	-0.0055	-	Dominated ^a
	24 hours EEG	194,115	0	15.737	0	0	
	48 hours EEG	194,259	144	15.738	0.0006	262,050 ^b	
0.03	No EEG	195,525	2,105	15.723	-0.0219	-	Dominated ^a
	1 hour EEG	194,027	608	15.737	-0.0083	-	Dominated ^a
	24 hours EEG	193,306	0	15.744	0.0000	0	
	48 hours EEG	193,419	113	15.745	0.0008	136,286 ^b	
0.04	No EEG	195,525	2,946	15.723	-0.0291	-	Dominated ^a
	1 hour EEG	193,505	926	15.741	-0.0110	-	Dominated ^a
	24 hours EEG	192,498	0	15.751	0.0000	0	
	48 hours EEG	192,579	81	15.752	0.0011	73,403 ^b	
0.05	No EEG	195,525	3,786	15.723	-0.0364	-	Dominated ^a
	1 hour EEG	192,982	1,561	15.746	-0.0138	-	Dominated ^a
	24 hours EEG	191,689	0	15.758	0.0000	0	
	48 hours EEG	191,738	49	15.760	0.0014	35,674 ^b	
0.06	No EEG	195,525	4,627	15.723	-0.0437	-	Dominated ^a
	1 hour EEG	192,459	1,561	15.750	-0.0165	-	Dominated ^a
	24 hours EEG	190,880	0	15.765	0.0000	0	
	48 hours EEG	190,898	17	15.767	0.0017	10,521 ^b	

Probability Management Improves Outcome	Strategy	Cost (\$)	Incremental Cost (\$)	Effect	Incremental Effect	Incremental Cost Effectiveness Ratio	Dominated
0.07	No EEG	195,525	5,468	15.723	-0.0510	-	Dominated ^a
	1 hour EEG	191,936	1,879	15.755	-0.0193	-	Dominated ^a
	24 hours EEG	190,072	14	15.772	-0.0019	-	Dominated ^c
	48 hours EEG	190,057	0	15.774	0.0000	0 ^c	

^a At all probabilities, the no EEG and 1 hour EEG strategies have lower EEG monitoring costs than the 24 or 48 hour strategies, but since fewer electrographic seizures are identified and managed outcomes are worse leading to higher subsequent care costs. Thus, on balance, the costs associated with the no EEG and 1 hour EEG strategies are higher despite having less effect than the 24 and 48 hour EEG monitoring strategies. Therefore, the no EEG and 1 hour EEG strategies are always dominated by the other strategies and would never be selected.

^b When the probability that management improves outcome is between 0.01 and 0.06, the costs of EEG monitoring are higher for 48 hours than 24 hours of EEG monitoring. Only slightly more patients experiencing electrographic seizures are identified and managed using the 48 hour EEG monitoring strategy, and this very small increase in effect leads to only a very small reduction in subsequent care costs. Thus, on balance, the costs associated with 48 hours of EEG monitoring are higher and the effect is only slightly higher. As the probability that management improves outcome increases from 0.03 to 0.06, the incremental cost effectiveness ratio decreases, so the willingness-to-pay per quality adjusted life year determines whether the 24 or 48 hour EEG monitoring strategy is selected.

^c When the probability that management improves outcome is 0.07 or greater, the costs of EEG monitoring remain higher for 48 hours than 24 hours of EEG monitoring. However, the 48 hour EEG monitoring strategy identifies more patients experiencing seizures, and this higher effect improves outcome and reduces subsequent care costs. On balance, the costs of the 48 hour EEG monitoring strategy are less than the costs for the 24 hour EEG monitoring strategy. The 24 hour EEG monitoring strategy has higher costs and lower effect than the 48 hour EEG monitoring strategy. The 24 hour EEG monitoring strategy is therefore dominated by the 48 hour EEG monitoring strategy and would never be selected.