Electrographic seizures in pediatric ICU patients: Cohort study of risk factors and mortality
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Cohort study of risk factors and mortality

ABSTRACT

Objectives: We aimed to determine the incidence of electrographic seizures in children in the pediatric intensive care unit who underwent EEG monitoring, risk factors for electrographic seizures, and whether electrographic seizures were associated with increased odds of mortality.

Methods: Eleven sites in North America retrospectively reviewed a total of 550 consecutive children in pediatric intensive care units who underwent EEG monitoring. We collected data on demographics, diagnoses, clinical seizures, mental status at EEG onset, EEG background, interictal epileptiform discharges, electrographic seizures, intensive care unit length of stay, and in-hospital mortality.

Results: Electrographic seizures occurred in 162 of 550 subjects (30%), of which 61 subjects (38%) had electrographic status epilepticus. Electrographic seizures were exclusively subclinical in 59 of 162 subjects (36%). A multivariable logistic regression model showed that independent risk factors for electrographic seizures included younger age, clinical seizures prior to EEG monitoring, an abnormal initial EEG background, interictal epileptiform discharges, and a diagnosis of epilepsy. Subjects with electrographic status epilepticus had greater odds of in-hospital death, even after adjusting for EEG background and neurologic diagnosis category.

Conclusions: Electrographic seizures are common among children in the pediatric intensive care unit, particularly those with specific risk factors. Electrographic status epilepticus occurs in more than one-third of children with electrographic seizures and is associated with higher in-hospital mortality.


GLOSSARY

CEEG = continuous EEG; CI = confidence interval; IQR = interquartile range; OR = odds ratio; PICU = pediatric intensive care unit.

Several single-center studies have reported electrographic seizures in 10%–40% of children who underwent clinically indicated continuous EEG (CEEG) monitoring in the pediatric intensive care unit (PICU) or emergency department.1–12 The majority of electrographic seizures were not accompanied by any clinical signs,1–3,8,10–14 even in nonparalyzed patients.1,14 Therefore, accurate seizure identification requires CEEG. Data obtained from CEEG reportedly affect clinical management in 59% of monitored children, most often by affecting anticonvulsant utilization.15 Several studies have reported an association between electrographic seizures or status epilepticus and worse outcome,11,12,16,17 occurring independently of potential confounders related to acute etiology and critical illness severity.1,12,16

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Since electrographic seizures are common and may be associated with worse outcome, an increasing number of children in the PICU are undergoing CEEG. A recent survey of 61 large pediatric hospitals in the United States and Canada reported a 30% increase in the number of monitored PICU patients from 2010 to 2011. In 2011, a median of 10 patients at institutions in the United States and 3 patients at institutions in Canada underwent CEEG per month. Since seemingly small changes in CEEG indications and strategies may have a substantial impact on required CEEG resources, data regarding seizure risk factors are needed to ensure limited neurophysiologic resources are targeted at children most at risk for seizures.

To date, studies of CEEG in children in the PICU have reported on cohorts from single institutions, limiting their generalizability. Therefore, we conducted a multicenter retrospective study of children undergoing CEEG in the PICU to estimate a more precise and generalizable incidence of electrographic seizures, describe electrographic seizure characteristics, identify risk factors for electrographic seizures, and determine whether electrographic seizures or electrographic status epilepticus were associated with higher in-hospital mortality.

METHODS Study design. This was a retrospective cohort study conducted at 11 sites in the United States and Canada.

Standard protocol approvals, registrations, and patient consents. Each site obtained institutional review board approval.

Patients. Each of the 11 sites provided data for 50 consecutive children aged 1 month to 21 years who underwent CEEG in the PICU. Continuous bedside video CEEG was performed using the international standard 10–20 system of electrode placement and the clinical EEG system at each institution. Children admitted to the PICU for planned epilepsy-related management such as epilepsy surgery or epilepsy partialis continua management were excluded. CEEG required performance of at least 6 hours of EEG recording. If there were multiple CEEG sessions during the same admission, then only data from the first session were included. CEEG interruptions lasting less than 12 hours were considered the same session.

Clinical variables. We collected information on age, sex, prior neurologic diagnoses (including prior epilepsy, epileptic encephalopathy, developmental delay/intellectual disability, and other neurologic diagnoses), acute neurologic disorder, occurrence of clinical seizures or status epilepticus prior to CEEG, mental status at CEEG onset, duration of PICU stay, and in-hospital mortality. Acute neurologic disorders were grouped into 3 general diagnosis categories: 1) epilepsy-related, 2) acute structural (stroke, CNS inflammation or autoimmune disorder, traumatic brain injury, CNS infection, brain malformation, tumor/oncologic, and hypoxic-ischemic encephalopathy), and 3) acute nonstructural (sepsis, metabolic, pharmacologic sedation, toxin, paralytic administration).

EEG variables. EEG data were obtained by an investigator at each center without central review. We collected information on electrographic seizure occurrence and characteristics, initial and typical EEG background category, and occurrence of interictal epileptiform discharges. Electrographic seizures were defined as abnormal, paroxysmal electroencephalographic events that were different from the background, lasted longer than 10 seconds (or shorter if associated with a clinical seizure), had a plausible electrographic field, and evolved in morphology and spatial distribution. Electrographic seizures were classified as electrographic status epilepticus if any single seizure lasted longer than 30 minutes or if recurrent seizures together lasted for more than 30 minutes in any 1-hour epoch (30% seizure burden). Electrographic seizure characteristics included typical duration, proportion with clinical correlate, and anatomical localization at onset and maximal extent. Subclinical seizures were defined as electrographic seizures without clinical signs on video review.

Statistical collection and analyses. Data were collected and managed using REDCap (Research Electronic Data Capture), a Web-based electronic data application hosted at the Children’s Hospital of Philadelphia Research Institute. Descriptive statistics are presented as medians and interquartile ranges (IQRs) for continuous variables and as counts and percentages for categorical variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for potential predictors. Possible risk factors for seizure occurrence were first analyzed by univariate logistic regressions. A 2-sided p value <.05 was used to denote statistical significance. Variables that were significant in the univariate analyses were then entered into a multivariable logistic regression model. The backward selection method was used to generate a final reduced model. The Hosmer-Lemeshow test was used to test the hypothesis of adequate fit. The same approach was used to analyze mortality and potential correlates of mortality. Fisher exact test was used to test whether the proportion of children with electrographic seizures was different within subcategories of traumatic brain injury, stroke, and hypoxic-ischemic encephalopathy. The Kruskal-Wallis rank test was used to compare PICU length of stay between seizure status categories, with subsequent bivariate comparisons performed using the Wilcoxon rank sum test. All statistics were performed using STATA/SE (version 12.0, Stata Corp., TX).

RESULTS A total of 550 subjects were included, of whom 295 were boys (54%). The median age was 36.5 months (IQR 9 months–10.2 years). To provide data on 50 consecutive subjects, sites required a median of 416 days (IQR 194–655 days). The CEEG duration was <12 hours in 16% (88 of 550), 12–24 hours in 34% (187 of 550), 24–48 hours in 23% (129 of 550), 48–72 hours in 8% (44 of 550), >72 hours in 17% (94 of 550), and unknown in 1% (8 of 550).

Incidence of electrographic seizures. Electrographic seizures occurred in 30% of subjects (162 of 550). Among subjects with electrographic seizures, 38% (61 of 162) had electrographic status epilepticus, which was categorized as continuous seizure activity lasting ≥30 minutes in 46% (28 of 61), recurrent seizures occupying more than 30 minutes within an hour in 51% (31 of 61), and unreported in 3% (2 of 61). Table 1 provides
Electrographic seizure characteristics including duration, clinical correlate, and localization.

**Risk factors for electrographic seizures.** Seizure occurrence by acute diagnosis is shown in table 2. Subanalyses were performed for several acute diagnoses. Among the 19 subjects with sepsis, electrographic seizures occurred in 6 of 12 subjects (50%) without any other neurologic diagnosis and 5 of 7 subjects (71%) with another neurologic diagnosis. Electrographic seizures were more common in children with abusive (58%, 14 of 24) than accidental (9%, 3 of 33) traumatic brain injury ($p < 0.001$). There was no difference in electrographic seizure occurrence in children with ischemic stroke (31%, 5 of 16), hemorrhagic stroke (30%, 3 of 7), and sinovenous thrombosis (67%, 2 of 3) ($p = 0.51$). There was no difference in electrographic seizure occurrence in children with hypoxic-ischemic encephalopathy secondary to cardiac arrest (20%, 10 of 49), near drowning (14%, 1 of 7), or with an etiology categorized as other (18%, 2 of 11) ($p = 1.0$).

The median age of children without seizures was 42 months (IQR 12.6–144 months) and with seizures was 23 months (IQR 5–87 months) ($p = 0.002$). Clinical seizures or status epilepticus occurred prior to CEEG in 48% (180 of 377) without seizures and 79% (125 of 159) with seizures (OR 4.02, 95% CI 2.62–6.17). The initial EEG background was normal in 22% (87 of 388) without seizures and 4% (7 of 162) with seizures (OR 6.40, 95% CI 2.94–13.89). Interictal epileptiform discharges occurred in 28% (110 of 388) without seizures and 75% (120 of 159) with seizures (OR 7.78, 95% CI 5.10–11.86). An epilepsy-related diagnosis was present in 21% (83 of 388) without seizures and 50% (81 of 162) with seizures (OR 3.67, 95% CI 2.48–5.43).

Table 3 provides an evaluation of electrographic seizure risk factors. Multivariable analysis showed that risk factors for electrographic seizures were younger age, clinical seizures prior to CEEG, abnormal initial EEG background, presence of interictal epileptiform discharges, and an epilepsy-related diagnosis.

Outcome. Thirteen percent (73 of 550) of subjects died. Death occurred in 12% (46 of 388) without seizures, 12% (12 of 101) with electrographic seizures, and 25% (15 of 61) with electrographic status epilepticus ($p = 0.02$). Table 4 provides an evaluation of in-hospital mortality risk factors. The occurrence of electrographic status epilepticus, an abnormal EEG background, and acute structural or nonstructural neurologic diagnoses were independently associated with mortality. Adjusting for neurologic diagnosis category and EEG background category, the odds of mortality remained higher among subjects with electrographic status epilepticus (OR 2.42, 95% CI

**Table 1** Electrographic seizure characteristics

<table>
<thead>
<tr>
<th>Electrographic seizure characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical seizure duration (n = 158)</td>
<td></td>
</tr>
<tr>
<td>10–59 s</td>
<td>60 (38)</td>
</tr>
<tr>
<td>1–5 min</td>
<td>63 (40)</td>
</tr>
<tr>
<td>6–30 min</td>
<td>25 (16)</td>
</tr>
<tr>
<td>&gt;30 min</td>
<td>10 (8)</td>
</tr>
</tbody>
</table>

| Clinical correlate (n = 162)          |               |
| All (100%)                            | 43 (27)       |
| Most (50%–99%)                        | 22 (14)       |
| Some (1%–49%)                         | 33 (20)       |
| None (0%)                             | 59 (35)       |
| Unknown                               | 5 (3)         |

**Table 2** Electrographic seizure occurrence by diagnosis

<table>
<thead>
<tr>
<th>Diagnosis (n)*</th>
<th>Electrographic seizures present, %</th>
<th>Electrographic seizures absent, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis (19)</td>
<td>58</td>
<td>42</td>
</tr>
<tr>
<td>Epilepsy (159)</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>Brain malformation (24)</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td>CNS inflammation or autoimmune disorder (24)</td>
<td>33</td>
<td>67</td>
</tr>
<tr>
<td>Stroke (33)</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>Traumatic brain injury (61)</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>Metabolic (59)</td>
<td>29</td>
<td>71</td>
</tr>
<tr>
<td>CNS infection (28)</td>
<td>29</td>
<td>71</td>
</tr>
<tr>
<td>Unknown (14)</td>
<td>21</td>
<td>78</td>
</tr>
<tr>
<td>Tumor/oncologic (21)</td>
<td>19</td>
<td>81</td>
</tr>
<tr>
<td>Hypoxic-ischemic encephalopathy (73)</td>
<td>18</td>
<td>82</td>
</tr>
<tr>
<td>Pharmacologic sedation—no known neurologic problem (15)</td>
<td>13</td>
<td>87</td>
</tr>
<tr>
<td>Toxin (8)</td>
<td>13</td>
<td>87</td>
</tr>
<tr>
<td>Paralytic administration (28)</td>
<td>8</td>
<td>92</td>
</tr>
</tbody>
</table>

*Subjects could have more than one diagnosis.
Table 3 Risk factors for electrographic seizures

<table>
<thead>
<tr>
<th>Variables (electrographic seizure prevalence)</th>
<th>Electrographic seizures present (162 [29.5%]), n (%)</th>
<th>Electrographic seizures absent (388 [70.5%]), n (%)</th>
<th>Univariate analysis</th>
<th>Multivariable analysis</th>
<th>Final reduced model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mo, median (IQR)</td>
<td>23 (5, 87)</td>
<td>42 (12.6, 144)</td>
<td>0.99 (0.99–0.99)</td>
<td>0.001</td>
<td>0.99 (0.99–0.99)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (26%)</td>
<td>76 (47)</td>
<td>219 (56)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Female (34%)</td>
<td>86 (53)</td>
<td>169 (44)</td>
<td>1.47 (1.01–2.12)</td>
<td>0.042</td>
<td>1.37 (0.87–2.20)</td>
</tr>
<tr>
<td>Prior developmental delay or intellectual disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (24%)</td>
<td>77 (48)</td>
<td>246 (63)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes (37%)</td>
<td>85 (52)</td>
<td>142 (37)</td>
<td>1.96 (1.35–2.86)</td>
<td>&lt;0.001</td>
<td>0.67 (0.33–1.36)</td>
</tr>
<tr>
<td>Prior epilepsy diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (22%)</td>
<td>84 (52)</td>
<td>292 (75)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes (45%)</td>
<td>78 (48)</td>
<td>96 (25)</td>
<td>2.84 (1.93–4.18)</td>
<td>&lt;0.001</td>
<td>1.17 (0.52–2.61)</td>
</tr>
<tr>
<td>Prior epileptic encephalopathy diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (27%)</td>
<td>132 (81)</td>
<td>359 (93)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes (51%)</td>
<td>30 (19)</td>
<td>29 (7)</td>
<td>2.79 (1.61–4.83)</td>
<td>&lt;0.001</td>
<td>0.93 (0.43–2.00)</td>
</tr>
<tr>
<td>Prior neurologic disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (26%)</td>
<td>102 (81)</td>
<td>283 (73)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes (18%)</td>
<td>60 (19)</td>
<td>105 (27)</td>
<td>1.60 (1.08–2.38)</td>
<td>0.019</td>
<td>0.83 (0.44–1.57)</td>
</tr>
<tr>
<td>Clinical seizures prior to EEG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (15%)</td>
<td>34 (21)</td>
<td>197 (52)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Seizures (45%)</td>
<td>93 (58)</td>
<td>114 (30)</td>
<td>4.73 (2.99–7.45)</td>
<td>&lt;0.001</td>
<td>2.62 (1.50–4.59)</td>
</tr>
<tr>
<td>Status epilepticus (33%)</td>
<td>32 (20)</td>
<td>66 (18)</td>
<td>2.81 (1.61–4.91)</td>
<td>&lt;0.001</td>
<td>0.97 (0.46–2.04)</td>
</tr>
<tr>
<td>Mental status at EEG onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (33%)</td>
<td>20 (13)</td>
<td>51 (14)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lethargic/obtunded (33%)</td>
<td>99 (62)</td>
<td>198 (54)</td>
<td>1.28 (0.72–2.26)</td>
<td>0.404</td>
<td></td>
</tr>
<tr>
<td>Comatose (25%)</td>
<td>40 (25)</td>
<td>118 (32)</td>
<td>0.86 (0.46–1.62)</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Initial EEG background category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/sleep (7%)</td>
<td>7 (4)</td>
<td>87 (22)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Slow/disorganized (33%)</td>
<td>112 (69)</td>
<td>225 (58)</td>
<td>6.19 (2.77–13.81)</td>
<td>&lt;0.001</td>
<td>6.08 (1.56–18.36)</td>
</tr>
<tr>
<td>Discontinuous (34%)</td>
<td>13 (8)</td>
<td>25 (6)</td>
<td>6.46 (2.33–17.94)</td>
<td>&lt;0.001</td>
<td>5.35 (1.56–18.36)</td>
</tr>
<tr>
<td>Burst-suppression (45%)</td>
<td>13 (8)</td>
<td>16 (4)</td>
<td>10.10 (3.49–29.21)</td>
<td>&lt;0.001</td>
<td>13.12 [3.36–51.27]</td>
</tr>
<tr>
<td>Attenuated/featureless (33%)</td>
<td>17 (10)</td>
<td>35 (9)</td>
<td>6.04 (2.30–15.82)</td>
<td>&lt;0.001</td>
<td>12.57 [3.80–41.52]</td>
</tr>
</tbody>
</table>

Continued
The relationship between electrographic status epilepticus and mortality was further explored within the acute neurologic diagnosis categories. Among subjects with an acute structural disorder, death occurred in 37% (10 of 27) with electrographic status epilepticus and 18% (40 of 218) without electrographic status epilepticus \((p = 0.02)\). Among subjects with an acute nonstructural neurologic disorder, death occurred in 33% (4 of 12) with electrographic status epilepticus and 12% (15 of 129) without electrographic status epilepticus \((p = 0.04)\). Among subjects with an epilepsy-related disorder, death occurred in 5% (1 of 22) with electrographic status epilepticus and 2% (3 of 142) without electrographic status epilepticus \((p = 0.49)\).

PICU length of stay was available for 525 subjects. The median length of stay was 5.5 days (IQR 2–16.5 days) in subjects without electrographic seizures, 8 days (IQR 3–20 days) in subjects with electrographic seizures, and 11 days (IQR 5–29 days) in subjects with electrographic status epilepticus. Length of stay was longer in patients with electrographic status epilepticus compared to both those without seizures \((p = 0.0001)\) and those with electrographic seizures but not electrographic status epilepticus \((p = 0.03)\). There was no difference between length of stay in subjects with electrographic seizures (not electrographic status epilepticus) vs those without electrographic seizures \((p = 0.06)\).

**DISCUSSION** We present a large retrospective cohort study of electrographic seizures among children in the PICU who underwent clinically ordered CEEG at 11 North American institutions. Electrographic seizures occurred in 30% of children, of whom 38% had electrographic status epilepticus.

Prior single-center studies have reported varying incidences of electrographic seizures or electrographic status epilepticus, ranging from 7% to 48% of monitored children.\(^1\)–\(^12\) This variability is likely due to the smaller size of these cohorts, variability in case mix across institutions, and interinstitution variability in CEEG indications. Furthermore, previous studies were performed over nearly a decade, during which CEEG indications and other components of critical care have evolved. The larger size of the present cohort permits a more precise estimate of seizure incidence and more detailed risk factor analyses with narrower OR CIs. The multicenter design provides more generalizable results.

This study provides an estimate of electrographic seizure incidence that is within the range suggested by smaller single-center studies, and confirms that a large proportion of children in the PICU are experiencing 1.08–5.40) but not subjects with electrographic seizures (OR 1.78, 95% CI 0.80–3.95).
Among children with electrographic seizures, 35% had no clinical signs associated with any electrographic seizures and only 27% had clinical signs associated with all electrographic seizures. This is consistent with prior single-center studies that have reported that many electrographic seizures are not accompanied by any clinical signs,\(^1,3,8,10\) even in non-paralyzed patients.\(^1,14\) Therefore, CEEG and not only close clinical observation is required to identify electrographic seizures in many patients.

Seemingly small variations in clinical pathways for PICU CEEG can lead to substantial differences in resource utilization.\(^20\) Determining which children are at highest risk for seizures may help optimize utilization of limited CEEG resources. The current study identified risk factors for seizure occurrence including younger age, clinical seizures prior to CEEG, abnormal initial EEG background of any type, presence of interictal epileptiform discharges, and an epilepsy-related diagnosis. These are consistent with risk factors identified in smaller single-center studies, although the associated risk can be better quantified in this larger cohort. Reported clinical risk factors for electrographic seizures in children include younger age,\(^1,10\) preceding convulsive status epilepticus,\(^10\) or clinically overt seizures,\(^11,13\) and structural brain injury,\(^11,13\) including traumatic brain injury\(^10\) and hypoxic-ischemic brain injury after cardiac arrest.\(^9\) Reported electrographic risk factors include epileptiform discharges,\(^10,13\) periodic epileptiform discharges,\(^3\) and lack of background reactivity.\(^3\) Most of these studies involved etiologically heterogeneous

### Table 4  Risk factors for in-hospital mortality

<table>
<thead>
<tr>
<th>Variables (death prevalence)</th>
<th>Dead 73 (13%), n(%)</th>
<th>Alive 477 (87%), n(%)</th>
<th>Univariate analysis</th>
<th>Multivariable/final reduced model(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mortality OR (95% CI)</td>
<td>p(^a)</td>
<td>Mortality OR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Age, mo, median (IQR)</td>
<td>13 (3, 91)</td>
<td>40 (11, 125)</td>
<td>0.99 (0.99-1.00)</td>
<td>0.159</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (12%)</td>
<td>36 (49)</td>
<td>259 (54)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Female (15%)</td>
<td>37 (51)</td>
<td>218 (46)</td>
<td>1.22 (0.75-1.99)</td>
<td>0.427</td>
</tr>
<tr>
<td>Prior developmental delay or intellectual disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (14%)</td>
<td>43 (63)</td>
<td>265 (57)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes (11%)</td>
<td>25 (37)</td>
<td>202 (43)</td>
<td>0.76 (0.45-1.29)</td>
<td>0.313</td>
</tr>
<tr>
<td>Prior neurologic disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (14%)</td>
<td>52 (72)</td>
<td>331 (70)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes (12%)</td>
<td>20 (28)</td>
<td>145 (30)</td>
<td>0.88 (0.51-1.52)</td>
<td>0.6444</td>
</tr>
<tr>
<td>Seizure category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (12%)</td>
<td>46 (63)</td>
<td>342 (72)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Seizures (12%)</td>
<td>12 (16)</td>
<td>89 (19)</td>
<td>1.00 (0.51-1.97)</td>
<td>0.994</td>
</tr>
<tr>
<td>Status epilepticus (25%)</td>
<td>15 (21)</td>
<td>46 (10)</td>
<td>2.42 (1.25-4.69)</td>
<td>0.008</td>
</tr>
<tr>
<td>Typical EEG background category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/sleep (1%)</td>
<td>1 (1)</td>
<td>91 (19)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Slow/disorganized (8%)</td>
<td>28 (37)</td>
<td>304 (64)</td>
<td>7.78 (1.04-58.14)</td>
<td>0.046</td>
</tr>
<tr>
<td>Discontinuous (18%)</td>
<td>8 (11)</td>
<td>37 (8)</td>
<td>19.68 (2.38-162.89)</td>
<td>0.006</td>
</tr>
<tr>
<td>Burst-suppression (31%)</td>
<td>8 (11)</td>
<td>18 (4)</td>
<td>40.44 (4.76-343.57)</td>
<td>0.001</td>
</tr>
<tr>
<td>Attenuated/featureless (53%)</td>
<td>30 (40)</td>
<td>27 (6)</td>
<td>101.11 (13.17-776.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neurologic diagnosis category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy related (2%)</td>
<td>4 (5)</td>
<td>160 (34)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Acute structural (20%)</td>
<td>50 (68)</td>
<td>195 (41)</td>
<td>10.26 (3.63-29.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute nonstructural (13%)</td>
<td>19 (26)</td>
<td>122 (26)</td>
<td>6.23 (2.07-18.78)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; IQR = interquartile range; OR = odds ratio.

\(^a\)Reference group is noted with 1.

\(^b\)Backwards stepwise regression was attempted to generate a reduced model but did not remove any covariates identified as significant in the initial multivariate logistic regression model.

\(^c\)Pairwise comparisons with the reference group were performed for variables with >2 categories.

\(^d\)Significant difference.
cohorts with only a small number of subjects with each etiology.

Sepsis was the diagnosis associated with the highest occurrence of electrographic seizures, and seizures occurred in children with and without other neurologic diagnoses. Encephalopathy in the setting of sepsis is often associated with neurophysiologic and neuroradiologic abnormalities and is likely multifactorial in etiology. A study of septic children demonstrated background patterns on EEG consistent with moderate to severe encephalopathy and elevated serum S100 beta and neuron-specific enolase compared to controls, indicating that neurologic injury may occur with sepsis. A study of adults in a medical intensive care unit reported that about one-third of patients with sepsis had electrographic seizures or periodic epileptiform discharges and the presence of sepsis was the only predictor of electrographic seizures or periodic epileptiform discharges. Furthermore, the presence of electrographic seizures or periodic epileptiform discharges was associated with death or severe disability at hospital discharge. Similarly, in children with convulsive status epilepticus, sepsis is an independent risk factor for death. The current data indicate that electrographic seizures may be common in children with sepsis, and further study is needed to evaluate the impact of these seizures on outcome.

The impact of CEEG and seizure identification on outcomes remains unclear. Presumably, identification of electrographic seizures by CEEG results in at least partially effective treatment and a reduced seizure burden, although this has only been demonstrated in neonates. When surveyed, most neurologists report that when electrographic seizures are identified, they generally initiate anticonvulsants immediately and aim to terminate all electrographic seizures. Similarly, observational studies have reported that CEEG results in anticonvulsant medication changes in about half of critically ill children and adults who undergo CEEG. A number of single-center studies have demonstrated an association between electrographic seizures or electrographic status epilepticus and worse outcome in critically ill children. Our data also indicate that electrographic status epilepticus was associated with higher mortality, even after adjusting for the neurologic diagnosis category and initial EEG background category. However, the current data cannot establish whether electrographic status epilepticus is a modifiable risk factor for mortality or is a nonmodifiable biomarker of severe brain injury leading to mortality. Further study is needed to establish whether optimal seizure identification and management approaches lower the seizure burden without injurious adverse effects, and thereby improve clinical outcomes.

Increasing awareness of the relatively high incidence of electrographic seizures among children in the PICU has led to increasing demand for CEEG, thereby necessitating development of efficient methods for seizure identification such as quantitative EEG tools. In one study, the median sensitivity for seizure identification was 83% using color density spectral array and 82% using amplitude-integrated EEG, but in individual EEG tracings sensitivity varied from 0% to 100%. Another study applying color density spectral array and envelope trend demonstrated that sensitivity for seizure identification depends on user experience, display size, and inherent seizure characteristics such as duration. We found that 38% of electrographic seizures in children in the PICU lasted less than 1 minute, indicating that a substantial proportion of seizures may be “averaged-out” by highly compressed displays. Both this study and a prior single-center study reported worse short-term outcome with electrographic status epilepticus but not electrographic seizures. If these data are replicated in studies with long-term outcome measures, then quantitative EEG methods may not need to identify every brief seizure if they can reliably identify a seizure burden that is sufficient to worsen outcome. There has also been interest in the use of more limited electrode montages in order to permit easier electrode application. However, only about half of the seizures in the present cohort were diffuse at their maximal extent, raising the concern that montages with a highly reduced number of electrodes may not have the spatial sensitivity to identify many electrographic seizures.

This study has several limitations. First, this was a retrospective study of clinically obtained CEEG and clinical practice. Therefore, it is not known whether every patient who met institutional criteria for CEEG actually underwent monitoring. Further, clinical practice likely varied across centers in terms of frequency of CEEG review, the timing of anticonvulsant administration following seizure onset, and anticonvulsant choices, and these factors may all influence outcome. Second, although we employed standard definitions for electrographic seizures and status epilepticus, EEG interpretation was performed by individual neuroradiologists at each center, and not by a central reading group. Third, electrographic status epilepticus represented a composite outcome involving both long seizures and recurrent seizures. These limitations could be improved by future studies that involve prospective screening of all children in the PICU for specified CEEG indications, multireader EEG scoring, and quantification of seizure burden. Fourth, we only assessed outcome as in-hospital mortality and PICU length of stay. Studies are needed with more detailed outcome measures performed after a longer follow-up period.

This multicenter study demonstrates that electrographic seizures occur in about one-third of children...
in the PICU who undergo clinically ordered CEEG. Among these children, the seizure burden is often high, with electrographic status epilepticus occurring in about one-third. Many electrographic seizures have no accompanying clinical signs, and thus would not be identified without CEEG. Risk factors for seizure occurrence include younger age, clinical seizures prior to CEEG, abnormal initial EEG background patterns, interictal epileptiform discharges, and an epilepsy-related diagnosis. Electrographic status epilepticus is associated with higher short-term mortality, even after adjusting for neurologic disorder category and EEG background category. Further study is needed to establish an optimal management approach and then determine whether seizure identification and optimized management is associated with improved outcome.

AUTHOR CONTRIBUTIONS
Nicholas S. Abend: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision. Daniel H. Amr t: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Jessica L. Carpenter: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Jessica L. Carpenter: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Christopher C. Guia: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Joshua L. Goldstein: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Cecil D. Hahn: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Jason T. Lerner: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Eric Payne: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. Amy Yang: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Dennis J. Dlugos: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval.

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PSYCHIATRIC DISORDERS IN EPILEPSY

Management of psychogenic nonepileptic seizures

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SUMMARY

The International League Against Epilepsy (ILAE) Neuropsychobiology Commission gave the charge to provide practical guidance for health professionals for the pharmacologic and nonpharmacologic treatment of patients with psychogenic nonepileptic seizures (PNES). Using a consensus review of the literature, an international group of clinician-researchers in epilepsy, neurology, neuropsychology, and neuropsychiatry evaluated key management approaches for PNES. These included presentation of the diagnosis, early phase treatment, psychological and pharmacologic interventions, and maintenance management. The aim of this report is to provide greater clarity about the range and current evidence base for treatment for patients with PNES, with the intention of improving the care of patients with PNES and patients who develop PNES as a comorbidity of epilepsy.

KEY WORDS: Psychogenic nonepileptic seizures, Epilepsy, Differential diagnosis, Electroencephalography, Video electroencephalography monitoring, Treatment, Pharmacotherapy, Psychotherapy.

The International League Against Epilepsy (ILAE) and its national affiliates, U.S. and United Kingdom research funding agencies (National Institutes of Health [NIH] and National Institute of Healthcare Research [NIHR]), and Epilepsy Foundations are increasingly paying attention to seizure disorders other than epilepsy and the comorbidities of epilepsy (Kelley et al., 2009). The ILAE supported an expert consensus report on management of neuropsychiatric conditions in epilepsy (Kerr et al., 2011). Included in the conditions described are nonepileptic seizures (NES) and, more specifically, psychogenic nonepileptic seizures (PNES). Given the absence of a fully powered randomized controlled treatment trial for patients with PNES, national funding agencies are now devoting resources to develop much needed treatments for the condition.

The ILAE Neuropsychiatry of Epilepsy consensus document provides an outline of management recommendations for PNES based on the best-known approaches in the field, observational data, and expert recommendations (LaFrance & Devinsky, 2002; Kerr et al., 2011). Having produced a much more detailed report on the investigation and diagnosis of patients with PNES (LaFrance et al., 2013a), the ILAE Neuropsychobiology Commission asked a committee of internationally recognized experts to produce a more detailed report on the treatment of PNES. A summary of the best current practice of the management of PNES compiled by these experts was then reviewed by the members of the ILAE Neuropsychobiology Commission. This article is the outcome of this international collaboration process. Its purpose is to provide specific recommendations for the management for patients with PNES. Management of PNES is divided into four stages; making the diagnosis, presenting the diagnosis, gaining control of the seizures, and management of seizures and life activities.

Making the Diagnosis

Best-practice diagnosis should include video-electroencephalography (vEEG) (video telemetry) for each individual with suspected PNES, as well as patients with refractory or pharmacoresistant seizures.

Patients with persistent seizures are often treated with antiepileptic drugs (AEDs) for presumed epilepsy in monotherapy or polytherapy. Of the 1% of the U.S. population diagnosed with epilepsy, 5–20% actually have PNES (LaFrance & Benbadis, 2006). Predictors of PNES
include “the rule of 2s,” which includes at least two normal electroencephalography (EEG) studies, with at least two seizures per week, resistance to two antiepileptic drugs (AEDs), yielding an 85% positive predictive value for PNES (Davis, 2004). Although characteristic features of ictal semiology may help distinguish epileptic seizures from PNES (Devinsky et al., 2011), vEEG remains the gold standard for the diagnosis of epilepsy and PNES, and is a test that allows clinicians to establish the diagnosis with a high level of confidence and reliability (Syed et al., 2011). Accurate diagnosis is an essential aid to subsequent management.

It is recognized that vEEG monitoring (inpatient or ambulatory EEG with video) is not available throughout the world. Moreover, inpatient vEEG may not be practical in patients with infrequent events, and for patients whose seizures occur only in circumstances unlike those found in a clinical monitoring environment, ambulatory EEG with video may not be accessible. This means that the diagnosis may be arrived at using a combination of history, semiology of the witnessed event, normal routine ictal and interictal EEGs, and a lack of elevated prolactin within 30 min of an apparent generalized tonic–clonic seizure. The relative diagnostic value of these diagnostic techniques and the level of diagnostic certainty that results from their use are described in depth in the recently completed ILAE commissioned paper mentioned above (LaFrance et al., 2013a). The “take home message” is that establishing the diagnosis of PNES, as securely as possible, is the first step in treatment of patients with PNES.

**Presenting the Diagnosis**

In most cases the diagnosis is likely to be communicated by a neurologist. The majority of neurologists accept that the explanation of PNES is part of their role (LaFrance et al., 2008; Mayor et al., 2011), although an early involvement of mental health professionals has also been suggested (Harden & Ferrando, 2001). No research has been undertaken to establish whether it is effective to involve the patients’ family members in the discussion of the diagnosis. However, having family members present during the presentation may facilitate understanding, as described later.

Doctors may feel they face a challenge when communicating the diagnosis of PNES. As a group, patients with PNES have experienced more negative life events prior to the development of their seizures than patients who have just developed epilepsy, but they are less likely to accept that these experiences could be relevant to the etiology of their seizure disorder (Binzer et al., 2004). Patients with PNES have an (even more) external health related locus of control than those with epilepsy (Stone et al., 2004). They are more aware of seizure-associated physical (than emotional anxiety) symptoms and may report symptoms characteristic of autonomic arousal without recognizing possible subjective emotional experiences associated with these symptoms (Goldstein & Mellers, 2006). In keeping with this, patients with PNES score highly on self-report scales of alexithymia (i.e., indicating difficulty understanding, processing, or describing emotions), although not in a manner that easily distinguishes them from patients with epilepsy (Tojek et al., 2000; Bewley et al., 2005).

Unlike patients, neurologists perceive PNES as a largely or entirely “psychological” problem (Whitehead & Reuber, 2012). They consider psychotherapy the treatment of choice for those patients who fail to improve with the communication of the diagnosis (LaFrance et al., 2008, 2012; Mayor et al., 2011).

A number of studies have shown how complex the conversations can be, in which neurologists try to “convince” patients with PNES of their own understanding of their disorder. One showed that almost all patients display resistance to the doctor’s attempts to link their apparently physical problem to emotional causes or adverse life events (Monzoni et al., 2011a). Another demonstrated that neurologists seem to anticipate this and treat the communication of the diagnosis of PNES (and that of other “functional” neurological problems) as highly problematic, perhaps provoking patients’ resistance and contributing to patients’ confusion in the process (Monzoni et al., 2011b). Clinical experience suggests that the clinician’s comfort level with explaining a somatoform disorder diagnosis is likely to impact the acceptance by the patient and their family.

However, there is increasing evidence that the process of communicating the diagnosis is a very important and potentially effective therapeutic step in the management pathway of patients with PNES. The number of PNES was reduced in the 24 h after the diagnosis was explained in one study (Farias et al., 2003). However, in contrast to the finding of immediate PNES reduction, the 1-year follow-up showed persistence of seizures in 87% of patients (Wilder et al., 2004). Several retrospective studies suggest that about one third of patients will report that PNES have stopped when asked 3–6 months after diagnosis with no further intervention (Aboukasm et al., 1998; Kanner et al., 1999; Arain et al., 2007). A prospective single-center audit showed that nearly one half of patients with recent-onset seizures were PNES-free 6 months after the diagnosis. Most patients who became PNES-free stopped having seizures immediately after the explanation of the condition (McKenzie et al., 2010; Duncan et al., 2011). Likewise, one prospective multicenter study confirmed that PNES can cease with the explanation of the diagnosis alone—although in this study only 16% of patients were PNES free at 6 months of follow-up (Mayor et al., 2010). So far it is uncertain which patients are particularly likely to stop having PNES with the communication of the
diagnosis alone. However, predictors of persistence of seizures include depression, personality disorder, and abuse history (Kanner et al., 1999). Proposed predictors of PNES cessation include recent onset, the absence of comorbid anxiety, depression, personality disorder or abuse history, and continued employment at the time of diagnosis/lack of reliance on state financial benefits. It may be that the level of diagnostic certainty at the time of the explanation of the diagnosis is relevant. Whereas the diagnosis had been proven by vEEG in almost all patients in the study by Duncan et al. (2011), (McKenzie et al., 2010), about one half of the patients in the study by Mayor et al. (2010) had diagnoses based on clinical features alone.

The communication of the diagnosis seems to have an even more impressive immediate effect on healthcare utilization than on seizure control. Several studies have demonstrated reductions in health care expenditure overall or in the use of emergency services more specifically (Martin et al., 1998; McKenzie et al., 2010; Razvi et al., 2012). Of interest, reductions in emergency service use were even seen in those patients who continued to experience PNES (McKenzie et al., 2010).

It is important to note that even patients whose PNES stop (at least temporarily) after the explanation of the diagnosis may still need further active psychological or psychiatric treatment. Across the whole PNES patient group, the impact of the explanation of the diagnosis on measures of psychological distress, functioning, or health-related quality of life is not impressive. The biggest prospective study of this issue showed no significant change in self-report measures after 6 months, even when PNES had improved or stopped (Mayor et al., 2012b). However, the risk of developing other somatoform problems when PNES have ceased may be smaller than often thought (at least in the short term) (McKenzie et al., 2011).

Several studies have demonstrated that the explanation of the diagnosis of PNES may also have adverse consequences. Many patients’ seizures do not experience a sustained improvement of their PNES with the relaying of the diagnosis. They may even show an increase in PNES frequency or experience an exacerbation of other mental health symptoms following delivery of the diagnosis. The likelihood of engaging patients in further treatment (such as psychological therapy) may be reduced if the explanation of the diagnosis received leaves the patient angry or confused (Carton et al., 2003; Thompson et al., 2009).

To maximize the possibility of a positive outcome and to reduce the risk of an ineffective discussion, four reasonably detailed communication strategies have been published (see Table 1) (Shen et al., 1990; Mellers, 2005; Duncan, 2010; Hall-Patch et al., 2010). If PNES had been captured by vEEG, all proposed strategies would begin with a search for confirmation that the recorded events were typical of the patient’s habitual events. The strategy proposed by Shen also involves clinicians showing patients and caregivers a video-recording of the PNES prior to delivering the explanation of the diagnosis. Not surprisingly there is considerable overlap between the strategies. One difference between the approaches is the discussion of etiology. The Shen model, for example, takes a “noncommittal” approach (stating “We may never know what these seizures are...”). A fifth approach to the discussion of the etiology communicates the understanding that PNES have two main causes, developmental emotional privation and acute or remote trauma (Kalogjera-Sackellaes, 1996).

Unfortunately, there are no comparative studies to guide practitioners in the route they should follow in those areas in which the strategies diverge. Only one of these strategies (consisting of a crib sheet for neurologists and a booklet for patients) has been subjected to a prospective study confirming that patients found the approach acceptable and that the strategy was effective at communicating the possibility of a “psychological” etiology of PNES (Hall-Patch et al., 2010). One in six patients who received the diagnosis in this way reported being PNES free 6 months later (Mayor et al., 2012b).

What the condition is called is a key feature of several of the communication approaches summarized in Table 1. The most appropriate name for PNES has sparked particular debate. It is clear that some possible labels (such as “hysterical seizures” and “pseudoseizures”) can offend patients (Stone et al., 2003). It is debatable whether the terms “attack” (differentiating PNES from epileptic “seizures” but potentially associating them with a traumatic attack sustained by patients) or “seizure” (communicating that the doctor is taking the problem seriously but associated with a potential risk of confusion with epileptic seizures) is most suitable (LaFrance, 2010). One small linguistic study of 13 patients with PNES suggested that they treated both terms as problematic (Plug et al., 2009).

More important than the preferred label (or whether a label is used at all) is likely to be how empathetically the diagnosis is presented, and whether the doctor communicates that s/he has understood the patient’s account of the problem. It is likely to be helpful if the person communicating the diagnosis has a thorough understanding of epilepsy and PNES and is able to communicate the diagnosis with conviction.

Given that it is one of the aims of the discussion to modify patients’ thoughts about their condition, and considering that patients may share unhelpful illness perceptions with family members or relevant others, encouraging patients to bring someone along when the diagnosis is discussed with them is preferred. Ideally, these significant others can help take in what the doctor has to say and help to reinforce the information after the encounter. It is also essential that the diagnosis is communicated clearly to other doctors involved in the patient’s care (i.e., copy the
medical record of the interview/examination to the other treatment providers), so that the considerable risk of diagnostic confusion and re-prescription of AEDs is minimized; one study showed that 4 years after diagnosis of PNES and withdrawal of AEDs, 40% of patients were taking AEDs again (Reuber et al., 2003b).

Although the short-term outcome (at least in terms of self-reported seizure control) of “minimal” therapeutic interventions such as the explanation of the diagnosis (or a brief psychoeducation approach) is relatively well documented now, the encouraging short-term outcomes are not matched by those seen over the longer term (Reuber et al., 2003b; Wilder et al., 2004). Some early relapses after initial seizure cessation have been described even in the short term (Duncan et al., 2011). It is likely that some patients can learn to control their PNES in the long term with minimal interventions, whereas most need more intensive treatment. Although there are no sufficiently sized comparative studies, a short (<1 year) PNES history may be a good prognostic factor (Duncan et al., 2011).

In view of the documented difficulties some patients have with the understanding of their seizures and the suboptimal longer term outcomes, a single conversation may not suffice to change patients’ perception of their problem and enable them to engage in potentially helpful interventions such as psychological treatment (Howlett et al., 2007; Thompson et al., 2009; Baxter et al., 2012). A number of more elaborate psychoeducational procedures have been proposed that give patients more time to understand and process the diagnosis of PNES. One such procedure involving multiple contacts with a psychiatric liaison nurse specialist during an admission for diagnostic vEEG monitoring was reportedly associated with a 100% success at getting patients to attend at least one psychotherapy session (Thompson et al., 2005). Other approaches using four sessions of individual psychoeducation provided by a therapist with minimal training in the delivery of psychological treatment have also been described (Baxter et al., 2012; Mayor et al., 2012a).

The explanation of the diagnosis is likely to be more involved in the 10% (or so) of patients who have PNES...
and epileptic seizures (Lesser et al., 1983; Benbadis et al., 2001), or in those patients who developed PNES after a significant medical problem affecting the brain (such as a head injury) (Hudak et al., 2004; LaFrance et al., 2013b). In such cases, health care professionals may need to invest time and effort to educate patients (and caregivers) about the differences between their PNES and other symptoms.

### Initiating Further Treatment(s)

When considering psychiatric treatment and psychotherapy, the following steps should be taken (Table 2).

(a) **Formal psychiatric assessment should be arranged and performed.**

A formal psychiatric assessment is the optimal path to follow and is recommended to occur early in the diagnostic workup. There are several reasons for this: the need to exclude psychiatric disorders that can be confused for PNES, the apparent complexity of presentation/psychiatric history of many patients, and the need to consider psychopharmacologic management of some comorbidities. Most neurologic examinations will not have teased out all the background factors that may be relevant to the etiology and maintenance of PNES. This assessment addresses and examines psychiatric symptomatology, developmental history, character traits, and psychosocial environment, all of which are relevant not only to the constitutional makeup of the individual, but also are germane to treatment approaches. Neuropsychological testing is sometimes performed while patients are admitted to a seizure monitoring unit, potentially providing important information about cognitive and emotional functioning. Neuropsychological testing, however, does not differentiate PNES from epilepsy and cannot be regarded as essential in this setting, although it may be helpful in patients with PNES who complain of significant cognitive problems. Moreover, a neuropsychological battery and its interpretation does not provide a five-axis assessment or replace a comprehensive psychiatic assessment.

Ideally, a mental health professional asked to assess and manage a patient with PNES should have some previous experience in this area, should be part of the team that has been assessing the patient, should have confidence in the diagnosis of PNES and other somatoform disorders, and, in particular, should not feel (as sometimes happens) that a difficult patient has been dumped in their lap by a neuropsych service eager to be rid of the patient. It should be made clear to the patient that they are seeing this professional because their condition has psychological/neuropsychiatric underpinnings. The mental health professional may be a neuropsychiatrist, psychiatrist, or psychologist who is comfortable and familiar with brain-behavior disorders, understands what characterizes PNES versus epilepsy, and who can properly assess relevant issues of developmental history, abuse and trauma, and psychosocial factors. This is important because patients who are not properly assessed and are told there is “nothing wrong psychologically” are subsequently dismissed and sometimes “bounce back,” resulting in their rapid return to the neurologic facility or, worse, the patient being abandoned by everybody and the whole diagnostic process to “rule out epilepsy” again, having to be restarted.

The psychiatric assessment should address the differential diagnosis, psychiatric comorbidities, psychopharmacologic and psychological treatments, and acute risks. PNES may be confused with panic attacks or may be accompanied by other conversion disorders, such as psychogenic movement disorders (Witgert et al., 2005). Depending on the results of the formal psychiatric assessment, and who has undertaken it, patients may need to be referred to the appropriate services (including neuropsychiatrists, liaison psychiatrists, community mental health teams, crisis intervention teams, or specialists for other psychiatric disorders). Indeed, where the psychiatric/psychological assessment is not initially undertaken by a psychiatrist or other doctor familiar with pharmacologic treatment options, the neurologist or psychologist/psychologist have a professional obligation to recognize when psychopharmacologic management of psychiatric comorbidities may be needed, and when a referral to a psychiatrist is required. Similarly the mental health professional (if not

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**Table 2. Management of psychogenic nonepileptic seizure and evidence basis (updated from Reuber & House, 2002)**

<table>
<thead>
<tr>
<th>Treatment steps</th>
<th>Direct evidence</th>
<th>Indirect evidence</th>
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<tbody>
<tr>
<td>Diagnosis</td>
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<tr>
<td>Consider early</td>
<td>X</td>
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<tr>
<td>Investigate (vEEG)</td>
<td>X</td>
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<tr>
<td>Assessment</td>
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<tr>
<td>Characterize:</td>
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<tr>
<td>Neurologic comorbidity</td>
<td>X</td>
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<tr>
<td>Psychiatric comorbidity</td>
<td>X</td>
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<tr>
<td>Social/family conflict</td>
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<tr>
<td>Communication of Diagnosis</td>
<td></td>
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<tr>
<td>Explain:</td>
<td>X</td>
<td>X</td>
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<tr>
<td>What PNES are not</td>
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<td>X</td>
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<td>What PNES are</td>
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<td>Psychiatric/psychological treatment</td>
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<tr>
<td>Patient engagement</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Psychotherapy: CBT for PNES</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Family therapy</td>
<td>X</td>
<td></td>
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<tr>
<td>Antidepressants</td>
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<tr>
<td>Case management</td>
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<tr>
<td>Rehabilitation</td>
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PNES, psychogenic nonepileptic seizures; vEEG, video electroencephalography; CBT, cognitive behavioral therapy.
medically trained) may also need to be able to consult with suitable medical experts if there are persisting doubts about the neurologic/medical contribution or otherwise of patients’ reported symptoms.

Psychiatric comorbidities are the rule, and not the exception, in patients with PNES. Only 5% of patients with PNES do not have a comorbid psychiatric disorder or stressor (Moore & Baker, 1997). A history of trauma or abuse is found in up to 80% of patients with PNES (Bowman & Markand, 1996), and a patient may often divulge this history in an examination where current and past stressors are assessed in a systematic and empathetic manner. This means that it is crucial that this assessment is undertaken by an individual with the skills required to handle such disclosures and in an appropriate setting. The “whole person” biopsychosocial/spiritual model provides an assessment approach that examines the patient in the context of his or her humanity (LaFrance & Devinsky, 2004; McGee & Torosian, 2006; Reuber, 2009), and gives a framework upon which a formulation is generated to inform treatment. This recommendation for psychiatric assessment is made acknowledging the unfortunate reality that psychiatric staff are not part of many teams undertaking PNES diagnoses.

(b) Predisposing, precipitating, and perpetuating factors should be listed.

PNES are a symptom, not the underlying “disease” (LaFrance & Barry, 2005). Merely labeling the events as psychogenic is not sufficient for a complete assessment. Along with the five-axis diagnostic approach (Axis I – psychiatric disorders; Axis II – personality disorders/characteristics; Axis III – medical diagnoses; Axis IV – stressors; Axis V – Global Assessment of Functioning), a problem list with predisposing, precipitating, and perpetuating factors, or “the 3 Ps,” is a key component to the formulation (LaFrance & Devinsky, 2002). These factors must be established in individual cases as the formulation may be complex and the Ps may at times, or at least initially, be difficult to identify. However, a common scenario found in patients is a prior history of childhood abuse (predisposing), an assault or injury as an adult leading to disability (precipitating), and recurrent marital discord (perpetuating). Another common scenario that is present is being raised in an alcoholic home leading to a people-pleasing and perfectionistic personality style (predisposing), with a recent motor vehicle accident leading to job loss (precipitating), and ongoing family stressors (perpetuating). In other cases some reminder of an earlier abuse history (e.g., a women whose child reaches the same age as that at which her own abuse occurred, or some other “anniversary”) may act as a precipitating factor for the current PNES. These factors contribute to the presentation and promulgation of conversion symptoms. Querying not only childhood abuse (Salmon et al., 2003), which may have been sexual/physical or emotional and may include more “everyday” childhood stressors such as bullying) but also assaults and events that may have occurred in adulthood (Roelofs et al., 2005) reveals a relevant event in the trauma history in many patients (Reuber et al., 2007b). The importance of examining a patient alone and also with family members or significant others cannot be overemphasized. Some patients may not remember details from past events, or may minimize or have compartmentalized historical factors, and may misreport previous med-ical details. Family members often provide key details of past events during the evaluation. Other times the patient may not divulge key pieces of data until a sense of trust is established, which occurs with rapport. Identifying and addressing not only the seizures but the problem list resulting from the 3 Ps is essential to the improvement in patients with somatoform disorders including PNES.

(c) Psychotherapy should be implemented when indicated.

Although psychotherapy is the recommended and best-validated approach to treating PNES, it may not be pursued by all patients, despite its “indication.” Of note, once a diagnosis of PNES is made we not only give a psychiatric diagnosis, in many cases we also take away a neurologic diagnosis (LaFrance, 2002). Patients who do not accept the diagnosis may not engage in treatment with a mental health provider. The degree of acceptance of a diagnosis and the proposed treatment may influence outcomes; however, this has not been studied as a formal outcome or moderator in controlled treatment trials. As noted above, merely telling a patient that their events are psychogenic or dissociative and are not epileptic in origin is not sufficient to maintain cessation of their seizures in the majority of patients (Wilder et al., 2004). The majority of studies show that PNES continue in long-term follow up in at least two thirds of patients (Reuber et al., 2003b).

Based on national surveys of clinicians who treat PNES in the United States, Chile, and the United Kingdom, the current standard medical care (or treatment as usual) for PNES could be described as a neurologist sharing the diagnosis of PNES with the patient, and family if present, while continuing to follow the patient, tapering the AED in lone PNES, and not initiating psychotropic medication but making a referral to a psychiatrist or psychologist for treatment (LaFrance et al., 2008; Mayor et al., 2011). An international survey showed similar results, cross-culturally (LaFrance et al., 2012). Unfortunately, many patients do not engage with a mental health provider, and they “fall through the cracks” between neurology and psychiatry (Howlett et al., 2007). Failing to address underlying pathology may explain the continuation or
transformation of symptoms, suggesting that psychotherapy may be indicated in all patients with PNES.

1. Individual psychotherapy should be considered to address (b) [predisposing, precipitating, and perpetuating factors].

What psychological treatments might be effective in treating PNES and its comorbidities?

Although psychotherapy is viewed as the treatment of choice for PNES (LaFrance et al., 2008; Mayor et al., 2011), there is no clear agreement as to the type of psychotherapy that is likely to achieve the best results in patients with PNES. It may be that different approaches are most suitable for different groups of patients (Reuber et al., 2005a). Although chapters and reviews have indicated the range of treatments that might be applicable to this patient group (Reuber et al., 2005a; LaFrance et al., 2007a) or which have been reported (e.g., (Brooks et al., 2007; Martlew et al., 2009; Goldstein & Mellers, 2012; Reuber & Mayor, 2012), there is an inadequate evidence base of fully powered, multicentered randomized controlled trials (RCTs) on which rational recommendations about treatment preferences may be made (LaFrance & Barry, 2005). What is evident from recent controlled pilot trials is that many patients enroll with persistent seizures after having had prior supportive therapy or standard medical care in the community.

Over the last 15 years, however, a number of predominantly but not exclusively uncontrolled treatment studies of groups or case series have suggested that psychological interventions are likely to reduce seizure frequency and/or improve health service use (e.g., Aboukasm et al., 1998; Rusch et al., 2001; Prigatano et al., 2002; Goldstein et al., 2004; Zaroff et al., 2004; Khattak et al., 2006; Barry et al., 2008; Kuyk et al., 2008; Mayor et al., 2010; Aamir et al., 2011; LaFrance et al., 2013c, 2009). The general approach within studies has been either to expose individuals to interventions on a one-to-one basis or, in a small number of cases, to undertake group-based work, often as an adjunct to individual psychotherapy. Studies have varied in their inclusion and exclusion criteria, most notably in terms of whether or not they have included people with comorbid epilepsy. The reported outcomes have used different definitions of improvement or seizure freedom (in terms of the period of time under consideration) making direct comparison across studies problematic. Nonetheless, summarized data (Goldstein & Mellers, 2012) suggest that high percentages of the samples studied in uncontrolled treatment trials reported at least a 50% reduction in seizures.

Cognitive behavioral therapy

The most substantial body of data relates to the application of cognitive behavioral therapy (CBT), which has been shown to be effective in the treatment of a range of somatoform disorders (Kroenke, 2007; Hopp & LaFrance, 2012) and is being extended in brief self-help format for patients with “functional neurological symptoms” (Sharpe et al., 2011). There is no single model of CBT for use by patients with PNES, since the therapy itself permits modification for specific groups according to the model of the disorder, despite containing core principles and techniques. Elements of CBT were present in a number of the approaches applied in the case series reported by Rusch et al. (2001) and characterized the approach adopted by Kuyk et al. (2008). However, the two CBT approaches described in most detail in the literature (Goldstein et al., 2010b) are those used by LaFrance et al. (2009, 2013c) and Goldstein et al. (2004, 2010a). To date, the approach developed by LaFrance et al. (2009) has been evaluated in an open-label study and a multicenter pilot RCT (LaFrance et al., 2013c) and that by Goldstein et al. (2004) in an open-label study and pilot RCT (Goldstein et al., 2010a).

The CBT evaluated by Goldstein et al. (2004, 2010a) was based on a fear escape-avoidance model that views PNES as dissociative responses to cues (cognitive/emotional/physiological or environmental) that have been associated with extremely distressing or life-threatening experiences (e.g., abuse or trauma) and which had produced unbearable feelings of fear and distress at an earlier point in the person’s life (Goldstein et al., 2010b). Based on an approach first developed and tested in a single case report (Chalder, 1996), Goldstein et al. (2010a,b) have described their model as focusing on cognitive, emotional, physiologic, and behavioral aspects of PNES. Treatment (delivered across 12 sessions) includes seizure-directed techniques, attention refocusing, relaxation, dealing with avoidance behaviors, negative cognitions, and other factors that may be key to the development and maintenance of PNES (e.g., history of abuse or trauma) and the involvement of family members. Homework tasks (including keeping seizure diaries) are assigned and reviewed in session; psychoeducational leaflets supplement the information provided in sessions. Five stages to the treatment have been outlined (Goldstein et al., 2010b); engagement and rationale giving; teaching and the use of seizure control techniques; reducing avoidance exposure techniques; dealing with seizure-related cognitions and emotions; and relapse prevention.

A pilot RCT (Goldstein et al., 2010a) compared outcomes in 33 patients randomized to CBT versus a group receiving psychiatric outpatient care (which in this case was treatment as usual – TAU). At the end of treatment, the CBT group was experiencing fewer seizures on a monthly basis than the TAU group. When considering the final 3 months of a 6-month follow-up period, the CBT group was approximately three times more likely than the TAU group to have been seizure free in that period, although the between-group differences in seizure frequency was not quite significant at that point (p = 0.082) in part due to further improvement by the TAU group. Both groups showed some improvement on measures of
health service use and on a measure psychosocial functioning, the Work and Social Adjustment Scale. The results were promising in relation to seizure frequency. The study was nonetheless modest in size, requiring replication with larger samples across multiple centers. LaFrance et al. (2009) reported the development of the CBT-informed model based on an approach initially derived to enhance self-control of epileptic seizures (Reiter et al., 1987), modified with a Beckian approach. The intervention is predicated on the assumption that life experiences and trauma in patients with PNES result in maladaptive core beliefs (negative schemas) and patients demonstrate cognitive distortions and somatic symptoms. The 12-session therapy is designed to promote behavioral change and self-control, self-efficacy, and has been tailored specifically for patients with PNES, in order to address directly both the seizures and the comorbidities that commonly occur in this disorder. As in the approach developed by Goldstein et al. (2004, 2010a), LaFrance et al. (2009) treatment has the advantage of being manualized, facilitating its evaluation in multicenter studies. The 12 treatment sessions involve (LaFrance et al., 2009; Goldstein et al., 2010b): an introduction contextualizing the person’s environment; a test on identifying moods, situations, and thoughts; training in healthy communication, support seeking, and goal setting; understanding central nervous system medications and seizures; identifying an aura, conducting a functional behavioral analysis; learning relaxation techniques; examining external stressors and internal triggers; promoting health and wellness, and preparing for life after completing the intervention. The therapy addresses connections between mood, cognitions, and the environment, as well as patients’ automatic thoughts, catastrophic thinking, maladaptive schemas, and somatic misinterpretations. An open-label evaluation found that 16 of 21 participants reported a 50% reduction in seizure frequency and 11 of 17 people completing the treatment were seizure free in the final week of treatment, although no follow-up data were available. Improvements were also found on measures of depression, anxiety, somatic symptoms, quality of life, and psychosocial (including family) functioning. The open-label study was followed by a pilot multicenter RCT (LaFrance et al., 2013c). Thirty-five patients in total with vEEG confirmed lone PNES were randomized at three sites to one of four treatment arms: Medication (sertraline) only, Cognitive Behavior Therapy (CBT) only, CBT and Medication combined, or Standard Medical Care (SMC). The CBT arm showed significant seizure reduction, and improvement in functioning and scores on symptoms scales. The combined treatment arm showed improvements, but less than the CBT only arm, and Medication showed trends for improvement. SMC showed no seizure reduction or improvement in any secondary outcomes, underscoring that supportive therapy does not work for PNES.

Psychodynamic therapy

Two psychodynamic therapeutic approaches have also been described in some detail. Kalogjera-Sackellares (2004) has provided an overview of the key psychodynamic features important in the diagnosis and treatment of PNES. Her model notes that trauma is a central feature of PNES. The trauma can be a single catastrophic event or the result of chronic recurrent traumata. Therefore, the key to recognizing, understanding, and treating patients with PNES is recognition of the key role of trauma and the response to trauma in the psychopathology of these patients. The model draws upon three major areas of psychodynamic theory: (1) psychoanalytic theory, (2) object-relations theory, and (3) self-psychology. Fundamental concepts from each of these areas are used to explain clinical symptomatology and to formulate therapeutic approaches. The working model of PNES centers around three cardinal features: (1) the importance of trauma, (2) the chronicity of symptoms, and (3) the wide range of symptoms experienced by individual patients. Cases treated with this model are described, but controlled data have not been reported using this model.

An augmented from of brief psychodynamic interpersonal therapy (PIT) for PNES has also been described (Howlett & Reuber, 2009). The effectiveness of this approach has not been proven in an RCT, but a service evaluation (describing treatment in >50 patients) have suggested that the treatment has clinically meaningful effects on seizure frequency and severity, psychological distress, quality of life, and functioning in the short term (Reuber et al., 2007a); that the effect on seizures is maintained in the long term (Mayor et al., 2010), and that the treatment is cost-effective (Reuber et al., 2007a; Mayor et al., 2010). The therapeutic approach is an adaptation of the model of brief PIT developed by Hobson (1985). The original model was found to have equivalent effects to cognitive-behavioral therapy for the treatment of depression (Shapiro & Firth, 1987), and an adapted model for functional somatic disorders, on which this therapy is based, was shown to be helpful and cost-effective in the treatment of functional bowel disorders (Guthrie et al., 1991; Creed et al., 2003).

The therapy uses an accessible, empathic approach, inviting correction and collaboration with the patient. Key features include (1) the assumption that the patient’s problems arise from or are exacerbated by disturbances of significant personal relationships, with dysfunctional interpersonal patterns usually originating earlier in their lives, and the explicit linking of this to the patient’s symptoms; and (2) a tentative, encouraging, supportive approach from the therapist, using the terms “I” and “we” to emphasize the collaborative nature of the work. Understanding hypotheses are used to develop awareness of the patient’s current feelings (e.g., “I guess you might be feeling quite angry when you remember that”). “Linking
hypotheses” are introduced to make connections between current feelings and other feelings both inside and outside therapy (e.g., “You say you’re feeling small and frightened now – I wonder if that’s a bit like how you felt as a child when your parents used to fight?”). “Explanatory hypotheses” look for possible underlying reasons for a patient’s behavior, particularly a repeated pattern of behavior (e.g., “When you try so hard not to get upset here with me, maybe it’s because your dad used to beat you more if you cried, so you came to feel that showing your feelings was bad and dangerous. Maybe it even feels as if it might make me angry”). The key mechanisms for therapeutic progress are seen as the identification and change of unhelpful patterns of interpersonal relationships, and the more effective processing of emotions, particularly in relation to painful memories or areas of patients’ lives that may not have been dealt with previously.

Because of the florid, easily triggered symptomatology and level of psychological traumatization of many patients with PNES, the augmented brief PIT for PNES combines this approach with concepts and techniques from a model of somatic trauma therapy, which includes techniques to control autonomic arousal, to track somatic symptoms and link them with emotional triggers, and to process traumatic memories without retraumatizing potentially fragile patients (Rothschild, 2000).

In practical terms this approach involves an initial extended session in which the patient is engaged and in which a diagnostic formulation is developed. Up to 19 subsequent sessions then use the approach described above to change the patients’ illness perceptions, achieve symptom control, improve emotional processing, increase independence, encourage self-care, and process trauma. The support of family, caregivers, and other health care professionals is enlisted if possible (Howlett & Reuber, 2009).

Other interventions

A number of other interventions have been studied either only in single case studies, small group studies, or in studies where the main patient group had other (especially motor) conversion disorders. Therefore, for example, although hypnosis has been tested as a diagnostic tool for PNES, with varying levels of sensitivity and specificity when PNES patients are compared to people with epilepsy (Kuyk et al., 1995, 1999; Barry et al., 2000; Khan et al., 2009), and studies have also shown that patients with PNES obtain higher scores than patients with epilepsy on measures of hypnotizability (Kuyk et al., 1999; Barry et al., 2000; Khan et al., 2009), thereby raising expectations of the potential utility of hypnosis as a therapeutic tool for PNES, little explicit use has been made of hypnosis in the treatment of PNES, and there is no robust evidence to recommend its use as a primary intervention for PNES, even when administered by an experienced hypnotist. However, a number of single case reports of its use as an adjunctive therapy can be found (e.g., Stonnington et al., 2006). Accounts of its use in motor conversion disorder, where hypnosis has been used directly and indirectly to influence the relevant symptoms or explore events likely to have triggered the symptoms (Moene & Hoogduin, 1999) have indicated that its use may not always be without problems, and other psychopathology may give rise to unexpected responses or the need to modify the hypnotic induction technique (Moene & Hoogduin, 1999). In RCTs of a hypnosis-based treatment versus waiting list for motor conversion patients (of whom only a minority had seizures as their main symptom), no data were presented specifically in terms of outcome for PNES occurrence (Moene et al., 2002, 2003).

Although eye movement desensitization and reprocessing (EMDR) has a strong evidence base for the treatment of posttraumatic stress disorder (e.g., Hogberg et al., 2008), there is no evidence for its use as a primary intervention in patients with PNES beyond the case series level (Chemali & Meadows, 2004; Kelley & Benbadis, 2007), or incorporated within a more complex intervention (Howlett & Reuber, 2009). Similarly although EEG biofeedback has been evaluated as a treatment for epilepsy, the use of sensorimotor theta biofeedback has been evaluated only at the level of single cases for PNES (Swingle, 1998), and then as an adjunct to psychotherapy rather than as a treatment in its own right. In one small study where there was (rather poorly reported) random allocation of patients to treatment groups (behavior therapy vs. pharmacotherapy and outpatient psychiatric review), behavior therapy (the use of positive reinforcement for seizure-free behavior and punishment—to reduce inappropriate behavior—as well as avoiding the use of negative reinforcement) was reported to lead to a reduction in PNES frequency, anxiety, and depression (Aamir et al., 2011). In an earlier study (Ataoglu et al., 1998, 2003), a paradoxical intention approach (where, for example, patients were instructed to imagine situations where they were likely to have their seizures or to provoke seizures) suggested a greater improvement in terms of seizure reduction and improvement in anxiety scores than in patients treated with diazepam. However, this therapeutic approach has not generated sufficient interest to provoke replication in more robust studies.

Group therapies

Group therapies have focused on psychoeducational approaches to intervention, using a multisession group approach (Myers & Zaroff, 2004; Zaroff et al., 2004) with mixed results on seizure occurrence but improvement in psychological well-being (Zaroff et al., 2004). Group therapy with a psychodynamic focus, which conceptualized the seizures as an expression of unconscious/
hidden emotions, has been undertaken (Barry et al., 2008), but with only small numbers of patients. Pilot data from seven female patients completing at least 75% of 32 weekly 90-min–long sessions suggest, based on measures of depression, global symptom severity, and PNES frequency, that there may be some benefit in using this approach as an adjunct to individual psychotherapy. However, the numerous methodologic limitations of this pilot study would necessitate further careful study of this approach.

2. Family therapy may be indicated if family system dysfunction is present.

Families of patients with PNES have higher levels of family dysfunction than patients with epilepsy (Krawetz et al., 2001). Patients with PNES see their families as having less commitment and support for each other compared to patients with epilepsy (Moore et al., 1994). Family dysfunction is a contributor to symptoms of depression and to poorer quality of life in PNES (LaFrance et al., 2011). Given these findings, aspects of family dysfunction may be a treatment target in PNES. A well-studied model used for family therapy is the McMaster’s approach (Ryan et al., 2005). The problem-centered, systems-based model addresses affective responsiveness, affective involvement, problem solving, roles, behavior control, communication, and transactional patterns in families (Miller et al., 1985). The systems approach addresses the isolating and restricting tendencies of the patient with PNES in the context of his or her social environment, which may influence integration into the community (LaFrance & Devinsky, 2004). The model has been used successfully in cases of PNES (Archambault & Ryan, 2010). Controlled trials of family therapy for patients with PNES are needed to assess efficacy.

(d) The pharmacologic treatment of patients should begin with early tapering and discontinuation of AEDs, which are an ineffective treatment for people with lone PNES, unless a specific AED has a documented beneficial psychopharmacologic effect in an individual (e.g., use for bipolar disorder or as a treatment for migraine).

It has been shown that the withdrawal of inappropriate prescribed AEDs is safe for people without comorbid epilepsy and that immediate as opposed to delayed AED withdrawal may have greater beneficial effects on a range of clinical outcomes (Oto et al., 2005, 2010) including seizures and health service use. The importance of early AED withdrawal lies partly in communicating to the patient that they do not have epilepsy and thus that such medication is unwarranted. In view of the potential teratogenic effects of some AEDs, this assumes additional importance for women of child-bearing age, who make up the majority of people with PNES.

(e) In people with mixed epileptic seizures (ES) and PNES, reduce high doses of AEDs or polytherapy if possible.

More rigorous studies show that approximately 10% of patients with PNES have epilepsy (Benbadis et al., 2001). In cases of mixed ES/PNES, identifying the different ictal semiologies of the ES and PNES is essential for directing treatment to the different etiologies. For the epilepsy, reduction of the AED dose to the minimum required to achieve optimal freedom from epileptic seizures was shown to be effective (Blumer & Adamolekun, 2006), given that AEDs can exacerbate PNES (Niedermeyer et al., 1970). AED toxicity was found to result in an increased seizure frequency in patients with PNES (Krumholz & Niedermeyer, 1983). Treating the ES with AEDs and the PNES with psychotherapy allows for targeted interventions for the different etiologies. Good communication between the neurologist/epileptologist and the health professional providing psychological treatment is needed to keep the patients with mixed ES/PNES out of the emergency department with recurrences of PNES.

(f) Use psychopharmacologic agents to treat comorbid mood, anxiety, or psychotic disorders, and possibly to treat somatoform symptoms directly.

Psychopharmacologic interventions for PNES have been used to treat the somatoform disorder directly and to treat the common comorbidities (LaFrance & Blumer, 2010). Medication treatment approaches historically have been prophylactic or symptomatic. As of yet, no acute pharmacologic treatment for PNES has been developed, except for stopping convulsions with excessive sedation and paralytic agents, used in psychogenic nonepileptic status (Walker et al., 1996). While paralysis, intubation, and coma-pharmacoinduction are indicated in epilepsy status, this is not the appropriate treatment algorithm for the patient with PNES-status, who is not at risk of brain damage from the seizure. Consulting treatment providers familiar with PNES during the acute presentation may mitigate iatrogenesis.

Open-label trials of antidepressants in patients with conversion disorders have shown some response (O’Malley et al., 1999; Varia et al., 2000; Voon & Lang, 2005). Phase III controlled studies of the benefit of psychotropics in patients with PNES, however, have not been conducted, and apart from anecdotal reports, their effect is unknown (LaFrance & Barry, 2005). The use of pharmacologic treatments for PNES with intravenous barbiturates, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), mixed mechanism antidepressants, dopamine receptor antagonists, beta-blockers, analgesics, or benzodiazepines has largely been reported anecdotally in case reports, journal review articles, or book chapters, with only three prospective open-label trials (Ataoglu et al., 1998; LaFrance et al., 2007b; LaFrance & Blumer,
Only one double-blind placebo-controlled pilot RCT for PNES has been published (Lafranc et al., 2010). Thirty-eight patients enrolled, and 26 (68%) completed the trial. Thirty-three subjects with non-zero baseline seizure rates were included in an intention-to-treat analysis of the primary outcome. Patients assigned to the sertraline arm experienced a 45% reduction in seizure rates from baseline to final visit (p = 0.03) versus an 8% increase in placebo (p = 0.78). The pilot study was not powered for efficacy but showed feasibility for a pharmacologic RCT. Data from this RCT and other open-label trials indicated that medications may help to reduce symptoms, but would likely require adjunctive psychotherapy to eliminate seizures.

### Treatment Maintenance

Good communication between treatment providers and a coordinated care approach should prevent further unnecessary interventions, investigations, or treatments.

The longer-term studies currently available suggest that many patients with PNES will continue to experience seizures despite neurologic and psychotherapeutic care (Reuber et al., 2003b). Even patients who become free of seizures may remain disabled (Reuber et al., 2005b). Given the association of PNES with serious and pervasive conditions such as borderline personality disorder, PTSD and somatization disorder (at least in important subgroups of patients) (Reuber et al., 2003a; Lacey et al., 2007), it is not surprising that many patients remain symptomatic and disabled. Some patients with chronic seizure disorders (and their families) may have become dependent on health-related benefits associated with PNES. While experts think that only a small minority of individuals (<5%) intentionally produce their symptoms, some chronic NES may be factitious or malingered (e.g., not psychogenic, rather feigning seizures to get out of military service or incarceration, or for remuneration or medication seeking). Unfortunately, there are no reliable medical tests for malingerers other than the careful observation of patient’s behavior or the patient’s admission. It is important for doctors who look after patients with PNES in the longer term to appreciate the limitations of the interventions at their disposal and to reappraise their own motivation for providing continuing care to these patients if they want to protect their patients from going through endless cycles of investigations, treatment proposals, and disappointments (Page & Wessely, 2003).

This is not to say that patients with refractory PNES should not be followed. Long-term follow-up with a doctor who has a good understanding of seizure disorders and the psychological needs of patients with PNES serves a number of important functions: (1) It gives the doctor the opportunity to review the diagnosis—one important reason for the patient’s failure to respond to psychological treatment would be that they have another condition, including epilepsy or another medical disorder (Parra et al., 1999). (2) It enables the doctor to make sure that the diagnosis of PNES does not change inappropriately—for instance to one of epilepsy—and that patients are not (re-)started on inappropriate AEDs. (3) It allows the doctor to limit the investigation of other symptoms for which a medical cause is unlikely. (4) It enables doctors to reduce the risk of iatrogenic injury (for instance by communicating the diagnosis clearly to anesthetists, dentists, or obstetricians who are likely to encounter a patient with PNES) (Reuber et al., 2000). (5) It provides an opportunity to interact with the patient’s caregivers to limit overprotection or inappropriate dependence and to limit the harm done by PNES or patients to others (for instance dependent children who end up caring for their mother or father with PNES). (6) It makes it possible for doctors to refer patients for treatments as their understanding of the disorder or their personal circumstances change—patients who were unable to engage in psychological treatment immediately after the diagnosis may well be able to accept a referral for treatment after some time (Howlett et al., 2007). (6) Doctors may be able to offer or refer patients for treatment approaches that are not intended to “cure,” but that aim to reduce handicap for instance by negotiating small changes in behavior, encouraging self-monitoring of behavior, and scheduling graded social and physical activity. This sort of approach may not need to involve a psychotherapist. Occupational therapists, physiotherapists or experts in rehabilitation may be able to oversee this approach. Whilst none of these techniques have been evaluated in patients with PNES, they have been shown to be effective in other conditions traditionally thought of as not amenable to psychological intervention such as the negative symptoms of schizophrenia (Hogg, 1996). (7) Doctors may also consider more intensive treatment programs (for instance for borderline personality disorder) (Linehan, 1993; Palmer et al., 2003; Kellett et al., 2011) or inpatient treatment, especially if the disruption of the patient’s home and care arrangements is desirable from a therapeutic point of view (Schöndienst, 2001; Kuyk et al., 2008).

### Conclusion

There is a range of key skills and expertise required to offer comprehensive treatment to patients with PNES (i.e., neurology, neurophysiology, neuropsychology, psychiatry, neuropsychiatry, psychotherapy, social work/rehabilitation), which is not available in all practice locations. Identifying key team members with appropriate training who can provide care for patients with PNES is a
necessary process in developing a management program for PNES. Good communication between those who make the diagnosis and who are involved with management is essential.

Proper diagnosis is the first step in treatment. Providing a definitive diagnosis of PNES and assessing the comorbidities are essential in understanding the patient. The presentation of the diagnosis is an important part of introducing the mental health component to the treatment. Communicating to the patient that the seizures have a psychological etiology and are not epilepsy may stop PNES in the short-term, but does little to improve associated psychological morbidity, distress, or health-related quality of life. Without dedicated further treatment, PNES are likely to re-start in the majority of patients. Treatment specifically addressing PNES is required in most patients with PNES. Underlying psychopathology, prior abuse history, and recurrent stressors may act as predisposing, precipitating, and perpetuating factors for the seizures. These factors can be addressed effectively in psychotherapy with a provider who is comfortable and familiar with PNES and somatoform disorders, and who understands how these disorders differ from their neurologic counterparts. Increasing evidence shows that cognitive behavioral, psychodynamic, and interpersonal modalities may be effective in managing PNES, although further treatment studies are required to establish the optimal treatment approach. Involving the family of the patient with PNES may aid in social reintegration in the community. Pharmacotherapy includes reducing unnecessary AEDs in lone PNES and titrating to limit potential side effects in mixed ES/PNES. Psychotropic medications may help reduce comorbid symptoms, including anxiety and depression, which commonly occur in PNES. Controlled pilot trials in the last decade have demonstrated benefit in treating PNES, and multi-centered, fully powered RCTs are needed for establishing their efficacy. Continued collaborative management between neurology, psychiatry, and psychology is essential to reduce morbidity and improve the lives of patients with PNES.

**DISCLOSURE**

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**References**


Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM

Abstract Objectives: Recommendations for EEG monitoring in the ICU are lacking. The Neurointensive Care Section of the ESICM assembled a multidisciplinary group to establish consensus recommendations on the use of EEG in the ICU.

Methods: A systematic review was performed and 42 studies were included. Data were extracted using the PICO approach, including: (a) population, i.e. ICU patients with at least one of the following: traumatic brain injury, subarachnoid hemorrhage, intracerebral hemorrhage, stroke, coma after cardiac arrest, septic and metabolic encephalopathy, encephalitis, and status epilepticus; (b) intervention, i.e. EEG monitoring of at least 30 min duration; (c) control, i.e. intermittent vs. continuous EEG, as no studies compared patients with a specific clinical condition, with and without EEG monitoring; (d) outcome endpoints, i.e. seizure detection, ischemia detection, and prognostication. After selection, evidence was classified and recommendations developed using the GRADE system.

Recommendations: The panel recommends EEG in generalized convulsive status epilepticus and to rule out nonconvulsive seizures in brain-injured patients and in comatose ICU patients without primary brain injury who have unexplained and persistent altered consciousness. We suggest EEG to detect ischemia in comatose patients with subarachnoid hemorrhage and to improve prognostication of coma after cardiac arrest. We recommend continuous over intermittent EEG for refractory status epilepticus and suggest it for patients with status epilepticus and suspected ongoing seizures and for comatose patients with unexplained and persistent altered consciousness. Conclusions: EEG monitoring is an important diagnostic tool for specific indications. Further data are necessary to understand its potential for ischemia assessment and coma prognostication.

Keywords EEG · Intensive care · Seizures · Cerebral ischemia · Prognosis · Recommendations
**Introduction**

Acute brain dysfunction is a leading cause of admission to the ICU, either due to structural diseases, for example traumatic brain injury (TBI), intracranial hemorrhage, cerebral ischemia and encephalitis, or to functional disorders, for example septic encephalopathy. Electroencephalography (EEG) provides information about brain electrical activity, even when brain function is depressed and cannot be explored otherwise, as in comatose patients. EEG is essential to detect electrical seizures and to document their duration and response to therapy. It can disclose alterations associated with the development of delayed cerebral ischemia (DCI) and improve coma prognostication. It is useful to monitor barbiturate coma for refractory intracranial hypertension [1] and is mandatory in several countries for the diagnosis of brain death [2].

Evidence, however, is sparse, and recommendations for EEG monitoring in the ICU are not well defined. The Neurointensive Care (NIC) Section of the ESICM assembled a multidisciplinary panel to establish a consensus statement on the use of EEG monitoring in adult ICU populations. The aim was to provide better guidance for EEG monitoring and to improve implementation of EEG in ICU practice. Two indications were excluded from this review: EEG for brain death diagnosis, since it is regulated by local legislation in many countries, and for barbiturate coma, since it has been reviewed in authoritative guidelines [1].

**Methods**

Authors and study selection

In 2010, the NIC section of the ESICM decided to develop evidence-based consensus recommendation on the indications for EEG monitoring for ICU patients. Authors were proposed during an official NIC section meeting and included neurointensivists (N.S., J.C.), medical/surgical intensivists (F.S.T., M.O.), anesthesiologists (N.S.), neurologists (J.C.), neurosurgeons (P.H.) and epileptologists (M.H.) who would review the existing literature and provide a consensus manuscript. This systematic review was reported following the PRISMA criteria [3].

Eligibility criteria

Studies were considered eligible based on the PICO approach, which includes:

(a) Population, i.e. ICU patients with at least one of the following: TBI, subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), acute ischemic stroke (AIS), coma after cardiac arrest (CA), sepsis/metabolic encephalopathy, encephalitis, and status epilepticus (SE).

(b) Intervention, i.e. EEG monitoring of >30 min duration.

(c) Controls, i.e. intermittent vs. continuous EEG, as no studies compared patient population with a specific clinical condition with and without EEG.

(d) Outcome endpoints, i.e. seizure detection, ischemia detection, prognostication.

**Search strategy**

Using the PubMed database, we conducted a systematic review from 1966 up to August 2012. The search strategy included the terms “EEG” or “electroencephalogram” or “electroencephalography”, used with one of the following: “intensive care” or “critical care” or “ischemia” or “prognosis” or “outcome” or “traumatic brain injury” or “subarachnoid hemorrhage” or “intracerebral hemorrhage” or “stroke” or “cardiac arrest” or “sepsis” or “metabolic encephalopathy” or “encephalitis” or “meningitis” or “status epilepticus”. Additional references for relevant studies were also searched from review articles. We restricted the language of the articles to English. No unpublished data or congress abstracts were considered.

**Study selection**

Two authors (M.O. and F.S.T.) independently reviewed citations, abstracts and full-text articles to select eligible studies. We excluded: (a) review articles, (b) case reports, (c) experimental studies, (d) studies in pediatric ICU populations, (e) studies that were not conducted on ICU patients. Data were abstracted (F.S.T.) according to the PICO system. No attempt was made to re-analyze the data; accuracy of data extraction was controlled thereafter (M.O.). No additional process to obtain data from investigators was attempted. Considering the lack of randomized or case-control studies, no meta-analysis of extracted data was performed nor did we assess risk of bias or consistency, or perform subgroup analyses.

**Grading of evidence**

The quality of evidence was judged based on the grades of recommendation, assessment, development and evaluation (GRADE) system, which assesses the quality of evidence for each of the selected outcomes from the
available studies, considering the benefit/risk balance and the costs related to the study intervention [4, 5]. This system classifies quality of evidence as high (grade A), moderate (grade B), low (grade C), or very low (grade D) [6, 7]. Thereafter, recommendations are classified as strong (grade 1) or weak (grade 2). One advantage of the GRADE system is that a strong recommendation can be made despite moderate/low evidence. Accordingly, the authors made strong recommendations when they were confident that the desirable effects of adherence to a recommendation would outweigh the undesirable effects. A strong recommendation reflects the possibility that following the given recommendation about EEG will result in more beneficial effects (detection and therapy of seizures, reduced injury associated with ongoing seizures, improved outcome, less burden on staff and patients, cost savings) than harm to ICU patients (inaccurate predictive value, useless antiepileptic drugs (AED), difficult EEG implementation). A weak recommendation reflects the opinion that the benefit/risk balance could be in favor of this recommendation, but the members of the task force were not confident because of limited evidence. Three authors (M.O., F.S.T., J.C.) proposed initial recommendations and asked for approval from the other participants. In case of disagreement, changes to recommendations were proposed and discussed to obtain a unanimous vote. It is important to recognize that strong recommendations do not necessarily represent standards of care.

**Results**

A total of 42 studies were selected (Fig. 1). All were retrospective or prospective observational single-center studies. No controlled trial—either nonrandomized or randomized—was identified (Table 1). Strong recommendations for EEG use, when given in the absence of high-quality evidence, are justified by the potential harm of unrecognized seizures and the low risk of the procedure; however, costs may be considerable and have to be weighed against the benefit. A summary of GRADE recommendations for the indications for EEG monitoring in the ICU is given in Table 2.

**Patient populations**

**EEG in patients with generalized convulsive SE**

**Seizure detection** Generalized convulsive SE (GCSE) is a clinical diagnosis that does not require EEG. However, nonconvulsive seizures (NCSz) and nonconvulsive SE (NCSE) are frequent (48 % and 14 %, respectively) after GCSE [8] and differentiating ongoing seizure activity from postictal or medication-induced encephalopathy can be challenging. As clinical symptoms are often missing, EEG is necessary to diagnose ongoing NCSz [9, 10]. EEG, especially continuous EEG (cEEG), is urgently required in patients not waking up after cessation of clinical seizures to rule out NCSz [8, 11]. Guidelines for

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**Fig. 1** Flow-chart representing the methodology for the systematic review, according to the PRISMA criteria.

![Flow-chart](image-url)

- PubMed Research: 36267 articles
- Articles selected: 4022 articles
- Articles included: 42 (4839 patients)
- 32245 Excluded:
  - Duplicates (n=7553)
  - Reviews/Letters/Editorials (n=7601)
  - Pediatric studies (n=11689)
  - Animal studies (n=4323)
  - Not in English (n=1079)
- 3980 Excluded:
  - Not focusing on ICU patients
  - Not reporting outcomes
- Traumatic Brain Injury (n=6)
- Subarachnoid Hemorrhage (n=6)
- Ischemic Stroke/ICH (n=2)
- Mixed Neuro-ICU (n=4)
- Cardiac Arrest (n=13)
- Status Epilepticus (n=3)
- General ICU (n=8)
<table>
<thead>
<tr>
<th>Population</th>
<th>Reference</th>
<th>Study N</th>
<th>Intervention</th>
<th>Risk factors</th>
<th>Seizures</th>
<th>Ischemia</th>
<th>Prognostication</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBI</td>
<td>Olivecrona [24]</td>
<td>P 47</td>
<td>cEEG</td>
<td>–</td>
<td>0 %</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Ronne-Engstrom</td>
<td>R 70</td>
<td>cEEG</td>
<td>–</td>
<td>33 %</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Vespa [19]</td>
<td>P 94</td>
<td>cEEG</td>
<td>–</td>
<td>12 %</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Vespa [33]</td>
<td>P 89</td>
<td>cEEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Reduced percentage of alpha variability was associated with worse outcome (PPV of 86 % for poor prognosis)</td>
</tr>
<tr>
<td></td>
<td>Gutling [31]</td>
<td>P 50</td>
<td>EEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Non-reactive EEG background predicted poor outcome</td>
</tr>
<tr>
<td></td>
<td>Steudel [32]</td>
<td>P 50</td>
<td>EEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>EEG abnormalities predicted outcome in 80 % of patients</td>
</tr>
<tr>
<td>SAH</td>
<td>Little [36]</td>
<td>R 389</td>
<td>cEEG</td>
<td>Advanced age, coma, Fisher 3 and 4, hydrocephalus</td>
<td>3 % (NCSE)</td>
<td>–</td>
<td>NCSE had 80 % mortality</td>
</tr>
<tr>
<td></td>
<td>Dennis [35]</td>
<td>R 233</td>
<td>cEEG</td>
<td>Advanced age, coma, brain edema, hydrocephalus</td>
<td>8 % (NCSE)</td>
<td>–</td>
<td>NCSE had 100 % mortality</td>
</tr>
<tr>
<td></td>
<td>Claassen [37]</td>
<td>P 34</td>
<td>cEEG</td>
<td>–</td>
<td>–</td>
<td>&gt;10 % decrease in ADR predictive of DCI (sensitivity 100 %, specificity 76 %)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Vespa [41]</td>
<td>P 32</td>
<td>cEEG</td>
<td>–</td>
<td>–</td>
<td>Decrease in relative alpha variability predictive of DCI (PPV 76 %, NPV 100 %)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Rathakrishnan</td>
<td>P 12</td>
<td>cEEG</td>
<td>–</td>
<td>–</td>
<td>Decrease in mean alpha power predictive of DCI (sensitivity 67 %)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Claassen [42]</td>
<td>R 116</td>
<td>cEEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Epileptiform discharges, NCSE, non-reactive EEG background predicted poor recovery</td>
</tr>
<tr>
<td>ICH</td>
<td>Claassen [44]</td>
<td>R 102</td>
<td>cEEG</td>
<td>≥30 % increase in ICH volume</td>
<td>18 % (NCSz)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Shoorajpanday [58]</td>
<td>P 110</td>
<td>cEEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>EE derived indexes (global ADR and Brain Symmetry Index) predictive of 6-month functional recovery (PPV 60 %)</td>
</tr>
<tr>
<td>Mixed neuro-ICU</td>
<td>Amantini [25]</td>
<td>P 68</td>
<td>cEEG</td>
<td>–</td>
<td>3 %</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TBI, ICH,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ischemic stroke</td>
<td>Coriat [22]</td>
<td>R 570</td>
<td>cEEG</td>
<td>Coma, previous seizures</td>
<td>9 % (NCSz)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Neuro-ICU</td>
<td>Kramer [99]</td>
<td>P 393</td>
<td>EEG n = 359,</td>
<td>HIE, CNS infections</td>
<td>13 %</td>
<td>–</td>
<td>NCSz not associated with outcome</td>
</tr>
<tr>
<td>GCS ≤12</td>
<td></td>
<td></td>
<td>cEEG n = 34</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>Reference</td>
<td>Study Type</td>
<td>N</td>
<td>Intervention</td>
<td>Risk factors</td>
<td>Seizures</td>
<td>Ischemia</td>
</tr>
<tr>
<td>---------------------</td>
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<td>--------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>SAH and ICH</td>
<td>Bosco [43]</td>
<td>P</td>
<td>68</td>
<td>cEEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Post-CA coma NT patients</td>
<td>Bassetti [66]</td>
<td>P</td>
<td>60</td>
<td>EEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Chen [70]</td>
<td>P</td>
<td>34</td>
<td>EEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Rothstein [76]</td>
<td>P</td>
<td>40</td>
<td>EEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Synek [80]</td>
<td>P</td>
<td>63</td>
<td>EEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Yamashita [82]</td>
<td>P</td>
<td>79</td>
<td>EEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Fugate [89]</td>
<td>P</td>
<td>192</td>
<td>EEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TH patients</td>
<td>Kawai [90]</td>
<td>R</td>
<td>26</td>
<td>cEEG</td>
<td>–</td>
<td>–</td>
<td>38.5%</td>
</tr>
<tr>
<td></td>
<td>Rittenberger [61]</td>
<td>R</td>
<td>101</td>
<td>cEEG</td>
<td>–</td>
<td>–</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>Legriel [60]</td>
<td>P</td>
<td>51</td>
<td>cEEG</td>
<td>–</td>
<td>–</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Rossetti [91]</td>
<td>P</td>
<td>111</td>
<td>EEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Rossetti [92]</td>
<td>P</td>
<td>34</td>
<td>cEEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Rundgren [63]</td>
<td>P</td>
<td>34</td>
<td>cEEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Rundgren [93]</td>
<td>P</td>
<td>111</td>
<td>cEEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>DeLorenzo [8]</td>
<td>P</td>
<td>164</td>
<td>cEEG</td>
<td>–</td>
<td>–</td>
<td>48%</td>
</tr>
<tr>
<td>≥65 years patients with NCSE</td>
<td>Litt [109]</td>
<td>P</td>
<td>25</td>
<td>EEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>NCSz General ICU</td>
<td>Young [11]</td>
<td>R</td>
<td>49</td>
<td>cEEG</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mixed ICU GCS &lt;9</td>
<td>Towne [29]</td>
<td>R</td>
<td>236*</td>
<td>cEEG</td>
<td>HIE, stroke</td>
<td>8%</td>
<td>–</td>
</tr>
<tr>
<td>Mixed ICU GCS &lt;9</td>
<td>Varelas [111]</td>
<td>R</td>
<td>129</td>
<td>EEG</td>
<td>Age, HIE</td>
<td>20%</td>
<td>–</td>
</tr>
<tr>
<td>Mixed ICU GCS &lt;9</td>
<td>Young [108]</td>
<td>P</td>
<td>55</td>
<td>cEEG</td>
<td>Primary brain injury has higher incidence of NCSz</td>
<td>9%</td>
<td>–</td>
</tr>
<tr>
<td>Medical ICU</td>
<td>Oddo [105]</td>
<td>R</td>
<td>201</td>
<td>cEEG</td>
<td>–</td>
<td>–</td>
<td>10%</td>
</tr>
</tbody>
</table>
the management of SE in the ICU have recently been published [6].

**Recommendations for patients with convulsive SE**

1. We recommend urgent EEG in patients with SE that do not return to functional baseline within 60 min after administration of seizure medication (strong recommendation, low quality of evidence—grade 1C).

**EEG in patients with refractory SE**

SE resistant to initial therapy, also known as refractory SE (RSE), is almost exclusively nonconvulsive and requires initiation of intravenous AED [12–14]. CEEG is required to guide therapy for RSE, aiming to stop ongoing electrographic seizures. One study showed that although RSE initially responded to intravenous therapy, many patients subsequently developed NCSz, detectable only with cEEG [15]. There is controversy as to the minimum duration of monitoring [16–19] (see section “Technological issues”). Video-cEEG monitoring helps with the interpretation of complex electrographic abnormalities, but its efficacy over standard EEG has not been demonstrated yet [20].

**Recommendations for patients with refractory SE**

1. We recommend urgent (within 60 min) EEG in patients with RSE (strong recommendation, low quality of evidence—grade 1C).

**EEG in patients with TBI**

*Seizure detection* Patients suffering from TBI are at risk of NCSz [21, 22]. Risk factors for NCSz are depressed skull fracture, penetrating injury and large cortical contusion/hematomas [22]. Observational studies in patients with TBI monitored by EEG have shown a variable prevalence of NCSz. Vespa et al. (n = 90 patients, duration of cEEG 7 days) found a 22 % prevalence of seizures, of which 52 % were NCSz, despite AED prophylaxis [19]. Ronne-Engstrom and Winkler studied 70 patients (duration of cEEG 58 h, no AED prophylaxis) and found a 33 % prevalence of seizures (starting on average 74 h after TBI), the majority of which were NCSz [23]. The frequency of NCSz depends on the amount of sedatives used. Two recent studies, in which patients were given high sedative doses with intrinsic antiseizure activity, showed no [24] or a very low (3 %) [25] rate of NCSz. NCSz are associated with intracranial pressure elevations [26], increased cerebral metabolic distress [26] and long-term hippocampal atrophy [27].
Despite variable results and lack of multicenter studies, there is a strong rationale for EEG monitoring after TBI. This is reinforced by the fact that primary AED prophylaxis is frequently unreliable in preventing or suppressing NCSz [28].

**Ischemia detection** No study has shown a role for EEG in detecting ischemia after TBI.

**Prognostication** Towne et al. [29] and Vespa et al. [19] were unable to demonstrate a difference in mortality between TBI patients with or without EEG seizures. EEG reactivity to auditory or nociceptive stimuli predicted good outcome after TBI, whereas absent EEG reactivity resulted in a poor outcome [30, 31] with a higher predictive value than GCS and somatosensory evoked potentials. In another study, EEG performed daily during the first week after admission reliably predicted outcome in 40/50 patients; however, prognosis could not be assessed in patients with alpha pattern coma or in those receiving barbiturate therapy [32]. Reduced percentage of alpha variability also predicted outcome in TBI patients with GCS ≤8 (positive predictive value 86 %) [33].

**Recommendations for patients with TBI**

1. We recommend EEG in all TBI patients with unexplained and persistent altered consciousness (strong recommendation, low quality of evidence—grade 1C).

2. We suggest EEG to rule out NCSz in patients with TBI and GCS ≤8, particularly in those with large cortical contusion/hematoma, depressed skull fracture or penetrating injury (weak recommendation, low quality of evidence—grade 2C).

**EEG in patients with SAH**

**Seizure detection** Acute seizures have been reported in between 3 % and 26 % of patients with comatose SAH [34–36]. Of those undergoing cEEG in the ICU, 3–19 %

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<sup>a</sup> Unexplained alteration in consciousness: reduced consciousness state that is not attributable to metabolic disorders (sodium, calcium, glucose, ammonium, urea), organ dysfunction (hypotension, hypoxemia, sepsis, hyperthermia) or structural brain lesions on imaging (cerebral CT scan) tests
have NCSz and 13% have NCSE, which cannot be diagnosed without EEG. Risk factors for seizures include older age, poor clinical grade, large intraparenchymal hemorrhage, large amount of cisternal blood, DCI, and anterior circulation aneurysm. Seizures may be less likely in patients that have undergone coil embolization of the aneurysm [34].

**Ischemia detection** In SAH patients, changes in EEG trends on cEEG (performed on days 2–10) correlate with DCI [37–41]. A number of quantitative EEG (qEEG) parameters may be useful, including changes in total power, alpha/delta ratio (ADR), composite alpha index, and relative alpha variability. There is controversy over which parameter is best, but all fundamentally relate to fast to slow frequencies. QEEG can detect EEG changes associated with DCI 24–48 h prior to other diagnostic tools [39, 41]. Reported sensitivity is variable but can be as high as 90% [37, 38], with 75% specificity [37], and 100% negative predictive value and 76% positive predictive value [41].

**Prognostication** Epileptiform discharges or NCSE and absent EEG background reactivity was associated with poor prognosis after SAH [42]. Despite this association, there are no unequivocal human data indicating that NCSz are causally linked to poor functional outcome or that treatment improves outcome [34, 35, 42]. Progressive deterioration on the basis of EEG (increased delta pattern) was associated with an increased risk of dying by almost 24% compared to patients whose condition did not worsen according to EEG [43].

**Recommendations for patients with SAH**
1. We recommend EEG to rule out NCSz in all SAH patients with unexplained and persistent altered consciousness (strong recommendation, low quality of evidence—grade 1C).
2. We suggest EEG to detect DCI in comatose SAH patients, in whom neurological examination is unreliable (weak recommendation, low quality of evidence—grade 2C).

**EEG in patients with ICH**

**Seizure detection** Seizures are seen in 3–17% of ICH patients, occurring at 1 day (50–70%) up to 3 days from ICH. Most seizures diagnosed in the ICU are non-convulsive (NCSz 53–76%, NCSE 39%) and can only be diagnosed by EEG [44–46]. Risk factors include cortical bleeding and arteriovenous malformations [44, 46].

**Ischemia detection** No study has provided data on ischemia detection in ICH patients.

**Prognostication** Seizures are associated with an increase in ICH volume and worsening midline shift [44, 46]. NCSZ worsen neurological status, but an independent association with outcome has not been demonstrated [44, 46].

**Recommendations for patients with ICH**
1. We recommend EEG to rule out NCSz in all ICH patients with unexplained and persistent altered consciousness (strong recommendation, low quality of evidence—grade 1C).

**EEG in patients with AIS**

**Seizure detection** One single-center study in which cEEG was performed in 177 patients with AIS showed a 7% incidence of seizures (more than 70% NCSz) in the acute (<24 h) phase [45]. Seizures are less frequent than in ICH, SAH or TBI patients.

**Ischemia detection** A decrease in cerebral perfusion pressure (CPP) may be associated with a concomitant reduction in faster EEG activity on qEEG [47], while rapid improvements in background EEG activity have been observed upon CPP/CBF increase following mannitol therapy [48] or hemodilution [49].

**Prognostication** Following hemicraniectomy for space-occupying middle cerebral artery infarction, the presence of faster EEG activity was associated with good recovery in patients monitored with cEEG [50]. Three studies have demonstrated that the disappearance or further slowing of delta activity in the acute phase (within 24 h) of AIS predicted a malignant course (cerebral edema) [51–53].

Preliminary studies showed a correlation between the neurological score in the acute stage of AIS and the degree of EEG abnormality [54], although this correlation was shown to be low by others [55]. CEEG improves outcome prognostication in AIS [56–59]: in particularly, the ADR and the so-called EEG brain symmetry index are significantly correlated with outcome at 6 months [56–59].

**Recommendations for patients with AIS**
1. We suggest EEG to rule out NCSz in all AIS patients with unexplained and/or persistently altered consciousness (weak recommendation, very low quality of evidence—grade 2D).
2. We do not recommend EEG to detect cerebral ischemia and target CPP in AIS patients (weak recommendation against, very low quality of evidence—grade 2D).
3. We do not recommend EEG to detect herniation in AIS patients (weak recommendation against, very low quality of evidence—grade 2D).

**EEG in patients with coma after CA**

**Seizure detection** Seizures occur in 10–30 % of patients with coma after CA [60–63]. EEG is required to detect seizures as most seizures after CA are nonconvulsive and to differentiate myoclonic SE from peripheral or subcortical myoclonus. When therapeutic hypothermia (TH) is applied, seizures can occur during TH and after rewarming [60, 61, 63]. “Early” seizures, occurring during TH under sedation, are an ominous sign [60–63]. “Late” seizures, occurring after TH and off sedation, carry a poor prognosis but may respond to therapy in certain cases [64]; EEG is indicated to titrate therapy [61, 64].

**Ischemia detection** No study has provided data on ischemia detection in comatose CA patients or used EEG to target blood pressure management.

**Prognostication** Previous to TH, a number of studies showed that adding EEG—performed at 72 h from CA—to standard neurological examination improved outcome prognostication after CA [65–84]. EEG findings associated with a poor prognosis included spontaneous burst suppression or generalized periodic discharges. Synnek analyzed EEG background activity (continuous vs. discontinuous pattern) and EEG background reactivity to auditory and painful stimulation, subsequently dichotomized as “reactive” vs. “non-reactive” [30, 80, 85]; the presence of a continuous and reactive EEG background (i.e. a change in EEG frequency and amplitude following stimulation) was associated with good prognosis. At this time TH is considered the standard of care after CA. Hypothermia and sedation used during cooling alter motor response and decrease the prognostic accuracy of neurological examination. Several studies performed in patients treated with TH demonstrated that EEG improves prognostic prediction of coma after CA [63, 86–95]. The presence of discontinuous and burst-suppression patterns, and of nonreactive EEG background, were strongly correlated (false-positive rates for poor prognosis <10 %) with a poor prognosis, whilst a continuous reactive background was associated with good recovery. Importantly, in some studies, coma prognostication could be achieved during TH [63, 92, 93].

**Recommendations for comatose patients after CA**

1. We recommend EEG during TH and within 24 h after rewarming to rule out NCSz in all comatose patients after CA (strong recommendation, low quality of evidence—grade 1C).

2. We suggest EEG to assist with prognostication of coma after CA, particularly in patients treated with TH (weak recommendation, low quality of evidence—grade 2C).

**EEG in patients with infectious and non-infectious encephalitis**

**Seizure detection** Central nervous system (CNS) infections, mainly acute meningitis/encephalitis, are a risk factor for seizures, ranging from 6–12 % in some studies [96], and seizures are associated with higher mortality rates [97]. In a small retrospective study, Carrera et al., found seizures in one-third of 42 patients with primary CNS infections, and the majority of these were NCSz [98]. In the large cohort of patients undergoing eEEG monitoring reported by the Columbia University group, CNS infections and metabolic encephalopathy accounted for 13 % of all patients and there was 23 % and 12 % frequency of NCSE and NCSz, respectively. Comatose patients needed more than 24 h of eEEG monitoring to detect NCSz [17]. In another large cohort of neurocritical care patients (n = 393) with admission GCS ≤12 and at least one EEG (eEEG, n = 34), the prevalence of NCSz was 13 % and was highest among those with CNS infection, together with anoxic encephalopathy [99]. NCSz are very frequent in noninfectious encephalitis (up to 78 % of cases) and are mostly nonconvulsive [100].

**Ischemia detection** No study has provided data on ischemia detection in patients with encephalitis.

**Prognostication** No study has analyzed the prognostic accuracy of EEG in patients with encephalitis but particular patterns such as “delta brush” may be associated with a more prolonged illness [100].

**Recommendations for patients with infectious and non-infectious encephalitis**

1. We recommend EEG in patients with encephalitis that are comatose or have unexplained neurological deficits to rule out NCSz (strong recommendation, low quality of evidence—grade 1C).

2. We suggest EEG in patients with encephalitis to assist with prognosis (weak recommendation, very low quality of evidence—grade 2D).

**EEG in comatose ICU patients without acute primary brain injury**

**Seizure detection** In a retrospective cohort of 238 general ICU comatose patients in whom EEG was performed, Towne et al. found a prevalence of NCSz of 8 % [29].
Postanoxic encephalopathy (42%) was the most common etiology, followed by AIS (22%), CNS infection, TBI, metabolic encephalopathy, alcohol or AED withdrawal (5%), and brain tumor (all 5%). Using standard 20-min EEG, Scozzafava found NCSz only in 2 of 169 patients with GCS <8 [101]. In 286 patients, of whom 22% had encephalitis and 24% metabolic encephalopathy, Firosh Khan et al. found that 4% had NCSE and 10% NCSz [102]. Patients with primary brain injury had a higher incidence of NCSz than those with metabolic encephalopathy (32% vs. 4%) [103]. Only two studies specifically focused on patients admitted to the ICU without a primary acute brain condition, in whom cEEG was performed because of altered consciousness. Young et al. found no NCSz among 62 patients with sepsis [104]. In a retrospective cohort of 201 medical ICU patients monitored with cEEG, Oddo et al. found a 10% frequency of seizures, of which 69% were purely NCSz [105]. Sepsis was the most common etiology and was the only independent risk factor for seizures. These findings confirm those of previous studies showing that septic encephalopathy and metabolic dysfunction (mainly renal and hepatic failure) are risk factors for NCSz [11, 106, 107].

Ischemia detection No study has provided data on ischemia detection in medical/surgical ICU populations.

Prognostication Patients with NCSz had the highest mortality rate in a large neuro-ICU population, although this finding was not significant after adjustment for confounding factors [99]. The same results were found in another study [101]. Firosh Khan et al. [102] found 42% and 21% of patients with NCSE and NCSz, respectively, had a poor outcome, but did not analyze the prognostic value of these findings. Young et al. [108] found that EEG suppression and lack of EEG reactivity were associated with a worse outcome in ICU patients; however, these data were only applicable to comatose CA patients. In a study of septic patients, the same group found that EEG abnormalities, but not NCSz, were associated with mortality (0% in patients with normal EEG, 19% in patients with theta rhythm, 36% in patients with delta rhythm, 50% in patients with triphasic waves and 67% in patients with suppression) [104]. NCSz was associated with a poor outcome in septic patients [105] and in critically ill elderly (>65 years of age) patients [109].

Recommendations for comatose ICU patients without acute primary brain injury

1. We suggest EEG in comatose ICU patients without an acute primary brain condition and with unexplained impairment of mental status or unexplained neurological deficits to rule out NCSz, particularly in those with severe sepsis or renal/hepatic failure (weak recommendation, low quality of evidence—grade 2C).

Technological issues

Duration of monitoring: continuous vs. intermittent EEG monitoring

Seizure detection Continuous EEG allows the detection of NCSz [11, 18, 103, 110] but there is controversy as to the minimum duration of cEEG. In a single-center retrospective study, about 50% of NCSz were detected within the first 60 min of EEG, but in comatose neuro-ICU patients at least 24 h and up to 48 h of monitoring may be required [17]. Continuous EEG is essential to titrate AED in RSE and to identify recurrent NCSz [15]. Intermittent (<30 min duration) EEG may be insufficiently sensitive to detect NCSz [101], but no studies have compared continuous to intermittent EEG. Standard EEG can provide useful information in selected clinical situations, such as epilepsy-related situations, CA and brain death examination [102, 111]. In a recent study, independent predictors of epileptiform activity included a history of convulsive seizure(s), increasing age, deeper coma, and female gender [99]. In this study, the “number needed to monitor” was seven, i.e. at least seven neuro-ICU patients should undergo intermittent EEG to diagnose one with seizures.

Ischemia detection Continuous EEG using qEEG analysis has been used to detect cerebral ischemia in comatose SAH patients and in subjects with AIS. In SAH patients at risk of DCI, monitoring is performed for several days, during maximum DCI risk [37, 39, 41], and on average for 7 days [39]. QEEG is similarly performed for several days after AIS, one study reporting an average of 83 h of monitoring [47].

Prognostication After CA and TH, EEG—intermittent or continuous—improves coma prognostication [63, 86–95, 112]. Whether cEEG has higher prognostic accuracy than intermittent EEG has not been evaluated. Early prognostication of AIS [56–59], ICH [44, 46] and SAH [42] has exclusively been assessed with cEEG.

Recommendations for continuous EEG over intermittent EEG monitoring

1. We recommend cEEG for seizure detection in patients with RSE (strong recommendation, low quality of evidence—grade 1C).
2. We suggest cEEG for seizure detection in patients with SE that do not return to functional baseline within 60 min after administration of seizure medication.
(weak recommendation, low quality of evidence—grade 2C).

3. We suggest cEEG for seizure detection in comatose ICU patients (TBI, SAH, ICH, coma after CA, encephalitis, and septic and metabolic encephalopathy) with unexplained and persistent altered consciousness (weak recommendation, low quality of evidence—grade 2C).

4. We suggest cEEG for ischemia detection in comatose SAH patients in whom neurological examination is unreliable (weak recommendation, low quality of evidence—grade 2C).

5. We suggest cEEG to assist with prognostication of coma after CA (weak recommendation, low quality of evidence—grade 2C).

**Montage: standard vs. simplified**

**Seizure detection** The placement of 21 electrodes is the standard method for EEG monitoring. Compared to standard EEG, the sensitivities of simplified EEG for seizure detection were 93% in one study using seven electrodes [113], 68% in another study using four electrodes [114], and 40% with single-channel EEG [115].

**Ischemia detection** All studies that examined the value of EEG for ischemia detection used a standard montage [37, 39, 41, 47].

**Prognostication** After CA and TH, EEG—intermittent or continuous—improves coma prognostication. The majority of the studies used a standard EEG montage [86, 88–92, 94, 95, 112], but others showed similar predictive values using simplified montages [63, 87, 93]. Prognostication of AIS [56–59], ICH [44, 46] and SAH [42] has exclusively been assessed with a standard montage.

**Recommendations for standard vs. simplified EEG montage in ICU patients**

1. We recommend a standard EEG montage (21 electrodes) for the detection of NCSz in ICU patients (weak recommendation, poor quality of evidence—grade 2C).

**Acknowledgments** This report has been endorsed by the European Society of Intensive Care Medicine. Mauro Oddo is Deputy Chair of the Neurointensive Care section of the European Society of Intensive Care Medicine.

**Conflicts of interest** None.

**References**


Original Research

Proposed Criteria for Referral and Evaluation of Children for Epilepsy Surgery: Recommendations of the Subcommission for Pediatric Epilepsy Surgery

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On behalf of the International League Against Epilepsy Subcommission for Paediatric Epilepsy Surgery, and the Commissions of Neurosurgery and Paediatrics

Summary: The Commission on Neurosurgery of the International League Against Epilepsy (ILAE) formed the Pediatric Epilepsy Surgery Subcommission in 1998 and charged it with formulating guidelines and recommendations for epilepsy surgery in childhood. Also endorsed by the Commission on Paediatrics, the following document is the consensus agreement after a meeting of 32 individuals from 12 countries in 2003. The panel agreed that insufficient class 1 evidence exists to recommend practice guidelines at this time. Instead, the panel generated criteria concerning the unique features of pediatric epilepsy patients to justify dedicated resources for specialty pediatric surgical centers, suggested guidelines for physicians for when to refer children with refractory epilepsy, and recommendations on presurgical evaluation and postoperative assessments. The panel also outlined areas of agreement and disagreement on which future research and consensus meetings should focus attention to generate practice guidelines and criteria for pediatric epilepsy surgery centers.

Key Words: Epilepsy surgery—Childhood epilepsy—Epilepsy syndromes.

1. Are the unique characteristics of children with epilepsy and their syndromes sufficiently different to justify dedicated pediatric epilepsy centers? and

2. Is adequate information available to propose guidelines regarding patient selection and surgical treatment for pediatric epilepsy surgery patients?

With the support of the ILAE Executive Committee and the Commissions on Neurosurgery and Pediatrics, the Pediatric Epilepsy Surgery Subcommission addressed these questions in a meeting with invited international experts in pediatric epileptology, neurosurgery, neuroimaging, psychology, and psychiatry (see Appendix 2).

The meeting was held in St. Avit de Vialard, Perigord Noir Dordogne, France, October 9–11, 2003, as a satellite of the ILAE Lisbon Congress. The following document represents the consensus agreement of this panel concerning the unique features of pediatric epilepsy patients that justifies dedicated resources and specialty pediatric surgical centers, guidelines for physicians for when to initiate the referral process for children with refractory epilepsy, and recommendations on presurgical evaluation and postoperative assessments. The document also outlines areas of disagreement on which future research and consensus meeting should focus attention.
Rationale for pediatric epilepsy surgical services

General medical agreement was reached (with evidence) that children are best cared for in clinical units with experience in providing pediatric care (1,2). The committee agreed that neurobiologic aspects of epilepsy are unique to children, especially the young, and as such require specific pediatric epilepsy expertise. Collectively, these features justify the unique approach necessary for dedicated pediatric epilepsy surgery centers.

The effect of epilepsy on early brain development

Rapid brain maturation during early infancy and childhood is responsible for a complex evolution of clinical seizure semiology, electroencephalographic, and neuroimaging findings. Developmental arrest or progressive disturbances in cognitive function, behavior, and psychiatric state (epileptic encephalopathy) are common in pediatric epilepsy surgery patients and can influence the decision for surgical management. In particular, a consensus was reached among the experts that early surgical intervention is critical in infants with catastrophic epilepsy to prevent developmental arrest/regression. Emerging clinical data exist in support for this concept (3,4). However, we also recognized that further studies of intractable epilepsy in childhood are needed to determine whether the developmental benefits of early surgery for epilepsy exist for the entire preadolescent population.

Pediatric epilepsy

The presentation of intractable localization-related epilepsy is often heterogeneous in childhood. Pediatric patients with hemispheric or unilateral focal etiologies can have generalized seizures and EEG patterns, rapid evolution of electroclinical features, progressive neurologic disorders, and bilateral congenital brain syndromes (5). In addition, with children, the spectrum of surgically amenable candidates, etiologies, and syndromes is often diverse. Familiarity with these diverse presentations requires specialized pediatric expertise.

Functional plasticity

The child’s brain is capable of significant reorganization of neurologic function after insult and surgery, a unique and complex phenomenon that is critical for surgical planning. Functional plasticity is particularly important to the recovery of linguistic competence in infants and very young children. Although brain plasticity is often a positive influence facilitating neurologic reorganization after treatment, it may also act as a negative influence in that early-onset epilepsy may trigger deviant or delayed development. Understanding functional plasticity related to pediatric epilepsy surgery candidates and the expected or unexpected neurologic deficits after surgery is a unique characteristic of this field (5,6).

Psychosocial factors

It is reasonable to assume that an earlier reduction in the burden of chronic epilepsy should confer psychosocial benefit and improve quality of life in children. Furthermore, surgical intervention at an earlier age would be expected to have a greater role in preventing cognitive regression than would that in older patients. However, few published data support these concepts. Accurate assessment of cognition, behavior, psychosocial adaptation, and quality of life is crucial for an understanding of pediatric epilepsy surgery candidates, and assessing outcome and documenting differences from presurgery should be a key goal of future clinical studies. Involving the child in the decision-making process and through an assent to surgery is an additional psychosocial consideration in pediatric epilepsy surgery patients. Many of these clinical features require expertise unique to the pediatric patient.

Epilepsy disorders in pediatric epilepsy surgery patients

The Committee recognized that surgical syndromes and etiologies were more diverse in children than in adults. However, it also was acknowledged that we do not know the incidence of these conditions, and a survey was recommended to determine the types of epilepsy surgery performed throughout the world. This will be the focus of a future consensus meeting. Recognized etiologies and syndromes more common in children include the following.

Cortical dysplasia

Cortical dysplasia is the most common neuropathologic substrate in pediatric epilepsy surgery. Its presentation includes multiple electrophysiologic syndromes that may be focal or multilobar. The clinical presentation and presurgical evaluation of children with cortical dysplasia often requires advanced specialty services because the neuroimaging may be very subtle. The lesion is not always apparent on magnetic resonance imaging (MRI), or the visible lesion may be only a small part of a diffuse structural abnormality. Complete resection of the entire lesion is associated with the best postsurgery seizure control. Assessing the potential cognitive gain versus the risk of a neurologic deficit is especially important in very young children with cortical dysplasia.

Tuberous sclerosis complex

Children with tuberous sclerosis may have a single epileptogenic region suitable for resection despite having multiple other tubers or multifocal/diffuse interictal EEG findings (7,8). Multiple epileptogenic regions pose a greater challenge in the evaluation process and the services of centers with additional expertise. A role may exist for multistaged resective procedures. Newer functional technology [e.g., \( \alpha \)-methyl tryptophan–positron...
emission tomography (PET), magnetoencephalography (MEG), diffusion tensor imaging (DTI) await validation.

Polymicrogyria
Epilepsy associated with polymicrogyria (PMG) has a wide electroclinical spectrum compared with other hemispheric syndromes, with some children having milder seizures that may spontaneously remit. PMG commonly involves the perirolandic and perisylvian regions, and abnormal tissue may retain critical function. It may commonly be bilateral, even when MRI suggests a unilateral lesion.

Hypothalamic hamartoma
Children with epilepsy and hypothalamic hamartomas often have pharmacoresistant seizures, which require referral to a specialist epilepsy unit. Developmental and behavioral problems are common. Several different surgical approaches, including stereotactic, endoscopic, and radiosurgical procedures, have been used successfully, but their relative efficacy and safety have not yet been established and require further study.

Hemispheric syndromes
Focal epilepsy in childhood may be associated with congenital pathologic conditions affecting an entire cerebral hemisphere. Examples include hemimegalencephaly and hemispheric dysplasia. Hemispherectomy or other hemispherotomy techniques are frequently used to treat epilepsy associated with hemispheric syndromes, and patients are usually evaluated and treated at pediatric centers with specialized expertise. In particular, children with hemimegalencephaly pose significant operative risks.

Sturge–Weber syndrome
Children with Sturge–Weber syndrome (SWS) are potential candidates for hemispheric and focal resections. Affected children may require urgent evaluation at a specialized surgical center when seizures first occur in infancy, or epilepsy is associated with developmental delay or progressive hemiparesis. Pediatric neurosurgical expertise is desirable, as the vascular pathology of SWS and its hemodynamic effects may compromise the contralateral hemisphere and increase operative risks.

Rasmussen syndrome
Rasmussen syndrome first appears primarily in childhood. Affected children should be followed up in epilepsy surgery centers with experience in the medical and surgical management of this condition. Hemispherectomy or hemispheric disconnection remains the only cure for progressive epilepsy and should be considered early in the course to prevent comorbidity. The decision to perform surgery is often challenging, as the risk–benefit assessment requires considerable clinical experience, particularly when the dominant hemisphere is affected.

Landau–Kleffner syndrome
The surgical management of children with Landau–Kleffner syndrome (LKS) has been discussed in the previous subcommission document (see Appendix 1). Few children are considered suitable for multiple subpial transection, but pediatric specialist review remains a requirement.

Other situations
Depending on age at seizure onset, certain epilepsies from lesions (e.g., dysplastic brain tumors, cerebrovascular insults) common to both the adult and pediatric population may require evaluation at a pediatric center because of the higher risk of behavior and cognitive morbidity associated with seizure presentation in childhood.

THE PEDIATRIC EPILEPSY SPECIALIST UNIT

The Committee found that pediatric surgical units vary worldwide in their access to advanced technologies, referral patterns, and operative experience. The Committee recognized that it is premature to establish minimal qualification/expertise and infrastructure requirements for a “pediatric epilepsy surgical unit” without a survey to establish the local availability of resources in centers around the world and a better understanding of the types of pediatric patients referred with intractable epilepsy. Such a survey will be a priority for a future meeting. It was acknowledged, however, that certain subgroups of surgical candidates, by virtue of extremely complex localization issues or high surgical risk–benefit ratios, should be referred to a surgical unit with experienced, multidisciplinary personnel and access to advanced technologies. Infants and toddlers represent a particularly high-risk group that requires a multidisciplinary approach with the highest level of expertise, including dedicated pediatric neurosurgeons, anesthesiologists, and critical care intensivists. Older candidates for hemispherectomy and multilobar resection are similarly vulnerable. Specific guidelines from the expert group include the following.

Indications for referral
Similar to adults, children with seizures that are uncontrolled by medical treatment (i.e., failure of two or three appropriate drugs) or are disabling (including medication side effects) are possible surgical candidates. In addition, childhood epilepsy that cannot be classified as a clearly defined electroclinical epilepsy syndrome (ILAE classification) (9,10) should be evaluated by a pediatric specialty center. This includes patients with stereotyped or lateralized seizures or other evidence of focality (that cannot be definitely attributed to idiopathic partial epilepsies) or in whom the MRI reveals a lesion amenable to surgical removal.

Referral of pediatric patients differs from that of adults in two important respects. First, seizures in childhood may
be associated with developmental arrest or regression, especially in children younger than 2 years. Second, focal epilepsy in childhood is often associated with age-specific etiologies (see prior list). In the pediatric surgical population, currently no preoperative clinical variables predict seizure outcome. Developmental delay or psychiatric morbidity should thus not be a contraindication for pediatric epilepsy surgery.

**The presurgical evaluation**

The following were agreed-on components in the evaluation of prospective pediatric epilepsy surgery candidates.

**EEG**

Interictal scalp EEG including natural sleep recording is mandatory for the presurgical evaluation, and video-EEG recording for ictal events was strongly recommended in all children. Video-EEG should be acquired by using standard and acceptable techniques (e.g., American Clinical Neurophysiology Society guidelines) (11). Serial studies may be necessary to document consistency or progression, especially in infants and young children. Invasive electrode recordings are being performed more selectively as the indications have evolved alongside advances in neuroimaging. Invasive electrode studies are indicated primarily to localize the epileptogenic region when alternative methods are inconclusive. As neocortical epilepsy is more common and the extent of the epileptogenic zone may be difficult to define based purely on imaging, invasive EEG monitoring may be necessary. The committee agreed that this required further discussion.

**Structural imaging**

In agreement with American Academy of Neurology guidelines, an MRI with a specified epilepsy protocol is mandatory as the primary imaging modality (12–15). A computed tomography (CT) scan is indicated under specific circumstances (e.g., possibility of calcification). Special MRI sequences may be required in the first 2 years of life because of immature myelination, and serial scans may be necessary to identify abnormalities during early postnatal brain development.

**Functional imaging**

The pediatric epilepsy specialist unit should have functional imaging capabilities [e.g., ictal and interictal single-photon emission CT (SPECT), PET], either on site or by collaboration. The contribution of new functional imaging techniques is promising but requires further clinical validation (16).

**Neuropsychology/neuropsychiatry**

It should be recognized that pediatric epilepsy surgery candidates have a high incidence of neurodevelopmental and mental health disorders [psychiatric Diagnostic and Statistical Manual of Mental Disorders (DSM) IVR criteria] (17). Age-appropriate neuropsychological/developmental assessments are a mandatory aspect of the pre- and postsurgery evaluation and require a team with expertise in assessing children. The committee agreed that neuropsychiatric evaluation is recommended but accepts that no psychiatric exclusion criteria exist for pediatric epilepsy surgery patients. At present, the goal of surgery in children is to achieve seizure control, with the potential for the added benefit of improved neurodevelopment. However, favorable seizure outcome after surgery does not guarantee improved behavioral or cognitive status (18–20).

**OUTCOME ASSESSMENTS FOR PEDIATRIC SURGICAL PATIENTS**

The Committee recommended that pediatric epilepsy surgery outcome scales should include appropriate measures of seizure frequency, antiepileptic drug (AED) use, quality of life (QOL), development, cognition, behavior, and psychosocial adjustment. Expected and unexpected adverse events (surgical and medical) and how they may affect the patient (immediately and in the long term) should be part of the documentation. Long-term follow-up assessments into adulthood are required, especially related to seizure freedom and psychosocial, behavioral, cognitive, and developmental outcomes. Until new pediatric specific-outcome scales are developed, the use of existing systems is acceptable. Outcome measures should be uniformly applicable, feasible, and validated to facilitate collaboration and comparison across centers.

**DISCUSSION**

The Committee’s guidelines and statements reflect the consensus of the experts despite a wide range of clinical perspectives across different pediatric specialty centers. At the same time, the statements also identified differences in opinion and the need for further evidence-based data to establish specific recommendations. These statements thus set the stage for an organized initiative extending over the next several years to enhance the clinical understanding of the surgical management of intractable epilepsy in children.

**Concepts on which we agreed**

It was clear that an overwhelming consensus exists that several concepts and strategies differentiate the approach to evaluating and treating intractable epilepsy in children. The Committee agreed on the rich diversity of disorders encountered, complex developmental issues involved, and the need to assess the success of surgical intervention, not only with respect to seizure control but also with developmental and psychosocial improvements. These critical differences were thought to justify the need to evaluate children within a dedicated pediatric epilepsy center.
A consensus view was reached that successful seizure control may facilitate cognitive development and help reduce the behavioral and/or psychological burden of epilepsy on the child and the family. These considerations were thus unanimously accepted as being critical in deciding the timing of surgical intervention in childhood. However, pending more definitive outcome data from prospective studies, the current goals of epilepsy surgery remain primarily to achieve seizure relief rather than cognitive/behavioral improvements; a point to be duly emphasized for parental counseling and influencing family expectations.

The Committee was readily able to identify common ground on many aspects of surgical candidacy and to establish guidelines for referral and clinical evaluation. It enumerated important epilepsy syndromes and special situations in childhood that should quickly alert referring clinicians to the potential for surgical intervention. The Committee also emphasized that contrary to the generally held notions, a child with intellectual disability, psychiatric disease, or very young age should not be excluded from being considered a surgical candidate. The Committee went on to emphasize that a subgroup of pediatric epilepsy surgery candidates, such as patients with extremely complex presentations or early catastrophic seizures, would be best served at pediatric surgical centers with advanced technologic capability and multidisciplinary dedicated expertise. At present, the number of pediatric surgical centers in the world with the necessary expertise, experience, and technology is limited.

**Concepts for further evaluation**

The Committee did not establish minimal criteria or suggest guidelines for defining a pediatric epilepsy specialty or surgical unit at this time. Not all centers have the expertise or the latest technologies for the optimal management of the entire spectrum of pediatric surgery cases. Similarly, a wide range was found in the availability of dedicated support personnel, operating room, and critical care unit infrastructure at each center. The average number of procedures performed annually across the polled centers was ~15, but some centers have several times that volume, and others perform far fewer operations. An argument could be made that establishing a minimal number of annual cases performed at each center would likely concentrate clinical experience, and we hope that it would improve proficiency in patient care. The Committee was, however, concerned that establishing “minimal” guidelines before assessing the global landscape of pediatric epilepsy surgery was premature, and restricting development of new centers could have a crippling effect on current resources.

The Committee also identified several key issues reflecting differences in opinion/clinical approaches and noted significant voids in scientific information. The Committee noted that few data existed to estimate the number of surgical candidates among children with intractable epilepsy. Many of the participants voiced their continued frustration at the lengthy delays between onset of intractable epilepsy and referral for surgical evaluation, especially in very young children. Therefore one of the first recommendations was to obtain reliable epidemiologic data concerning the incidence and frequency of surgically remediable epilepsy in the pediatric population and to define the “patterns” and “time-course” of regional referrals. These data would provide important public health information, facilitate the development of strategies to optimize prompt referral of children to the specialty unit, and guide the establishment of network infrastructure.

Although the Committee agreed on minimal requirements for presurgical evaluation including EEG, imaging, and age-specific neuropsychological assessment, no consensus was reached on the routine use of additional investigative techniques such as PET, magnetic resonance spectroscopy (MRS), functional MRI (fMRI), MEG, SPECT, and invasive EEG. These need further validation in pediatric patients by age and seizure syndrome. Given the paucity of clinical trials, no attempt was made to define the comparative utility of these techniques at this meeting. Very few centers offer all modalities, and future collaborative studies should compare and contrast clinical approaches and techniques in the presurgical evaluation of children. As with the presurgical evaluation, the lack of comparative data on different surgical strategies also limited informed discussion and will be an area of future study.

The participants agreed that we must develop and use common outcome measures at each center that have been validated in children and that are suitable for serial measurements. Measures of cognition, behavior, mood, quality of life, and psychosocial adjustment were highlighted as important areas for future studies. However, the committee could not now agree on specific instruments and measures, and this area will require future consensus meetings. As a guideline, reports of outcome will include unexpected and expected adverse events. The frequency of these events will be important in risk–benefit discussions with family members and in evaluating new surgical technologies as they emerge. Outcomes measures will have to be standardized across centers, systematically assessed, and documented so that accurate worldwide comparisons can be made. This would allow the much-needed multicenter trials to be conducted in specific pediatric epilepsy syndromes, resulting in improved care for children with difficult-to-manage seizure disorders.

**Acknowledgment:** The Committee thanks Cyberonics, Digi, GlaxoSmithKline, Pfizer, Sanofi, and the ILAE for financial support; Drs. Wieser and Guerrini for their guidance; and Drs. Helen Cross and Olivier Delalande for their immense efforts in organizing the first successful comprehensive initiative.
This article is dedicated to the memory of John Gates, M.D., who enthusiastically participated in the meeting preorganization.

APPENDIX 1.

ILAE Commission on Neurosurgery Advances, Conclusions and Recommendations of the ILAE Commission on Neurosurgery of Epilepsy
Chairpersons: Dr. J. Helen Cross, Dr. Hans Holthausen

The pediatric epilepsy surgery Subcommission of the ILAE was formulated within the context of the Commission on Neurosurgery. The Subcommission had its initial meeting at the American Epilepsy Society in Orlando in 1999 and has subsequently met on two further occasions, Cleveland, in 2000, and the American Epilepsy Society in Los Angeles in 2000.

In parallel with the plan of the Commission to define guidelines with regard to the palliative procedures in epilepsy surgery, the primary task of the Subcommission would be to comment on such procedures with regard to children. To achieve this, working groups were set up for each of the palliative procedures considered: corpus callosotomy, multiple subpial transection, and vagus nerve stimulation. The aim was to review the literature with possible further data collection and subsequent identification of guidelines.

1. Corpus Callosotomy
   Leader: Frank Ritter, Minnesota.

A review of the literature revealed many studies involving corpus callosotomy were performed and reported before 1990. However, outcome of such studies suggested that anterior corpus callosotomy resulted in a 25–30% seizure-free rate, whereas with a complete callosotomy, 80% were seizure free at 12 months, decreasing to 60% after 3 years. The reduction in seizure relief with time appears to be more pronounced with regard to generalized tonic–clonic seizures and relatively stable with regard to drop attacks. Complications are few, with no disconnection syndrome reported with the procedure carried out before age 10 years.

Current recommendations are that the procedure should be directed at the seizure type rather than the seizure syndrome. A resectable lesion should be fully excluded with full presurgical evaluation and workup. An MRI after surgery would be recommended to determine the degree of completion. However, it must be recognized that responder identification still remains difficult.

2. Multiple Subpial Transection
   Leader: Professor Charles Polkey, London.

Multiple subpial transection (MST) may be considered when seizures originate from within eloquent cortex and more specifically in the Landau–Kleffner syndrome (epileptic aphasia) performed over the Wernicke area and deep into the sylvian fissure. It has also been reported in cases in which widespread multifocal epileptogenesis occurs, although these reports are from one center, and outcome data are limited. Specifically MST, alone with regard to seizure origin, appears to lead to an approximate 30% improvement in seizures, increasing to 60% when it is performed in conjunction with resection. Although it is relatively widely accepted as the surgical treatment for Landau–Kleffner syndrome, reports are indeed limited. In Morrell’s original series (Chicago), 11 of 14 children demonstrated improvement, and it was thought that the remaining three patients had been poorly selected. Within Professor Polkey’s own series, he has operated on nine patients, twice in one case, with good results in eight in regard to abolition of seizures, with evidence of improvement in language and in behavior.

Overall, MST should be considered where seizure onset is demonstrated to be within eloquent cortex, either alone or preferably in combination with resection. It remains the surgical procedure of choice in the Landau–Kleffner syndrome, although no doubt exists that specialist evaluation is required in a center used to evaluating such patients, in view of the detailed neurophysiology required. Its role in multifocal epilepsy with autistic regression is yet to be proven.

3. Vagal Nerve Stimulation
   Leader: Dr. Helen Cross, London.

Data with regard to vagal nerve stimulation (VNS) in children remains limited, with much reported data in abstract form with relatively short-term follow-up of <6 months. A literature review revealed patients with 10 to 12 months of follow-up; only two were seizure free. Adverse events were reported in only one publication, with hoarseness in six patients and throat pain in one. Attempting to address data on specific syndromes, however, was more difficult from the publications available. Most information was available for the Lennox–Gastaut syndrome, but involved only 11 patients, with four demonstrating a >50% reduction in seizures.

In an attempt to increase these numbers and obtain further data with regard to specific seizure syndromes, a survey of centers was carried out. Data were available from 129 patients from 12 centers, five with completed questionnaires and seven from papers in preparation from the United States collaborative study group. Seventy-two of the children had a ≥12-month follow-up, with all 129 having ≥6 months’ follow-up. Overall, only one child was seizure free, 43% demonstrated >50% improvement, but 43% had no change in seizure frequency. With regard to seizure syndrome, symptomatic generalized epilepsy (the majority of which were Lennox–Gastaut syndrome) appeared to have the most beneficial effect, with 45% showing a >50% reduction. It is of note, however, that
no improvement was seen in any of 10 patients with a VNS inserted for infantile spasms. With regard to specific seizure types, 13 patients were recorded as having VNS inserted specifically for drop attacks, of which nine demonstrated >50% reduction, two of whom were seizure free. Within the focal epilepsy group, only 10 of 27 patients demonstrated a >50% improvement, with notably three deteriorating.

From these limited data, it was thought that VNS could not be recommended for infantile spasms. However, it could be considered in children with symptomatic or cryptogenic focal or generalized epilepsy who are medication resistant (having been tried on at least four anticonvulsant drugs) and having undergone full evaluation at an epilepsy surgery center to exclude the possibility of focal resection. No doubt some promising data are available with regard to drop attacks, but the role of VNS versus callosotomy requires further evaluation.

### Subcommission Members

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<th>Chairpersons</th>
<th>Hans Holthausen</th>
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**APPENDIX 2. ILAE Subcommission for Pediatric Epilepsy Surgery (**present at St. Avit de Vialard)**

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<td>Marja-Lisa Granström*</td>
<td>Helsinki, Finland</td>
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<td>Renzo Guerrini*</td>
<td>Pisa, Italy; Chair, ILAE</td>
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<td>Simon Harvey*</td>
<td>Melbourne, Australia</td>
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<td>Deepak Lachhwan*</td>
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<td>Utrecht, The Netherlands</td>
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**Invited participants (**present at St. Avit de Vialard**)

- Sarah Aylett* — London, United Kingdom
- Christine Bulteau* — Paris, France
- Rochelle Caplan — Los Angeles, California, U.S.A.
- Catherine Chiron* — Paris, France
- Harry Chuang — Detroit, Michigan, U.S.A.
- Youssef Comair — Beirut, Lebanon
- Thierry Dionna* — Lausanne, Switzerland
- Olivier Dulac* — Paris, France
- Natalio Fejerman — Buenos Aires, Argentina
- Martine Fohlen* — Paris, France
- William Harkness* — London, United Kingdom
- Brian Harding* — London, United Kingdom
- Lacy Hertz Pannier — France
- Isabel Heyman* — London, United Kingdom
- Claude Jalin* — Paris, France
- Philippe Kahane* — Grenoble, France
- Solomon L. Moshe — New York, U.S.A.
- Brian Neville* — London, United Kingdom
- Andre Palmini* — Porto Allegre, Brazil
- Perrine Plouin — Paris, France
- Don Shields* — Los Angeles, California, U.S.A.
- Shlomo Shinnar — New York, U.S.A.
- Carter Snedd — Toronto, Ontario, Canada
- Tatsuya Tanaka* — Tokyo, Japan
- Patrick Van Bogaert* — Brussels, Belgium
- Eileen Vining* — Baltimore, Maryland, U.S.A.
- Harry Vinters — Los Angeles, California, U.S.A.

### 4. Future Considerations

The formation of the Subcommission on Pediatric Epilepsy Surgery has brought together a large number of individuals from epilepsy surgery centers around the world. The group has gained momentum over the past 12 months and believes strongly that a forum for continued discussion should be organized specifically on guidelines for minimum requirements with regard to selection of children for epilepsy surgery, but also with regard to standardizing measures of assessment of outcome, not only with regard to seizure control but also with regard to cognition, behavior, and quality of life.

### REFERENCES


