Chapter 1

Overview of Continuous EEG Monitoring in Critically Ill Neonates and Children

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Key Points

- Seizures are common in critically ill children with acute encephalopathy. Most seizures have no accompanying clinical signs, and therefore detection requires continuous EEG monitoring.
- Guidelines recommend at least 24 hours of continuous EEG monitoring in critically ill neonates and children with clinical and EEG risk factors for seizures.
- Seizures have been associated with worse short- and long-term outcomes in neonates and children, even after adjusting for acute encephalopathy etiology and markers of brain injury severity.
- Although EEG-guided anti-seizure therapy has been shown to reduce seizure burden, it remains to be proven that the resulting reductions in seizure burden improve outcomes.

Introduction

Continuous EEG (cEEG) monitoring offers bedside, noninvasive, diffuse, and continuous information about brain function. These characteristics allow clinicians to assess brain function, evaluate for changes in brain function over time, and identify electrographic seizures that are often not clinically observable (Figure 1.1). These advantages have led to widespread and increasing use of cEEG in critically ill patients across the age spectrum. This chapter introduces cEEG in critically ill neonates and children including seizure epidemiology (incidence and risk factors), the relationship between electrographic seizures and outcome, available consensus statements and guidelines, and role of quantitative EEG.

Electrographic Seizures in Critically Ill Neonates

Incidence

Seizures are a common manifestation of neurological injury and dysfunction in the neonatal period. Across childhood, the occurrence of seizures is highest during the neonatal period [1], with an estimated incidence of 1–3.5 per 1000 live births in term neonates, greater than 25 per 1000 live births in preterm neonates, and 58 per 1000 live births for very low birth weight neonates [1, 2]. A 1998–2002 population-based study from the California Office of Statewide Planning and Development identified the seizure incidence as 0.95 per 1000 live births in term neonates. Risk factors for neonatal seizures were categorized as intrinsic to the neonate, mother, and birthing process [1, 3]. Intrinsic neonatal risk factors were male sex and low birth weight. Maternal risk factors included nulliparity, age greater than 40 years, race (with a decreased risk in Asian and Hispanic mothers compared to Caucasian mothers), and the presence of diabetes independent of macrosomia. The most significant intrapartum risk factor was maternal fever (as a marker for maternal infection). Additional risk factors included prolonged second stage of labor, fetal distress, cesarean section or surgically assisted vaginal delivery, and "catastrophic" delivery involving placental abruption, uterine rupture, or cord prolapse. Additional risk factors have been less consistent and include an increased risk for African American mothers, young maternal age (18–24 years), preeclampsia, heavy smoking, obesity, and asthma [1].

Risk Factors

There are many etiologic precipitants for neonatal seizures. Hypoxic-ischemic encephalopathy, stroke, intracranial hemorrhage, intracranial infection, and cerebral malformations are reported to cause up to 85% of neonatal seizures [4]. The Neonatal Seizure Registry consortium of seven tertiary care pediatric centers in the United States prospectively studied a cohort of 426 neonates with seizures who underwent cEEG. The most common seizure etiologies were hypoxic-ischemic encephalopathy in 38%, ischemic stroke in 18%, neonatal onset epilepsy in 13%, intracranial hemorrhage in 11%, neonatal genetic epilepsy syndrome in 6%, congenital cerebral malformation in 4%, and benign familial neonatal epilepsy in 3% [5]. In term neonates, hypoxic-ischemic encephalopathy is the most common precipitant, accounting for about 40–50% of cases [1, 2, 5]. Hypoxic-ischemic encephalopathy occurs in 1–2.5 per 1000 live births, is a clinical syndrome characterized by neonatal depression with laboratory evidence of systemic acidosis [6], and is associated with increased rates of acute mortality, seizures, prolonged hospitalizations, and subsequent neurodevelopmental problems, particularly in neonates with moderate and severe hypoxic-ischemic encephalopathy [7–9]. Therapeutic hypothermia is often used as a neuroprotective strategy [10], and it may reduce acute seizure exposure in neonates with moderate hypoxic-ischemic encephalopathy [11–14]. Less common etiologies include metabolic derangements, mitochondrial or metabolic disorders, inborn errors of metabolism, and neonatal epilepsy syndromes. Fewer studies in the preterm population indicate intraventricular hemorrhage is the most common seizure precipitant [12–14].

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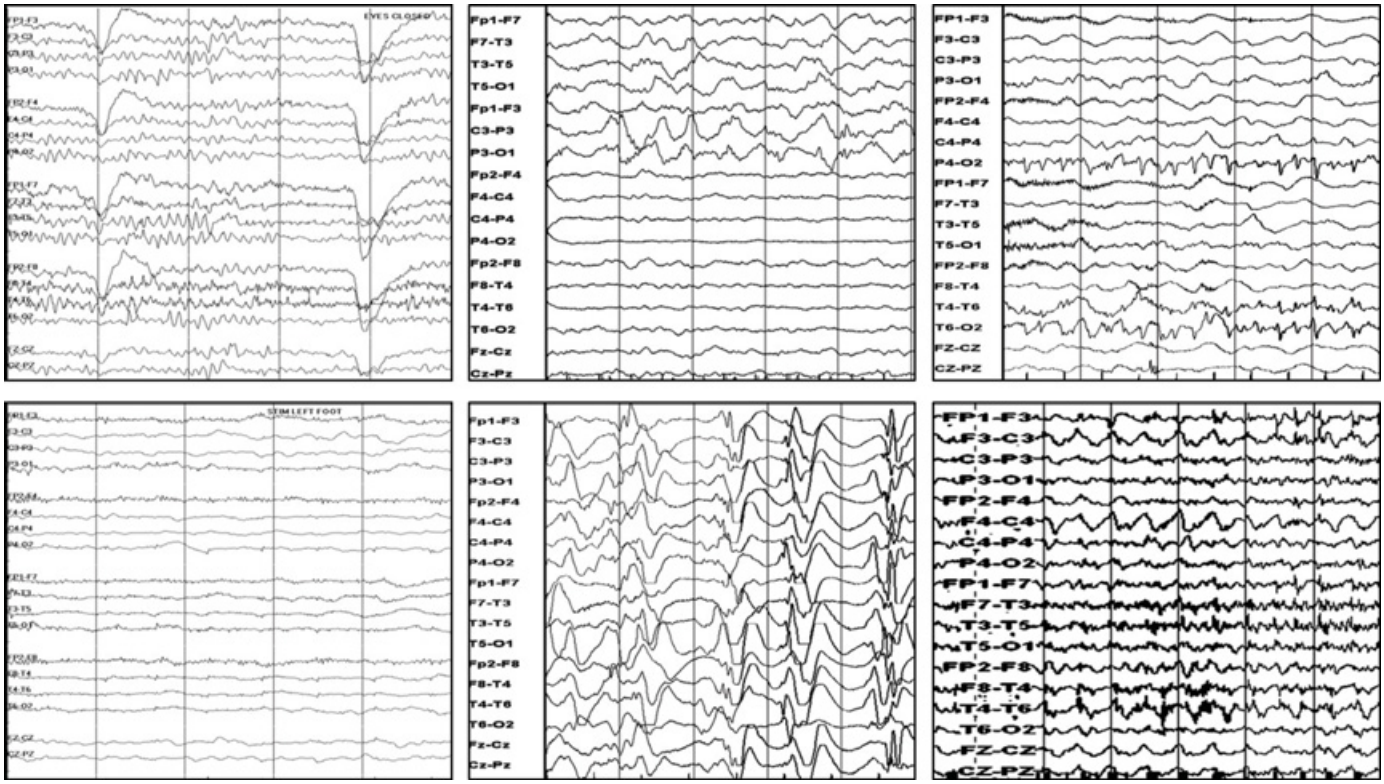

Figure 1.1 Five-second conventional EEG images from critically ill children who all appeared similarly encephalopathic to clinicians. Left top shows a normal EEG pattern, bottom left shows attenuation, middle top shows hemispheric asymmetry, middle bottom shows periodic epileptiform discharges, and the right top and bottom show electrographic seizures.

The EEG background may also help identify neonates at risk for electrographic seizures [15]. A cohort of 51 neonates, including 8 premature neonates, was monitored with cEEG, and the EEG background was graded in five categories: normal, immature for gestational age, mild abnormalities, moderate abnormalities, and severe abnormalities. Seizures occurred in 45% of the cohort, and 96% of the neonates with seizures had an abnormal EEG background. A severely abnormal EEG background predicted the highest risk for seizures while neonates with normal or immature backgrounds had a low risk for seizures. All premature neonates with seizures had mild to severely abnormal background while premature neonates without seizures all had normal or immature EEG backgrounds. The EEG backgrounds remained relatively consistent over the course of the recording (ranging 16–119 hours), with nearly 70% maintaining identical grading from onset to the end of the recording [16].

Diagnosis

There are three broad neonatal seizures types: (1) "clinical-only," which is a sudden paroxysm of abnormal clinical change that does not correlate with a simultaneous EEG seizure; (2) "electroclinical," which is a clinical seizure coupled with an EEG seizure; and (3) "EEG-only," which is an EEG seizure that is not associated with any outwardly visible clinical signs [17]. EEG-only seizures are also called subclinical or nonconvulsive seizures. An electrographic neonatal seizure is defined as a sudden, abnormal EEG event defined by a repetitive and evolving pattern with a minimum 2 microvolt voltage and duration of at least 10 seconds (Figure 1.2) [17].

Neonatal seizure diagnosis has evolved from a clinical diagnosis to a frequently EEG-based diagnosis for two main reasons. First, paroxysmal abnormal movements or events are common, and it can be very difficult to determine which represent seizures. In a study that included 415 clinically diagnosed neonatal seizures, the suspected seizures were categorized by the four semiology categories: clonic, tonic, myoclonic, and subtle [4]. All clinically diagnosed seizures classified as focal clonic or focal tonic had an EEG correlate. Alternatively, none of the clinically diagnosed seizures classified as generalized tonic or subtle had an EEG correlate. About one-third of clinically diagnosed myoclonic seizures had an EEG correlate. Interestingly, the seizures that had a consistent electrographic correlate (focal clonic and tonic) only comprised about 16% of the clinically diagnosed seizures, while the suspected seizures that more often had no electrographic correlate (generalized tonic and subtle) comprised 55% of the clinically diagnosed seizures. Myoclonic seizures that inconsistently had an electrographic correlate were also common, comprising 25% of the clinically diagnosed seizures. Focal EEG seizures had a high correlation with focal brain lesion and favorable short-term outcome, while clinical seizures without electrographic correlate were associated with diffuse processes, such as hypoxic-ischemic encephalopathy, and unfavorable short-term

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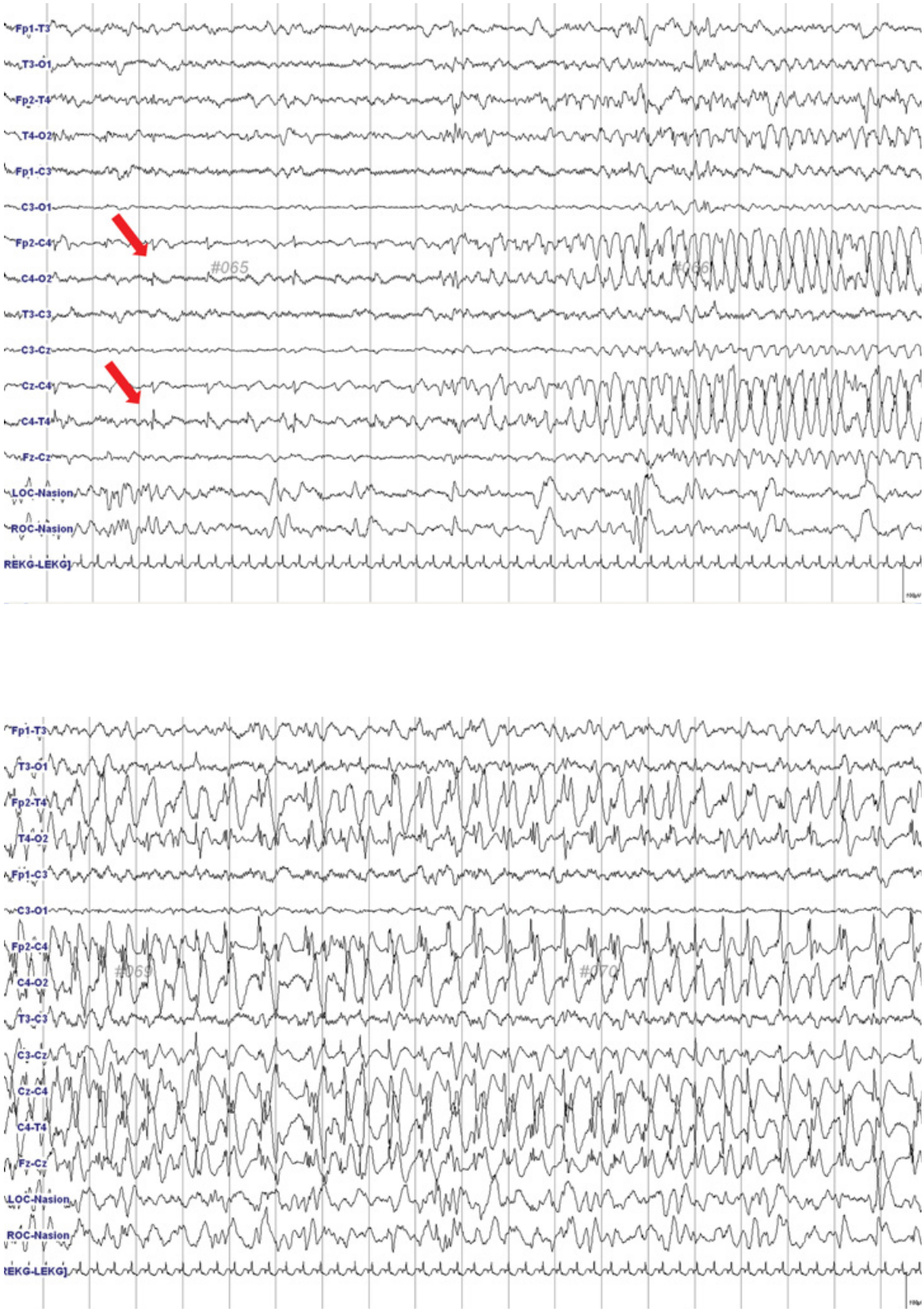

Figure 1.2 Electroclinical seizure in a full-term neonate. (a) The seizure begins with rhythmic 1 Hz sharp waves in the right central region (C4). (b) The sharp waves evolve in amplitude and frequency in the right central region (C4) and spreads to the right temporal region (T4). Thirty seconds after electrographic onset of the seizure, the infant exhibited a left arm clonic seizure.

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outcomes [18]. Similarly, a retrospective audit of 43 neonates with 160 electrographic seizures found 56% of the neonates had clinical signs with the electrographic seizure, and, of those, 89% had multiple clinical features. The most common clinical features seen were subtle seizures: ocular movements (70%), oro-lingual movements (56%), and autonomic changes (56%). In contrast, clonic movements and tonic movements were seen at any point during seizure in only 23% and 25% of neonates, respectively [19]. These studies indicate that although focal tonic and clonic movements are often associated with electrographic seizure, they occur less commonly than subtle clinical movements, which are inconsistently associated with electrographic seizures.

Considering the aforementioned studies, it is understandable that a solely clinical diagnosis of neonatal seizures is difficult for clinicians. A study of 51 neonates undergoing video EEG demonstrated the difficulties that practitioners face. Nine neonates had electrographic seizures and three neonates had clinical seizures. On video review, only one-third of the electrographic seizures had a clinical correlate while two-thirds of the seizures were EEG-only. In total, clinical staff correctly identified only 9% of the seizures based on clinical observation. Simultaneously, clinical staff identified numerous movements that were clinically concerning for seizures, and only 27% had an electrographic correlate [20]. Similarly, a study showed video clips from 20 neonates with abnormal movements to 137 healthcare professionals, including nurses and doctors with varying degrees of experience, each of whom opined on the nature of the movements. Overall, 50% of the abnormal movements were correctly identified as seizures, with clonic movements more often correctly identified than subtle movements. Inter-observer agreement was poor [21]. These data indicate that clinical seizure diagnosis is problematic since clinicians underdiagnose seizures without an identifiable clinical correlate and incorrectly classify paroxysmal neonatal movements as seizures, potentially leading to unnecessary anti-seizure medication administration.

The second reason clinical seizure diagnosis is difficult is that electroclinical seizures represent a minority of the true neonatal seizure burden in most neonates experiencing seizures. EEG-only seizures are very common in neonates. Across neonatal cohorts, rates of EEG-only seizures identified by both cEEG and amplitude-integrated EEG (aEEG) range from 10% to 79% [22–25]. EEG-only seizures may occur before any treatment, and they are even more common after anti-seizure medication administration. Further, about 50% of neonates experience electroclinical dissociation in which there is an uncoupling of electrographic seizure activity and clinical signs following treatment with an anti-seizure medication [26]. Thus, administration of an anti-seizure medication terminates clinically evident seizures, but EEG-only seizures persist.

For these reasons, it is now recognized that clinical diagnosis alone is insufficient to optimally quantify neonatal seizures. Clinical seizure diagnosis both overestimates that non-ictal events are seizures (leading to unnecessary exposure to anti-seizure medications with potential adverse effects) and underestimates the true incidence of seizure in neonates (potentially missing treatment and yielding seizure-induced secondary brain injury). As a result, there is increasing use of cEEG in neonatal intensive care units [27, 28–30].

Among neonates with seizures, the seizure exposure is often high. Neonatal status epilepticus has been defined as present when the summed duration of seizures comprising $\geq$50% of an arbitrarily defined 1 hour epoch [17]. Across critically ill neonates, the incidence of status epilepticus has been reported as 10%–60% [24, 25, 31, 32].

Prognostication Using Neonatal EEG

While seizure identification and the differential diagnosis of paroxysmal events are the primary reasons to perform cEEG monitoring in neonates, another important indication is assessment of the EEG background (Figure 1.3) [15]. EEG background assessment may help to predict neurodevelopmental outcomes, particularly in neonates with hypoxic-ischemic encephalopathy, in whom clinical variables are not reliable predictors of outcomes [31, 33]. However, EEG background, while more objective than some clinical features or examination signs, also only imperfectly predicts outcomes [34–37]. A 2016 systematic review included EEG and aEEG studies from 1960 to 2014 assessing EEG background features in neonates with hypoxic-ischemic encephalopathy. A total of 31 studies were identified with 1948 term neonates (≥36 weeks gestational age) with hypoxic-ischemic encephalopathy who had neurodevelopmental outcome information available at 12 months of age or older. Given the time span of the studies, therapeutic hypothermia was only used in 23% of neonates. The review found that burst suppression, low voltage, and flat EEG tracings were the most accurate predictors of unfavorable neurodevelopmental outcomes, having both high sensitivity and specificity. Individual studies used a mixture of structured and unique measures to determine outcomes. For the meta-analysis, neurodevelopmental outcomes were recorded in a binary fashion with normal outcome defined as any normal, minor, or mildly abnormal outcomes in individual testing and abnormal outcome defined as a moderate or severely abnormal or death outcome. Burst suppression had a pooled sensitivity of 0.87 and pooled specificity of 0.82, low voltage had a pooled sensitivity of 0.92 and pooled specificity of 0.99, and flat tracing had a pooled sensitivity of 0.78 and pooled specificity of 0.99. Though three predictive background features were found, the authors noted a lack of standardized definitions used for neonatal EEG background terms across the studies. EEG type was also not standardized across studies, with 45% using cEEG, 45% using aEEG, and 10% using a combination [38].

Serial EEGs, particularly when background abnormalities persist, have stronger predictive value for outcomes than single EEG assessments. A retrospective study reviewed a heterogeneous group of 58 newborns with neonatal seizures who had at least two EEG recordings during the neonatal period and follow-up at 30–40 months. The persistence of abnormal background activity on sequential EEGs was more significantly

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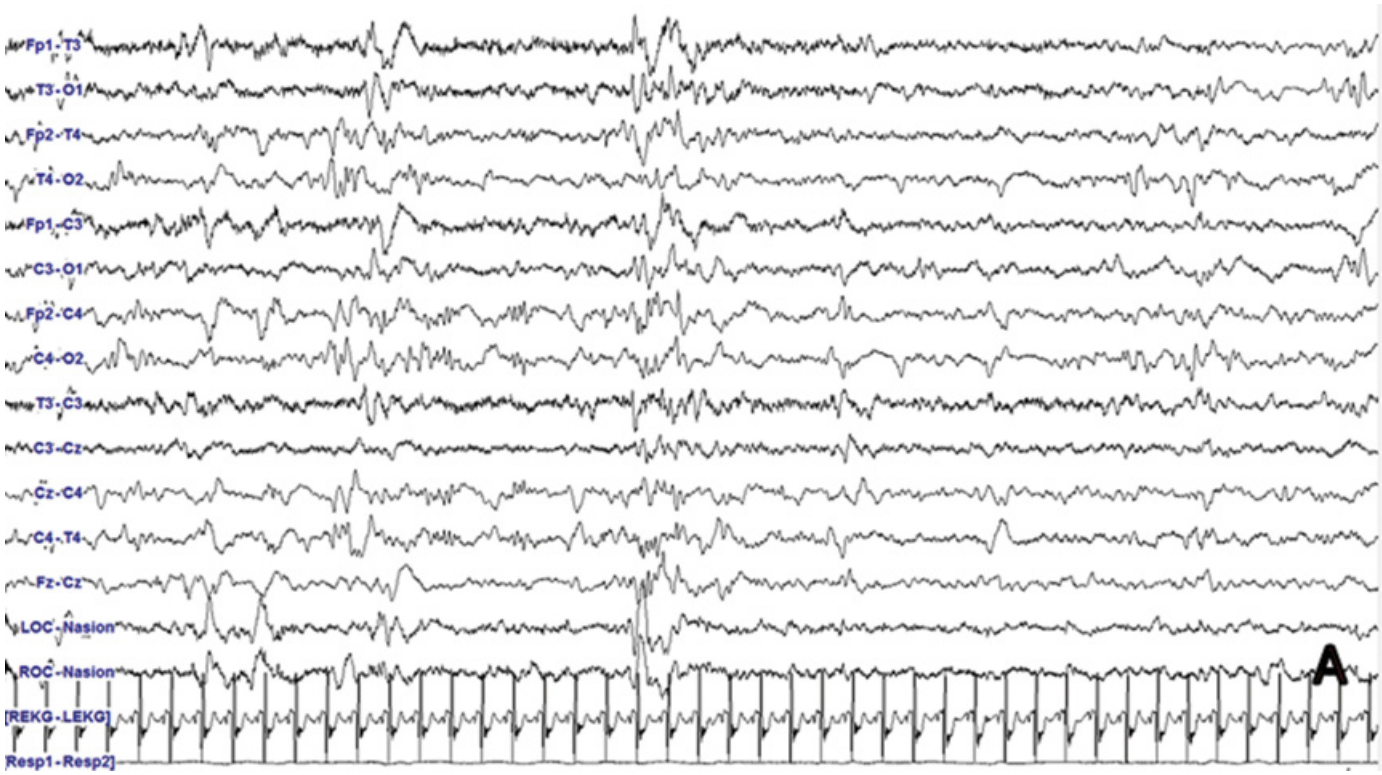

Figure 1.3 Neonatal EEG background patterns. (A) Normal EEG background of an awake term neonate consisting of continuous, low-moderate voltage (25–50 microvolts peak-to-peak) delta and theta activity with overriding beta activity. This pattern is also referred to as "activité moyenne." (B) Excessively discontinuous EEG of a term neonate in quiet sleep. The EEG is considered discontinuous because of prolonged (greater than 6 seconds) inter-burst intervals [arrow denotes onset] that are composed of low-voltage (less than 25 microvolts) mixed-frequency activity. (C) Burst suppression EEG of a term neonate, defined as invariant EEG bursts separated by prolonged and attenuated (less than 5 microvolts) inter-burst intervals. Bursts [denoted by stars] are characterized by sharply contoured, high-voltage (often greater than 200 microvolts) mixed-frequency activity with imbedded spike wave discharges. (D) Electrocerebral inactivity on EEG with the absence of all discernable cerebral activity, defined by lack of any EEG activity greater than 2 microvolts. This is also referred to as "electrocerebral silence" or "isoelectric EEG."

associated with neurodevelopmental delays (relative risk 2.20; p=0.006), as well as the development of postnatal epilepsy (relative risk 1.8; p=0.041). The development of an abnormal EEG background between the first and second EEG (first EEG is normal, second EEG is abnormal) increased the risk of neurodevelopmental delays (relative risk 2.20). Regarding specific background abnormalities, the presence of burst suppression on any EEG was associated with postnatal epilepsy (p=0.013) and postnatal death (p=0.034) [39]. Continuous EEG monitoring carries the benefit of assessing EEG background across multiple time points, like the benefit of serial EEGs.

Electrographic Seizures in Critically Ill Children

Incidence

Observational studies of interdisciplinary neurological critical care services at large pediatric institutions describe seizures and status epilepticus as the most commonly managed conditions [40, 41]. A study in a quaternary care children's hospital described that among 373 pediatric neurocritical care consultations over one year, 18% of consults related to an admission diagnosis of status epilepticus, 35% of consultations related to evaluation of seizures or possible seizures, and cEEG monitoring was performed in 19% of patients [40]. A second study from a quaternary care children's hospital described that among 615 pediatric neurocritical care consultations over a 32-month period, 48% of diagnoses related to epilepsy, seizures, or status epilepticus. EEG was often used, including cEEG monitoring in 28% [41].

Studies of critically ill children undergoing clinically indicated cEEG monitoring report electrographic seizures occur in 10%–50% of patients (Figure 1.4). Further, about one-third of critically ill children with electrographic seizures have a sufficiently high seizure burden to be categorized as electrographic status epilepticus [42–63]. Studies have used varying definitions for electrographic status epilepticus, but a common criterion has been 50% of any 1-hour epoch containing seizure activity. For example, this could constitute a single 30-minute seizure or five 6-minute seizures. The largest epidemiological study of cEEG monitoring in the pediatric intensive care unit was a retrospective study in which 11 tertiary care pediatric institutions each enrolled 50 consecutive subjects, thereby yielding 550 subjects. Electrographic seizures occurred in 30% of subjects. Among subjects with electrographic seizures, electrographic status epilepticus occurred in 33% of subjects and exclusively EEG-only seizures occurred in 35% of subjects [54]. These data are consistent with other single center studies [44, 47, 49–51, 53, 55–57, 59, 61–63]. The indications for cEEG

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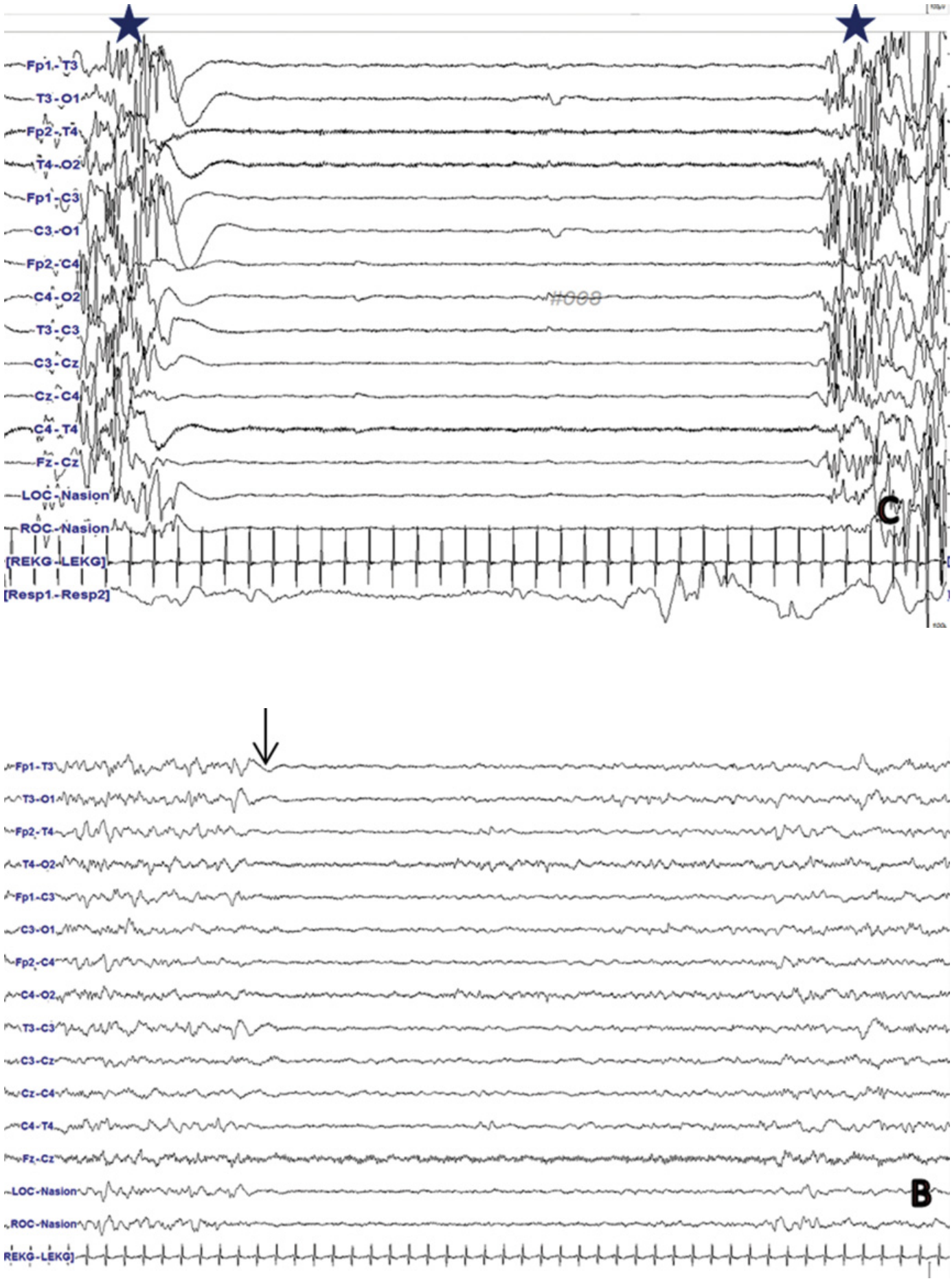

Figure 1.3 (Cont.)

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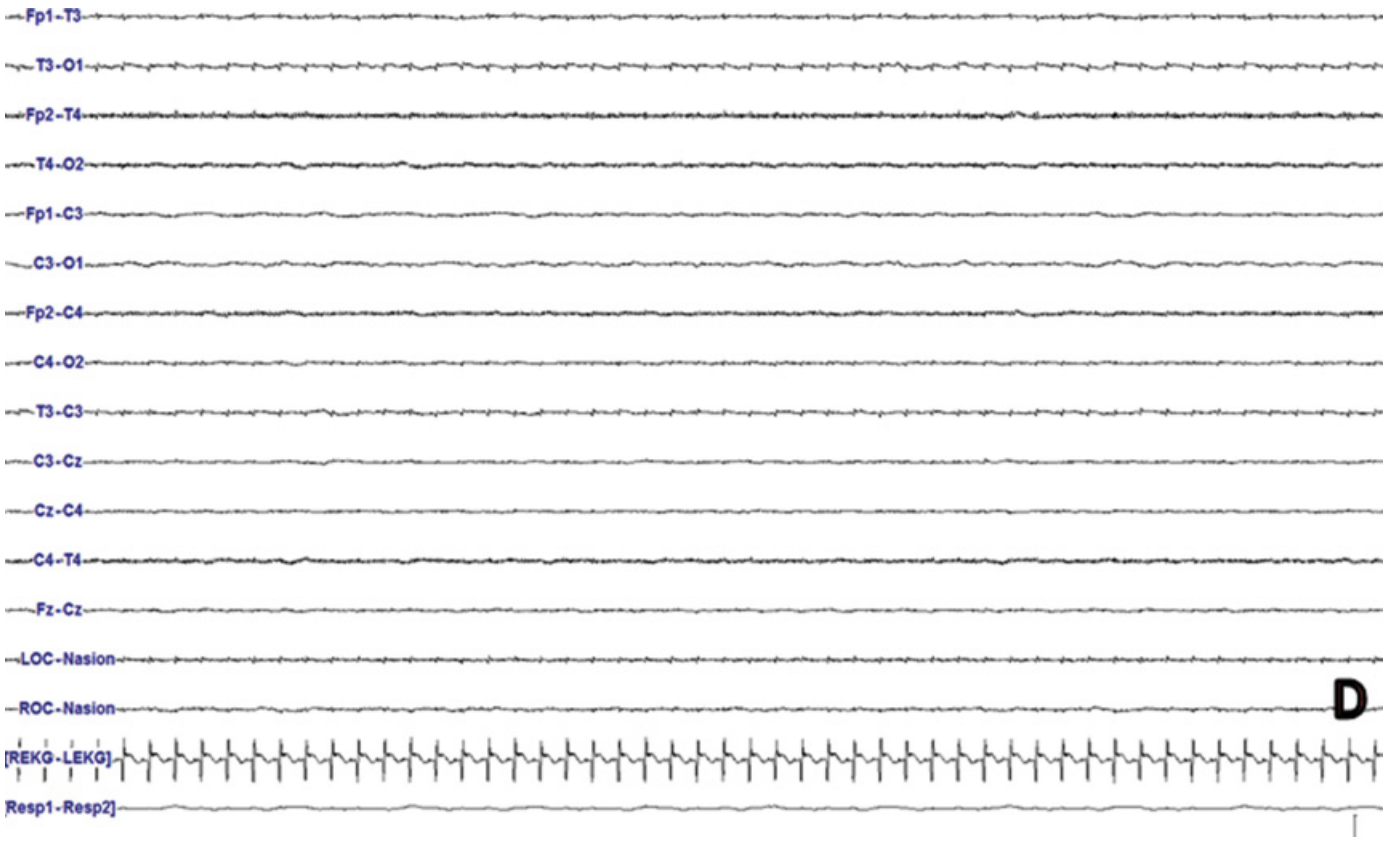

Figure 1.3 (Cont.)

monitoring varied across these studies. Some studies included only patients with known acute structural neurological disorders (e.g., hypoxic-ischemic brain injury, encephalitis, or traumatic brain injury), while other studies included patients with encephalopathy due to broader and more heterogeneous diagnoses (e.g., both primary neurological and primary medical conditions). Inclusion criteria variability may explain the broad reported electrographic seizure incidences since lower electrographic seizure incidences are reported by studies with broader inclusion criteria. Additionally, many of the studies were small as reflected in the wide 95% confidence intervals in Figure 1.4. When individual subjects from these studies are combined, the overall electrographic seizure diagnosis rate is 34% and the electrographic status epilepticus diagnosis rate is 14% [64].

Risk Factors

Continuous EEG monitoring is resource-intensive, and seemingly small utilization and workflow changes have substantial impacts on equipment and personnel needs [65, 66]. Thus, identifying children at higher risk for experiencing electrographic seizures may be beneficial in optimally directing limited cEEG monitoring resources. Several risk factors for electrographic seizures have been reported: (1) younger age (infants as compared to older children) [49, 52, 54, 57, 59]; (2) the occurrence of convulsive seizures [50, 54, 55] or convulsive status epilepticus [49] prior to initiation of cEEG monitoring; (3) the presence of acute structural brain injury [48–50, 52, 53, 55, 57, 61]; and (4) the presence of interictal epileptiform discharges [49, 53–55] or periodic epileptiform discharges [44]. Importantly, EEG-only seizures occur in children who have not received paralytics recently or ever during their intensive care unit stay [56, 59]. This indicates that clinically evident changes are not simply masked by paralytic administration, but that there is an electromechanical uncoupling (or electromechanical dissociation) between the electrographic seizures and observable seizure manifestations.

Unfortunately, these risk factors may have limited clinical utility in selecting patients to undergo cEEG monitoring. Although statistically significant, the absolute difference in the proportion of children with and without electrographic seizures based on the presence or absence of a risk factor is often only 10%–20%. Seizure prediction models combining multiple risk factors might allow better targeting of cEEG monitoring within the resource limitations of an individual medical center. A recent study derived and validated an electrographic seizure prediction model with fair to good discrimination, indicating that most, but not all, patients were appropriately classified. If a center implemented the broadest cEEG monitoring use recommended by the model, 58% of patients without electrographic seizures would be identified as not needing cEEG monitoring, thereby reducing cEEG monitoring utilization. However, 14% of patients with

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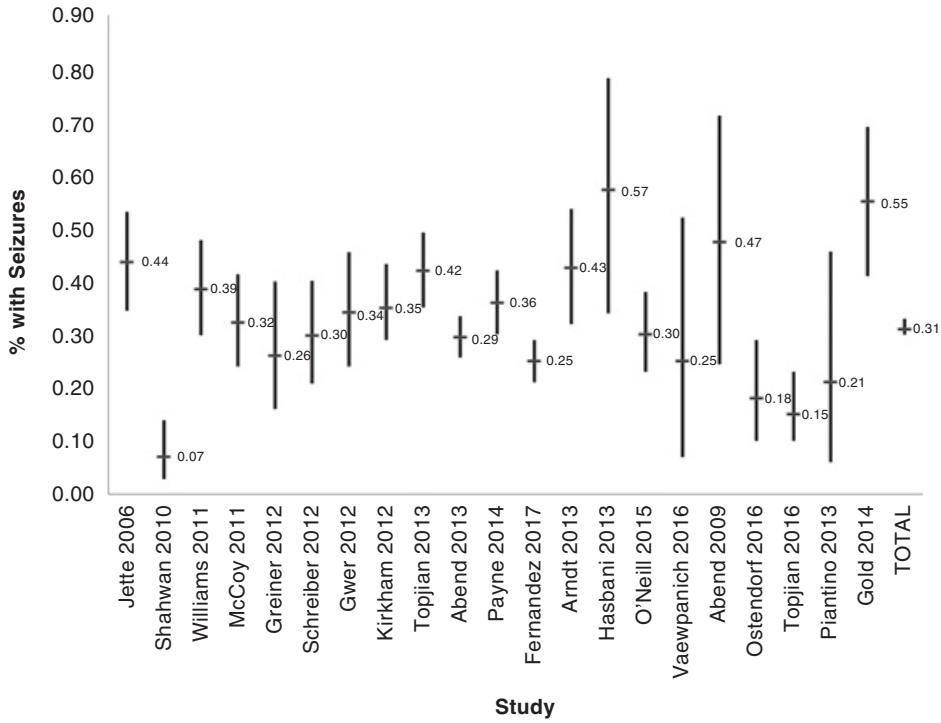

Figure 1.4 Proportion of critically ill children who underwent clinically indicated continuous EEG monitoring with electrographic seizures and electrographic status epilepticus. Each individual study is listed on the x-axis, with vertical lines representing the 95% confidence interval for each. Adapted to add additional publications from original image reprinted from *Epilepsy and Behavior*, 49, Abend NS, Electrographic status epilepticus in children with critical illness: Epidemiology and outcome. 223–7, 2015, with permission from Elsevier.

electrographic seizures would not undergo cEEG monitoring, so their seizures would not be identified and managed [67]. Further development of seizure prediction models in more homogeneous cohorts using additional variables might yield improved performance characteristics.

Timing

Decisions regarding the duration of cEEG monitoring must balance the goal of identifying electrographic seizures against practical concerns regarding resources required to perform cEEG monitoring. Observational studies of critically ill children undergoing clinically indicated cEEG monitoring have reported that about 50% of patients with electrographic seizures are identified with 1 hour of cEEG monitoring and 90% of patients with electrographic seizures are identified with 24–48 hours of cEEG monitoring (Figure 1.5) [44, 47, 49, 50, 53, 55, 56, 59]. However, there are limitations to these data. Most of the studies calculated timing based on cEEG monitoring initiation, which is generally not the same as the onset of the acute brain insult. Additionally, patients generally underwent 1–3 days of clinically indicated cEEG monitoring, so some patients may have had electrographic seizures after cEEG monitoring was discontinued. Based on these data, the Neurocritical Care Society's Guideline for the Evaluation and Management of Status Epilepticus strongly recommends performing cEEG monitoring for 48 hours to identify electrographic status epilepticus in comatose children following an acute brain insult [68]. Similarly, the American Clinical Neurophysiology Society's Consensus Statement on CEEG monitoring in Critically Ill Children and Adults recommends performing cEEG monitoring for at least 24 hours in children at risk for electrographic seizures [69]. A survey of neurologists regarding cEEG monitoring utilization described that most perform 24–48 hours of cEEG monitoring when screening for electrographic seizures [70].

Determining whether to monitor for 24 or 48 hours has a substantial impact on resource utilization. Monitoring for 48 hours identifies slightly more patients with electrographic seizures than monitoring for 24 hours, but since all patients including those who don't experience electrographic seizures must be monitored for an extra day, there is substantial additional resource utilization [65, 66]. A cost-effectiveness analysis used estimated variable costs directly related to cEEG monitoring and estimates of electrographic seizure occurrence from a literature review; this found that the cost-effectiveness of 24 hours of cEEG monitoring per patient identified experiencing seizures was relatively stable across seizure probabilities. However, for 48 hours of cEEG monitoring, as the probability of electrographic seizures decreased the incremental cost-effectiveness ratio increased substantially [66]. Optimized value-based cEEG monitoring approaches might use broad inclusion criteria for 24 hours of cEEG monitoring but select only high-risk patients using a seizure prediction model to determine which patients need additional monitoring to 48 hours or longer.

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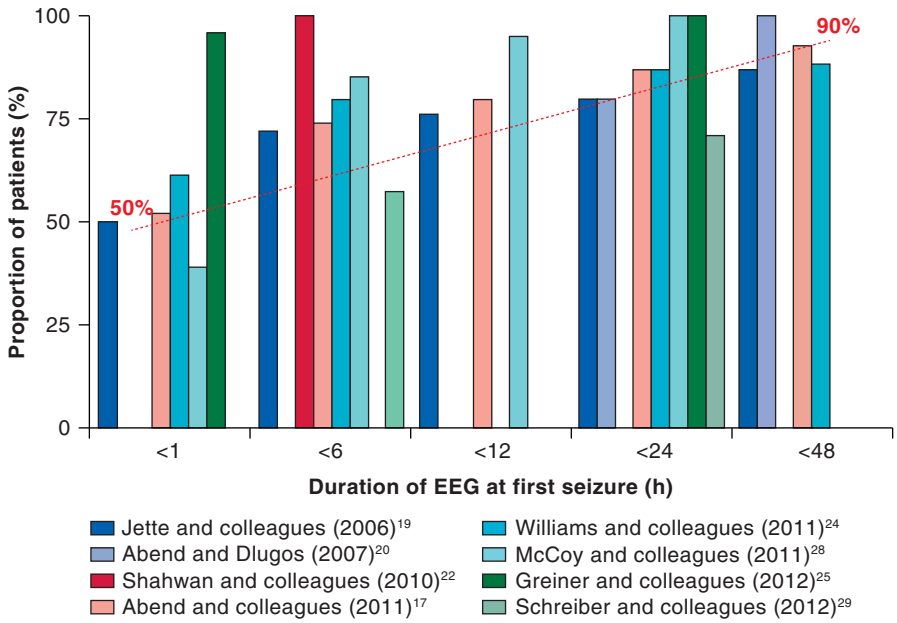

Figure 1.5 Duration of EEG monitoring at onset of the first electrographic seizure in critically ill children. Reprinted from *Lancet Neurology*, 12(12), Abend NS, Wusthoff CJ, Goldberg EM, Dlugos DJ. Electrographic seizures and status epilepticus in critically ill children and neonates with encephalopathy. 1170–9, 2013, with permission from Elsevier.

Relationship between Seizures and Outcomes

Greater electrographic seizure exposures are associated with worse outcomes in critically ill neonates and children. However, the extent to which electrographic seizures produce secondary brain injury versus serve as biomarkers of more severe acute brain injury remains uncertain. Further, the extent to which electrographic seizures produce secondary brain injury is likely dependent on a complex interplay between acute brain injury etiology, seizure exposure, and seizure management strategies. Even seizure exposure may be complex and related to multiple seizure characteristics including duration, anatomical extent, morphology, frequency, and voltage. Despite these complexities, many studies have identified associations between seizures, particularly high seizure exposures, and unfavorable outcomes. This holds true even after adjusting for variables reflecting acute brain injury etiology, acute brain injury severity, and critical illness severity. These data indicate that in at least some patients, electrographic seizures may cause secondary brain injury and subsequently worse neurobehavioral outcomes.

Observational Studies in Neonates

Neonates with seizures have increased short-term and long-term risks of mortality and morbidity. While the underlying seizure etiology substantially determines outcome, there is some evidence that seizures independently worsen outcomes.

Retrospective studies have assessed the relationship between seizures and neurodevelopmental outcomes. A study evaluated 56 neonates with hypoxic-ischemic encephalopathy who underwent therapeutic hypothermia, cEEG monitoring, and subsequent magnetic resonance imaging (MRI). Seizures occurred in 30% of the cohort. The presence of seizures conferred an increased risk of moderate to severe injury on MRI (relative risk 2.3, p=0.02). Neonates with seizures were more likely to display cortical or near total brain injury on MRI [71]. Similarly, in a heterogeneous cohort of 68 neonates at risk for seizures who underwent cEEG monitoring, the presence of seizures was associated with increased risk of death due to neurological causes in the first year of life (relative risk 7, p<0.02) and of cerebral palsy (relative risk 2, p<0.05). Seizure burden was associated with microcephaly (p=0.04), severe cerebral palsy (p=0.03), and failure to thrive (p=0.03) [72]. In a study of 311 full-term neonates with seizures monitored with aEEG, 65 neonates (18%) had clinical or electrographic status epilepticus. Among the subgroup of neonates with hypoxic-ischemic encephalopathy, longer duration of status epilepticus was associated with worse outcome (215 minutes of seizures in poor outcome versus 85 minutes of seizures in good outcome, p<0.05) [73].

Two studies have evaluated the response to anti-seizure medications to assess the relationship between neonatal seizures and outcomes. A retrospective study of 52 neonates monitored with EEG for seizures graded both seizure severity (mild, moderate, severe) and change in severity over time. Neonates were stratified by their response to anti-seizure medications in the neonatal period. There was no association between anti-seizure medication response and later developmental outcomes. However, seizure severity did predict outcomes, with mild- and moderate-severity seizures associated with normal (p=0.002) or moderate (p=0.007) outcomes [74]. Seizure refractoriness may also confer worsened outcomes. A retrospective study of 46 term neonates with refractory neonatal seizures due to heterogeneous etiologies used the number of anti-seizure medications administered as a surrogate measure

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of seizure severity. Among neonates who received ≤2 anti-seizure medications versus ≥3 anti-seizure medications, normal development occurred in 50% versus 5%, moderate disability occurred in 20% versus 27%, and severe disability occurred in 30% versus 68% (p<0.01) [75].

Although the above studies demonstrate a consistent association between seizure burden, refractoriness to treatment, and outcome, their univariate analyses did not adjust for the severity of the underlying brain injury, an important potential confounder. Several studies have performed multivariate analyses adjusting for variables reflecting brain injury severity [76–79]. A multicenter prospective study of 85 neonates ≥36 weeks gestational age with moderate-severe hypoxic-ischemic encephalopathy treated with therapeutic hypothermia and undergoing aEEG identified seizures in 52%, including 35% with high seizure burden (>15 minutes per hour) or status epilepticus. In multivariate analyses accounting for severity of underlying injury as reflected by aEEG background and Apgar scores, high seizure burden remained associated with a severe pattern of MRI injury (odds ratio 5, 95% confidence interval 1.47–17.05, p=0.01) [76]. Similarly, a prospective study of 77 neonates with hypoxic-ischemic encephalopathy of at least 36 weeks gestational age evaluated for largely clinical seizure occurrence and seizure severity. Even after adjustment for MRI severity of hypoxic-ischemic brain injury, every 1-point increase in the seizure severity scale was associated with a 4.7-point reduction in intelligence quotient (IQ). The median IQ for neonates with no seizures, mild/moderate seizures, and severe seizure burdens were 97, 83, and 67, respectively. After adjustment for MRI severity, the seizure severity score was also associated with an increased odds of an abnormal neuro-motor score (odds ratio 20, 95% confidence interval 3–140) [77]. A multicenter prospective cohort of 49 neonates of at least 36 weeks gestational age with moderate to severe hypoxic-ischemic encephalopathy treated with therapeutic hypothermia was monitored with aEEG for occurrence of seizure. Seizures occurred in 59% of neonates and seizure burden was scored as low (no seizures or <15 minutes of seizure per 1 hour) or high (>15 minutes of seizure per 1 hour). A multivariate analysis that included seizure burden and aEEG discontinuity demonstrated an association between high seizure burden and severe MRI brain injury with an odds ratio of 4.2 for severe MRI injury with high seizure burden (95% confidence interval 1.01–17.5, p=0.05). Although severe MRI injury was associated with unfavorable neurodevelopmental outcomes (Pearson's R 0.62, p<0.001), the direct relationship between seizure burden and neurodevelopmental outcome was not assessed [78]. Together, these studies using multivariate analyses indicate that even after adjusting for variables reflecting hypoxic-ischemic injury severity, seizures are associated with worse MRI injury and worse neurobehavioral outcomes.

Randomized Controlled Trials in Neonates

Two randomized controlled trials exploring the effects of treating subclinical seizures in neonates with hypoxic-ischemic encephalopathy have demonstrated that EEG-guided therapy can reduce seizure burden and that higher seizure burden is associated with worse neurodevelopmental and neuroimaging outcomes [80, 81]. A multicenter study of 63 infants with hypoxic-ischemic encephalopathy monitored all neonates ≥37 weeks gestational age with aEEG. At the time of the first seizure on aEEG, 33 neonates who experienced seizures were randomized to treatment of all seizures (clinical and aEEG) or treatment of only the clinically evident seizures. However, all neonates underwent aEEG, so the true seizure burden was available for all. There was a non-significant trend toward lower seizure burden on aEEG in the group with treatment of all seizures (195 versus 503 minutes). Further, neonates who died had experienced a higher seizure burden than survivors (428 minutes versus 164 minutes). Additionally, MRI injury severity correlated with seizure burden among the entire cohort (p<0.001) and among the neonates treated for only clinical seizures (p=0.001). However, there was no significant difference in MRI injury severity between the two treatment groups (p=0.292) [80].

A second randomized controlled trial enrolled neonates ≥36 weeks gestational age with moderate to severe hypoxic-ischemic encephalopathy or neonates with clinical seizures. All underwent continuous EEG to assess seizure burden, but neonates were randomized to treatment of all seizures (clinical and cEEG) or only the clinically evident seizures. Thirty-five neonates who had been randomized experienced seizures and thus provided the analyzed study cohort with 15 in the EEG-guided treatment group and 20 in the group treating only clinical seizures. Neonates with status epilepticus were excluded from analysis. The median duration of seizures was significantly lower in the EEG than clinical group (449 versus 2226 seconds, p=0.02). There were also a lower number of seizures in the electrographic seizure group than the clinical seizure group (median of 7 versus 12, [p=0.04]), and the time to treatment completion was lower in the electrographic seizure group than the clinical seizure group (mean of 79 minutes versus 170 minutes, [p=0.04]). When combining both treatment groups, higher seizure burden was associated with worse MRI injury scores (p<0.03) and lower performance on Bayley neurodevelopmental testing (cognitive composite R=0.502 p=0.03; motor composite R=0.497 p=0.01; language composite R=0.444 p=0.03). However, there were no significant differences in MRI injury score or neurodevelopmental outcome between the two treatment groups, likely due to the small sample size [81].

Observational Studies in Children

Several studies in critically ill children have identified an association between electrographic seizures, particularly with high seizure exposures, and worse outcomes. This association holds even after adjustment for potential confounders related to acute encephalopathy etiology, acute encephalopathy severity, and critical illness severity. A prospective observational study of EEG in 204 critically ill neonates and children found occurrence of electrographic seizures was associated with a higher risk of unfavorable neurological outcome (odds ratio 15.4) in a multivariate analysis that included age, etiology, pediatric

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index of mortality score, Adelaide coma score, and EEG background categories [51].

Several other studies aimed to evaluate the effect of seizure burden and categorically classified children as having no seizures, electrographic seizures, or electrographic status epilepticus. A single-center study of 200 children in the pediatric intensive care unit with outcome assessed at discharge identified an association between electrographic status epilepticus and higher mortality (odds ratio 5.1) and worsening Pediatric Cerebral Performance Category scores (odds ratio 17.3) in multivariate analyses including seizure category, age, acute neurological disorder, prior neurodevelopmental status, and EEG background categories. Electrographic seizures less than electrographic status epilepticus were not associated with worse outcomes [82]. A multicenter study of 550 children in the pediatric intensive care unit reported an association between electrographic status epilepticus and mortality (odds ratio 2.4) in a multivariate analysis that included seizure category, acute encephalopathy etiology, and EEG background categories. Electrographic seizures not classified as electrographic status epilepticus were not associated with mortality [54].

A single-center prospective study evaluated 259 critically ill infants and children who underwent cEEG monitoring. There were electrographic seizures in 36% of subjects, and 9% of those with seizures had electrographic status epilepticus. The mean maximum hourly seizure burden (proportion of each hour containing seizures) was 16% in subjects with neurological decline versus 2% in subjects without neurological decline. In a multivariate analysis that adjusted for diagnosis and illness severity, for every 1% increase in the maximum hourly seizure burden, the odds of neurological decline increased by 1.13. Maximum hourly seizure burdens of 10%, 20%, and 30% were associated with odds ratios for neurological decline as measured using the Pediatric Cerebral Performance Category scores of 3.3, 10.8, and 35.7, respectively. [58].

A study addressing long-term outcome obtained follow-up data at a median of 2.7 years following admission to the pediatric intensive care unit in 60 encephalopathic children who were neurodevelopmentally normal prior to admission to the pediatric intensive care unit and underwent clinically indicated cEEG monitoring. Multivariate analysis including acute neurological diagnosis category, EEG background category, age, and several other clinical variables identified an association between electrographic status epilepticus and unfavorable Glasgow Outcome Scale (Extended Pediatric Version) category (odds ratio 6.36), lower Pediatric Quality of Life Inventory scores (median of 23.07 points lower), and an increased risk of subsequently diagnosed epilepsy (odds ratio 13.3). Children with electrographic seizures not classified as electrographic status epilepticus did not have worse outcomes in this study [83].

Summary

Taken together, these studies indicate that at least in some critically ill neonates and children, there may be a dose-dependent or threshold effect of electrographic seizures upon outcomes, with high seizure exposures having clinically relevant adverse impacts. This threshold may vary based on age, brain injury etiology, and seizure characteristics such as the extent of brain involved and electroencephalographic morphology. However, an important caveat to these data is that most of these were observational studies in which clinicians did identify and manage electrographic seizures, yet despite this management, electrographic seizures remained associated with worse outcomes. It is possible that seizure identification and management did partially improve outcomes that would have been worse if the seizures had not been identified and managed. Thus, optimized seizure identification and management approaches might yield improved outcomes. Further study is needed to develop optimal management strategies and assess their impact on outcomes.

Clinical Practice Guidelines and Consensus Statements

Neonates

There are three guidelines and consensus statements related to EEG in neonates: those published by the American Clinical Neurophysiology Society [15, the World Health Organization [84], and the American Academy of Pediatrics [10].

In 2011 the American Clinical Neurophysiology Society published a guideline on cEEG monitoring in the neonate created by a panel of expert neurophysiologists based on extensive literature review [15]. The guideline describes two main purposes of cEEG monitoring in the neonate: (1) electrographic seizure identification, and (2) encephalopathy assessment. There are several indications related to electrographic seizure identification (Table 1.1). First, cEEG monitoring may be used to determine whether paroxysmal clinical events are seizures. The likelihood that such events are electroclinical seizures is increased in high-risk populations, including those with acute encephalopathy, cardiac or pulmonary conditions that increase the risk for acute brain injury, central nervous system infection, brain trauma, inborn errors of metabolism, perinatal stroke, prematurity with intraventricular hemorrhage, and genetic syndromes. Second, cEEG monitoring may be used to identify EEG-only seizures that have no identifiable clinical correlate and can only be identified using cEEG monitoring. Third, cEEG monitoring may be used during weaning of anti-seizure medications to evaluate for recurrent seizures. Fourth, cEEG monitoring can be used to characterize burst suppression. Regarding encephalopathy assessment, cEEG provides a marker of brain function. Tracking changes in the EEG background over time may identify changes in an encephalopathic infant whose neurological status may not be assessed by clinical examination. Some EEG background features are predictive of long-term outcomes [15] and a normal EEG background has been associated with a low risk of acute seizures [85]. All high-risk neonates should be monitored for at least 24 hours to screen for electrographic seizures,

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Table 1.1 Neonatal populations at high risk for seizures, adapted from the American Clinical Neurophysiology Society's Guideline on Continuous Electroencephalography Monitoring in Neonates, *J Clinical Neurophysiology* 2011.

Category	Examples
Acute neonatal encephalopathy	HIE, postnatal collapse
Cardiac or pulmonary risk for brain injury	ECMO, congenital heart defects perioperatively
CNS infection	Meningitis, encephalitis
CNS trauma	Subarachnoid bleeding, nonaccidental trauma
Inborn errors of metabolism	Organic and amino acidurias, urea cycle defects
Stroke	Arterial stroke, venous thrombosis
At-risk preterm infants	Acute IVH
Genetic/syndromic disease	Cerebral dysgenesis, multiple anomalies with encephalopathy
Use of paralytic medications	As indicated by postoperative or ventilatory management

even if clinically concerning movements have not occurred. Multiple studies in high-risk groups show that most acute seizures occur within 24–72 hours of the acute brain insult [24, 76, 86–89]. If seizures are identified, then the guideline recommends continuing cEEG monitoring for an additional 24 hours after the last electrographic seizure to ensure full resolution. If cEEG monitoring is used for differential diagnosis of abnormal paroxysmal events, then it is recommended that cEEG monitoring continue until all events have been captured adequately on EEG and the presence or absence of an electrographic correlate can be assessed. Technical standards for EEG recording and reporting are further detailed in the American Clinical Neurophysiology Society's Standardized EEG Terminology and Categorization for the Description of CEEG monitoring in Neonates (see Chapter 2) [17].

In 2011 the World Health Organization published a guideline on neonatal seizures that was a multidisciplinary effort based on a formal literature review published with the guideline [84]. While neonatal seizure treatment recommendations were considered weak with low evidence, all recommendations regarding cEEG monitoring were considered strong, with the expert panel finding that desirable effects of cEEG monitoring outweigh any undesirable effects. More specifically, the guideline strongly recommended that in specialized facilities where cEEG monitoring is available, all clinical seizures should be confirmed by EEG and all electrical seizures should be treated, including those without clinical correlate only identifiable using cEEG.

In 2014 a clinical report from the American Academy of Pediatrics reviewing neonatal encephalopathy and the use of therapeutic hypothermia recognized that there was variation in the neuromonitoring capabilities of centers performing therapeutic hypothermia [10]. The committee concluded that centers offering therapeutic hypothermia should be capable of providing comprehensive care for affected neonates, which includes seizure detection and monitoring with some form of EEG (conventional EEG or amplitude-integrated EEG).

Children

There are two guidelines and consensus statements related to cEEG monitoring in critically ill children: those published by the Neurocritical Care Society [68] and the American Clinical Neurophysiology Society [69, 90].

The Neurocritical Care Society's Guidelines for the Evaluation and Management of Status Epilepticus recommends 48 hours of cEEG monitoring to identify electrographic seizures in at-risk patients including (1) patients with persisting altered mental status for more than 10 minutes after convulsive seizures or status epilepticus, and (2) encephalopathic children after resuscitation from cardiac arrest, with traumatic brain injury, with intracranial hemorrhage, or with unexplained encephalopathy. If status epilepticus occurs (including electrographic status epilepticus), then the guideline recommends that management should continue until both clinical and electrographic seizures are halted [68].

The American Clinical Neurophysiology Society's Consensus Statement on Continuous EEG monitoring in Critically Ill Children and Adults recommends cEEG monitoring for 24–48 hours in children at risk for seizures. EEG monitoring indications include: (1) recent convulsive seizures or convulsive status epilepticus with altered mental status, (2) cardiac arrest resuscitation or with other forms of hypoxic-ischemic encephalopathy, (3) stroke (intracerebral hemorrhage, ischemic stroke, and subarachnoid hemorrhage), and (4) encephalitis and altered mental status with related medical conditions. The consensus statement provides additional detailed recommendations regarding personnel, technical specifications, and overall workflow [69, 90].

Summary

Multiple guidelines regarding cEEG monitoring in neonates and children provide a wide range of indications focused on identification of electrographic seizures that may be difficult or impossible to diagnose by clinical observation alone. These guidelines call for relatively wide use of cEEG monitoring based on the presumption that seizure identification and management reduce secondary brain injury and improve outcomes. While seizures are certainly common in many of the cohorts recommended for monitoring making cEEG monitoring reasonable, few data are available to guide management when seizures are identified. Further study of both specific anti-seizure medications and overall seizure management approaches is needed, since to serve as a neuroprotective strategy, seizure identification using cEEG monitoring must be followed by evidence-based optimized seizure management.

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Quantitative EEG for Electrographic Seizure Identification

There are two key problems with expanding cEEG monitoring in critically ill neonates and children. First, cEEG monitoring among critically ill patients is resource-intensive and requires substantial electroencephalographer time to review the full tracing. Second, since cEEG monitoring is generally only reviewed intermittently by electroencephalographers and EEG technologists, delays may occur between electrographic seizure onset and management initiation. Quantitative EEG techniques may improve cEEG monitoring review efficiency by electroencephalographers and allow more involvement by bedside clinicians, which could improve the speed of electrographic seizure identification.

Quantitative EEG techniques separate the complex EEG signal into components (such as amplitude and frequency) and compress time in the display, thereby permitting display of several hours of EEG data on a single image that may be interpreted more easily and rapidly than conventional EEG [91]. The most commonly utilized quantitative EEG techniques are amplitude-integrated EEG (aEEG), which is based on amplitude, and color density spectral array (CDSA), which is based on both amplitude and frequency.

Neonates

The most commonly used form of quantitative EEG monitoring for neonates is aEEG (Figure 1.6). This is a bedside EEG monitoring tool that employs 2–4 electrodes that yield either a single- or dual-channel EEG recording. Often, electrodes are placed in the bilateral central regions for maximal seizure detection [92]. Alternative strategies involve placing electrodes over bilateral frontal or bilateral parietal regions or an averaged hemispheric or regional recording, though this may decrease sensitivity. Compared to cEEG, aEEG allows more rapid electrode application and interpretation of aEEG data by neonatologists and neonatal nurses at bedside. A survey of perinatal practitioners in the United States found that 55% of respondents reported aEEG use in their neonatal intensive care units, with higher rates in academic centers. The most common reasons for aEEG use were decisions regarding seizure treatment (~80%), decisions regarding therapeutic hypothermia initiation (~50%), to guide counseling and prognosis (~50%), and to aid decisions surrounding medication dosages and treatment durations (~35%) [30].

The aEEG has an established role in encephalopathy assessment despite variable concordance between aEEG background features and clinical outcomes [93, 94]. The role of aEEG for seizure identification is more nuanced since although seizure identification with aEEG is imperfect, it is readily available and superior to clinical seizure identification. A study in neonates with hypoxic-ischemic encephalopathy performed aEEG in all neonates but randomized neonates to have management based on clinical observation alone or clinical observation plus use of aEEG data. Neonates in whom clinicians could use aEEG data had shorter total duration of seizures [95]. These data indicate that while imperfect, aEEG may have a meaningful clinical

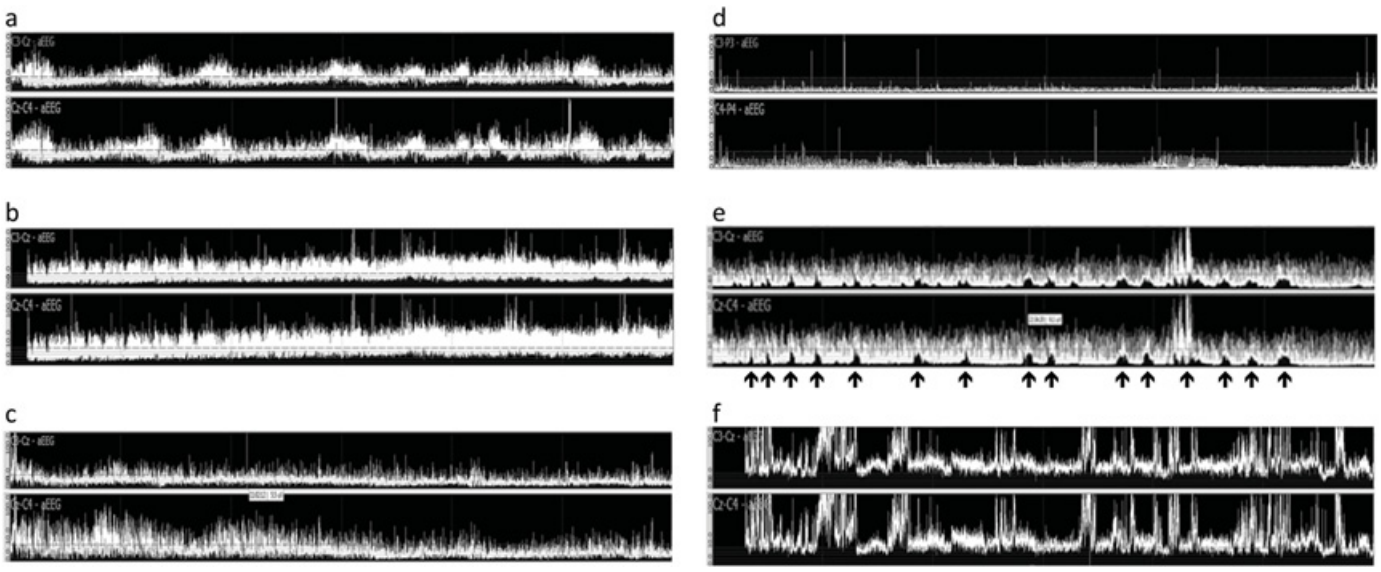

Figure 1.6 Amplitude-integrated EEG (aEEG) examples. (a) Normal aEEG with 6-hour compressed time scale using bilateral central channels (C3-Cz, Cz-C4). Minimum amplitudes are consistently between greater than 5 microvolts and maximum amplitudes are greater than 10 microvolts. There is evidence of variability with sleep–wake cycling. (b) Improving aEEG with 24-hour compressed time scale and bilateral central channels (C3-Cz, Cz-C4). Initially, minimum amplitudes are low (≤5 microvolts) with maximum amplitudes of 5 microvolts and greater. During the 24-hour recording, amplitudes gradually improve with minimum amplitudes greater than 5 microvolts and maximum amplitudes greater than 10 microvolts. (c) Abnormal aEEG with 6-hour compressed time scale and bilateral central channels (C3-Cz, Cz-C4). Amplitudes are persistently diminished with minimum amplitudes of ≤5 microvolts and the majority of maximum amplitudes ≤10 microvolts. (d) Severely abnormal aEEG with 6-hour compressed time scale and bilateral central channels (C3-Cz, Cz-C4). Amplitudes are persistently attenuated with all minimum and maximum amplitudes less than 10 microvolts. (e) Seizures on aEEG with 6-hour compressed time scale and bilateral central channels (C3-Cz, Cz-C4). Seizures are characterized by a sudden change in amplitude in a notch-like or bell-shaped morphology. There are numerous seizures in this 6-hour recording, denoted by arrows. (f) Electrode artifact on aEEG with 6-hour compressed time scale and bilateral central channels (C3-Cz, Cz-C4). Note the abrupt and extremely high voltage (100 microvolts) of the nature of the tracing.

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impact in reducing seizure exposure. While aEEG may answer the binary question of whether an EEG record contains any seizures with relatively high accuracy, individual seizure discrimination is lower than with cEEG, potentially resulting in an under-estimate of seizure burden, including underdiagnosis of status epilepticus [96, 97].

The discordance in seizure identification between cEEG and aEEG is due to both modifiable and non-modifiable factors. An aEEG is less accurate in identifying seizures that are brief in duration, slow in frequency, or low in amplitude, or originate from cerebral locations that are distant from the recording electrodes [98]. These factors are innate to the seizure and generally not influenced by aEEG display characteristics or user training, though once seizure location is established a limited electrode scheme could be placed to maximize specific regional seizure identification. One modifiable factor affecting aEEG interpretation is the experience of the aEEG interpreter; non-experienced users have been shown to miss at least 50% of seizures using aEEG alone [99]. Though users with more experience theoretically have improved seizure identification, some studies show that individual seizure detection by this experienced group remains low, with aEEG readers with at least one year of experience identifying only 12–38% of individual seizures [97]. In addition to the false negatives associated with aEEG, false positives may occur. Given the lack of additional EMG, EKG, respiratory, and ocular channels that often aid the electroencephalographer in distinguishing between cerebral and artifactual changes on the EEG, artifact can be misinterpreted as seizure [96]. Finally, the majority of aEEG is interpreted by neonatology staff rather than electroencephalographers, and neonatologists self-report low confidence in their ability to perform aEEG interpretation. Survey data of neonatologists describe that only 7% of neonatologists report feeling very confident about aEEG interpretation while 31% feel not confident about aEEG interpretation [27].

Given the above limitations of aEEG, the American Clinical Neurophysiology Society's guideline on EEG monitoring in neonates recommended that cEEG monitoring remain the gold standard for seizure identification in neonates and that cEEG should be used whenever available. The guideline described that aEEG can act as a complementary tool to aid in rapid bedside diagnosis of seizures followed by confirmation with cEEG. When cEEG is not available, aEEG can be used for seizure screening, but if a seizure is suspected on aEEG, then it should be confirmed on cEEG when cEEG is available [15].

Children

Quantitative EEG test characteristics are still being established in critically ill children, and use of quantitative EEG is not as widespread as aEEG in neonates (Figure 1.7). In one study, 27 color density spectral array and aEEG tracings were reviewed by 3 electroencephalographers. The median sensitivity for seizure identification was 83% using CDSA and 82% using aEEG. However, for individual tracings the sensitivity varied from 0 to 100%, indicating excellent performance for some patients and poor performance for other patients, likely related to individual seizure characteristics. A false positive (event identified as a seizure that was not a seizure based on conventional EEG review) occurred about every 17–20 hours [100]. In a second study, 84 CDSA images were reviewed by 8 electroencephalographers. Sensitivity for seizure identification was 65%, which indicated that some electrographic seizures were not identified. Only about half of seizures were identified by 6 or more of the raters, indicating problems with inter-rater agreement. Specificity was 95%, which indicated that some non-ictal events were misdiagnosed as seizures [101]. A study of CDSA and envelope trend EEG review by electroencephalographers found that seizure identification was impacted by both modifiable factors (interpreter experience, display size, and quantitative EEG method) and non-modifiable factors inherent to the EEG pattern (maximum spike amplitude, seizure duration, seizure frequency, and seizure duration) (Figure 1.7) [102].

Critical care providers are generally continually in the pediatric intensive care unit and have expertise using other screening modalities. Involving these providers might allow more rapid electrographic seizure identification. A study provided 20 critical care physicians (attending physicians and fellows) and 19 critical care nurses with a brief training session regarding color density spectral array and then asked participants to determine whether each of 200 CDSA images contained electrographic seizures. The images were created from conventional EEG derived from critically ill children resuscitated from cardiac arrest, and the true seizure incidence was 30% based on electroencephalographer review of the conventional EEG tracings. Among critical care providers reviewing CDSA images, the sensitivity was 70% (indicating that some electrographic seizures were not identified) and the specificity was 68% (indicating that some images categorized as containing EEG seizures did not contain seizures based on conventional EEG review). Given the 30% seizure incidence used in the study, the positive predictive value was 46% and the negative predictive value was 86% [103].

Summary

Data in neonates and children indicate that commercially available quantitative EEG techniques permit identification of many but not all seizures, and sometimes non-ictal events might be misidentified as seizures based on isolated quantitative EEG review. While imperfect, these techniques may be valuable when conventional cEEG is not available and may improve the efficiency of cEEG monitoring review by electroencephalographers. Since quantitative EEG techniques lead to misclassification of some non-ictal events as seizures, potentially leading to unnecessary anti-seizure medication administration, confirmation by conventional EEG review is indicated when quantitative EEG techniques suggest seizures are present. Such confirmation is particularly important for patients with refractory events to confirm that these events represent seizures prior to escalating to management with high-dose or multiple anti-seizure medications.

Further development of quantitative techniques, display optimization (including specific quantitative EEG trends and the duration of EEG displayed on a screen), and improved quantitative EEG training methods may allow these techniques to become even more valuable adjuvants to cEEG data. Additionally, synergistic methods could make use of the efficiency and bedside availability of quantitative EEG methods and the accuracy of

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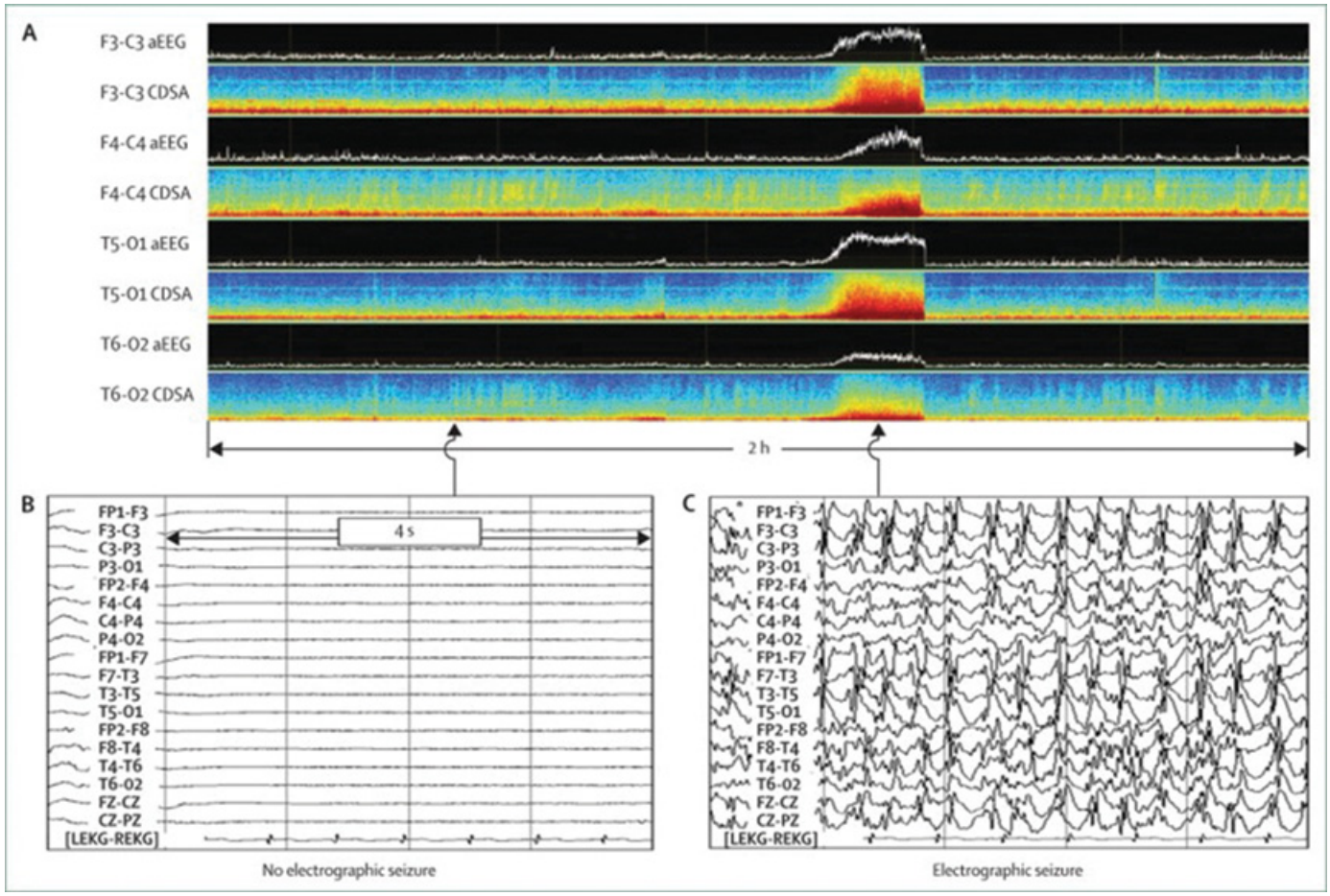

Figure 1.7 Amplitude-integrated EEG (aEEG) and color density spectral array (CDSA) image showing an electrographic seizure in a critically ill child. The electrographic seizures are characterized by increases in amplitude (displayed as increases on the y-axis) on the aEEG and CDSA tracings, and also by an increase in power (displayed as warmer colors) on the CDSA tracing. Reprinted from *Lancet Neurology*, 12(12), Abend NS, Wusthoff CJ, Goldberg EM, Dlugos DJ. Electrographic seizures and status epilepticus in critically ill children and neonates with encephalopathy. 1170–9, 2013, with permission from Elsevier.

conventional cEEG tracings. Quantitative EEG might be used at bedside to allow for rapid and frequent screening with confirmation of ongoing seizures by conventional EEG review prior to treatment initiation. Additionally, review of the initial portion of conventional EEG might be used to fine-tune the optimal quantitative EEG display at bedside for individual patients. This type of strategy was utilized by a randomized controlled trial of electrographic versus clinical seizure treatment in neonates that found that the combined strategy resulted in decreased acute seizure burden [81].

Conclusions

Continuous EEG monitoring of critically ill neonates and children offers an opportunity to assess and monitor cerebral function to guide overall therapy and identify electrographic seizures which are associated with unfavorable outcomes. Further research is needed to optimally target cEEG monitoring resources to the highest risk patients, develop management strategies that synergistically utilize quantitative EEG and conventional EEG, better understand the impact of electrographic seizures on patient outcomes, and develop optimized evidence-based seizure management strategies.

References

1. Glass HC, Wu YW. Epidemiology of neonatal seizures. *J Pediatr Neurol.* 2009;**7**:13–17.
2. Lawrence R, Inder T. Neonatal status epilepticus. *Semin Pediatr Neurol.* 2010;**17**(3):163–8.
3. Glass HC, Pham TN, Danielsen B, et al. Antenatal and intrapartum risk factors for seizures in term newborns: a population-based study, California 1998–2002. *J Pediatr.* 2009;**154**(1):24–8 e1.
4. Volpe JJ. Neonatal seizures. In Volpe JJ, editor. *Neurology of the Newborn.* Philadelphia: WB Saunders Elsevier; 2008, pp. 203–7.
5. Glass HC, Shellhaas RA, Wusthoff CJ, et al. Contemporary profile of seizures in neonates: a prospective cohort study. *J Pediatr.* 2016;**174**:98–103.e1.
6. Allen KA, Brandon DH. Hypoxic ischemic encephalopathy: pathophysiology and experimental treatments. *Newborn Infant Nurs Rev.* 2011;**11**(3):125–33.
7. Robertson CM, Perlman M. Follow-up of the term infant after hypoxic-ischemic encephalopathy. *Paediatr Child Health.* 2006;**11**(5):278–82.

https://doi.org/10.1017/9781316536001.001 Published online by Cambridge University Press

8. Massaro AN, Murthy K, Zaniletti I, et al. Short-term outcomes after perinatal hypoxic ischemic encephalopathy: a report from the Children's Hospitals Neonatal Consortium HIE focus group. *J Perinatol*. 2015;**35**(4):290–6.
9. Simbruner G, Mittal RA, Rohlmann F, et al. Systemic hypothermia after neonatal encephalopathy: outcomes of neo.nEURO.network RCT. *Pediatrics*. 2010;**126**(4): e771–8.
10. Committee on Fetus and Newborn; Papile, L-A, Baley JE, Benitz I, et al. Hypothermia and neonatal encephalopathy. *Pediatrics*. 2014;**133**(6):1146–50.
11. Low E, Boylan GB, Mathieson SR, et al. Cooling and seizure burden in term neonates: an observational study. *Arch Dis Child Fetal Neonatal Ed*. 2012;**97**(4): F267–72.
12. Vasudevan C, Levene M. Epidemiology and aetiology of neonatal seizures. *Semin Fetal Neonatal Med*. 2013;**18**(4):185–91.
13. Pisani F, Facini C, Pelosi A, et al. Neonatal seizures in preterm newborns: a predictive model for outcome. *Eur J Paediatr Neurol*. 2016;**20**(2):243–51.
14. Sheth RD, Hobbs GR, Mullett M. Neonatal seizures: incidence, onset, and etiology by gestational age. *J Perinatol*. 1999;**19**(1):40–3.
15. Shellhaas RA, Chang T, Tsuchida T, et al. The American Clinical Neurophysiology Society's guideline on continuous electroencephalography monitoring in neonates. *J Clin Neurophysiol*. 2011;**28**(6):611–17.
16. Laroia N, Guillet R, Burchfiel J, McBride MC. EEG background as predictor of electrographic seizures in high-risk neonates. *Epilepsia*. 1998;**39**(5):545–51.
17. Tsuchida TN, Wusthoff CJ, Shellhaas R, et al. American clinical neurophysiology society standardized EEG terminology and categorization for the description of continuous EEG monitoring in neonates: report of the American Clinical Neurophysiology Society Critical Care Monitoring Committee. *J Clin Neurophysiol*. 2013;**30**(2): 161–73.
18. Mizrahi EM, Kellaway P. Characterization and classification of neonatal seizures. *Neurology*. 1987;**37**(12):1837–44.
19. Nagarajan L, Palumbo L, Ghosh S. Classification of clinical semiology in epileptic seizures in neonates. *Eur J Paediatr Neurol*. 2012;**16**(2):118–25.
20. Murray DM, Boylan GB, Ali I, et al. Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures. *Arch Dis Child Fetal Neonatal Ed*. 2008;**93**(3):F187–91.
21. Malone A, Anthony Ryan C, Fitzgerald A, et al. Interobserver agreement in neonatal seizure identification. *Epilepsia*. 2009;**50**(9):2097–101.
22. Clancy RR, Legido A, Lewis D. Occult neonatal seizures. *Epilepsia*. 1988;**29**(3):256–61.
23. Connell J, Oozeer R, de Vries L, Dubowitz LM, Dubowitz V. Continuous EEG monitoring of neonatal seizures: diagnostic and prognostic considerations. *Arch Dis Child*. 1989;**64**(4 Spec No):452–8.
24. Naim MY, Gaynor JW, Chen J, et al. Subclinical seizures identified by postoperative electroencephalographic monitoring are common after neonatal cardiac surgery. *J Thorac Cardiovasc Surg*. 2015;**150**(1):169–78.
25. Hahn JS, Vaucher Y, Bejar R, Coen RW. Electroencephalographic and neuroimaging findings in neonates undergoing extracorporeal membrane oxygenation. *Neuropediatrics*. 1993;**24**(1):19–24.
26. Scher MS, Alvin J, Gaus L, Minnigh B, Painter MJ. Uncoupling of EEG-clinical neonatal seizures after antiepileptic drug use. *Pediatr Neurol*. 2003;**28**(4):277–80.
27. Boylan GB, Burgoyne L, Moore C, O'Flaherty B, Renni JM. An international survey of EEG use in the neonatal intensive care unit. *Acta Paediatr*. 2010;**99**(8):1150–5.
28. Glass HC, Kan J, Bonifacio SL Ferriero DM. Neonatal seizures: treatment practices among term and preterm infants. *Pediatr Neurol*. 2012;**46**(2):111–15.
29. Filan PM, Inder TE, Anderson PJ, Doyle LW, Hunt RW. Monitoring the neonatal brain: a survey of current practice among Australian and New Zealand neonatologists. *J Paediatr Child Health*. 2007;**43**(7–8):557–9.
30. Shah NA, Van Meurs KP, Davis AS. Amplitude-integrated electroencephalography: a survey of practices in the United States. *Am J Perinatol*. 2015;**32**(8):755–60.
31. Glass HC, Wusthoff CJ, Shellhaas RA, et al. Risk factors for EEG seizures in neonates treated with hypothermia: a multicenter cohort study. *Neurology*. 2014;**82**(14):1239–44.
32. Nash KB, Bonifacio SL, Glass HC, et al. Video-EEG monitoring in newborns with hypoxic-ischemic encephalopathy treated with hypothermia. *Neurology*. 2011;**76**(6):556–62.
33. Murray DM, Ryan CA, Boylan GB, et al. Prediction of seizures in asphyxiated neonates: correlation with continuous video-electroencephalographic monitoring. *Pediatrics*. 2006;**118**(1):41–6.
34. Monod N, Pajot N, Guidasci S. The neonatal EEG: statistical studies and prognostic value in full-term and pre-term babies. *Electroencephalogr Clin Neurophysiol*. 1972;**32**(5):529–44.
35. Rowe JC, Holmes GL, Hafford J, et al. Prognostic value of the electroencephalogram in term and preterm infants following neonatal seizures. *Electroencephalogr Clin Neurophysiol*. 1985;**60**(3):183–96.
36. Murray DM, Boylan GB, Ryan CA, Connolly S. Early EEG findings in hypoxic-ischemic encephalopathy predict outcomes at 2 years. *Pediatrics*. 2009;**124**(3):e459–67.
37. Takeuchi T, Watanabe K. The EEG evolution and neurological prognosis of neonates with perinatal hypoxia [corrected]. *Brain Dev*. 1989;**11**(2):115–20.
38. Awal MA, Lai MM, Azemi G, et al. EEG background features that predict outcome in term neonates with hypoxic ischaemic encephalopathy: A structured review. *Clin Neurophysiol*. 2016;**127**(1):285–96.
39. Khan RL, Nunes ML, Garcias da Silva LF, Costa da Costa J. Predictive value of sequential electroencephalogram (EEG) in neonates with seizures and its relation to neurological outcome. *J Child Neurol*. 2008;**23**(2):144–50.
40. Bell MJ, Carpenter J, Au AK, et al. Development of a pediatric neurocritical care service. *Neurocrit Care*. 2009;**10**(1):4–10.
41. LaRovere KL, Graham RJ, Tasker RC, Pediatric Critical Nervous System Program (pCNSp) Pediatric neurocritical care: a neurology consultation model and implication for education and training. *Pediatr Neurol*. 2013;**48**(3):206–11.

https://doi.org/10.1017/9781316536001.001 Published online by Cambridge University Press

42. Abend, NS, Wusthoff CJ, Goldberg EM, Dlugos DJ. Electrographic seizures and status epilepticus in critically ill children and neonates with encephalopathy. *Lancet Neurol*. 2013;**12**(12):1170–9.
43. Hosain SA, Solomon GE, Kobylarz EJ. Electroencephalographic patterns in unresponsive pediatric patients. *Pediatr Neurol*. 2005;**32**(3):162–5.
44. Jette N, Claasen J, Emerson RG, et al. Frequency and predictors of nonconvulsive seizures during continuous electroencephalographic monitoring in critically ill children. *Arch Neurol*. 2006;**63**(12):1750–5.
45. Abend NS, Dlugos DJ. Nonconvulsive status epilepticus in a pediatric intensive care unit. *Pediatr Neurol*. 2007;**37**(3):165–70.
46. Tay SK, Hirsch LJ, Leary L, et al. Nonconvulsive status epilepticus in children: clinical and EEG characteristics. *Epilepsia*. 2006;**47**(9):1504–9.
47. Shahwan A, Bailey C, Shekerdemian L, Harvey AS. The prevalence of seizures in comatose children in the pediatric intensive care unit: a prospective video-EEG study. *Epilepsia*. 2010;**51**(7):1198–1204.
48. Abend NS, Topjian A, Ichord R, et al. Electroencephalographic monitoring during hypothermia after pediatric cardiac arrest. *Neurology*. 2009;**72**(22):1931–40.
49. Williams K, Jarrar R, Buchhalter J. Continuous video-EEG monitoring in pediatric intensive care units. *Epilepsia*. 2011;**52**(6):1130–6.
50. Greiner HM, Holland K, Leach JL, et al. Nonconvulsive status epilepticus: the encephalopathic pediatric patient. *Pediatrics*. 2012;**129**(3):e748–55.
51. Kirkham FJ, Wade AW, McElduff F, et al. Seizures in 204 comatose children: incidence and outcome. *Intensive Care Med*. 2012;**38**(5):853–62.
52. Arango JI, et al. Posttraumatic seizures in children with severe traumatic brain injury. *Childs Nerv Syst*. 2012;**28**(11):1925–9.
53. Piantino JA, Wainwright MS, Grimason M, et al. Nonconvulsive seizures are common in children treated with extracorporeal cardiac life support. *Pediatr Crit Care Med*. 2013;**14**(6):601–609.
54. Abend NS, Arndt DH, Carpenter JL, et al. Electrographic seizures in pediatric ICU patients: cohort study of risk factors and mortality. *Neurology*. 2013;**81**(4):383–91.
55. McCoy B, Sharma R, Ochi A, et al. Predictors of nonconvulsive seizures among critically ill children. *Epilepsia*. 2011;**52**(11):1973–8.
56. Schreiber JM, Zelleke T, Gaillard WD, et al. Continuous video EEG for patients with acute encephalopathy in a pediatric intensive care unit. *Neurocrit Care*. 2012;**17**(1):31–8.
57. Arndt DH, Lerner JT, Matsumoto JH, et al. Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort. *Epilepsia*. 2013;**54**(10):1780–8.
58. Payne ET, Yan Zhao X, Frndova H, et al. Seizure burden is independently associated with short term outcome in critically ill children. *Brain*. 2014;**137**(Pt 5):1429–38.
59. Abend NS, Gutierrez-Collina AM, Topjian AA, et al. Nonconvulsive seizures are common in critically ill children. *Neurology*. 2011;**76**(12):1071–7.
60. Gold JJ, Crawford JR, Glaser C, et al. The role of continuous electroencephalography in childhood encephalitis. *Pediatr Neurol*. 2014;**50**(4):318–23.
61. Greiner MV, Greiner HM, Caré MM, et al. Adding insult to injury: nonconvulsive seizures in abusive head trauma. *J Child Neurol*. 2015; **30**(13):1778–84.
62. Gwer S, Idro R, Fegan G, et al. Continuous EEG monitoring in Kenyan children with non-traumatic coma. *Arch Dis Child*. 2012;**97**(4):343–9.
63. Hasbani DM, Topjian AA, Friess SH, et al. Nonconvulsive electrographic seizures are common in children with abusive head trauma. *Pediatr Crit Care Med*. 2013;**14**(7):709–15.
64. Abend NS. Electrographic status epilepticus in children with critical illness: Epidemiology and outcome. *Epilepsy Behav*. 2015;**49**:223–7.
65. Gutierrez-Colina AM, Topjian AA, Dlugos DJ, Abend NS. EEG monitoring in critically ill children: indications and strategies. *Pediatric Neurology*. 2012;**46**:158–161.
66. Abend NS, Topjian AA, Williams S. How much does it cost to identify a critically ill child experiencing electrographic seizures? *J Clin Neurophysiol*. 2015;**32**(3):257–64.
67. Yang A, Arndt DH, Berg RA, et al. Development and validation of a seizure prediction model in critically ill children. *Seizure*. 2015;**25**:104–11.
68. Broph GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care*. 2012;**17**(1):3–23.
69. Herman ST, Abend NS, Bleck TP, et al. Consensus statement on continuous EEG in critically ill adults and children, part I: indications. *J Clin Neurophysiol*. 2015;**32**(2):87–95.
70. Abend NS, Dlugos DJ, Hahn CD, et al. Use of EEG monitoring and management of non-convulsive seizures in critically ill patients: a survey of neurologists. *Neurocrit Care*. 2010;**12**(3):382–9.
71. Glass HC, Nash KB, Bonifacio SL, et al. Seizures and magnetic resonance imaging-detected brain injury in newborns cooled for hypoxic-ischemic encephalopathy. *J Pediatr*. 2011;**159**(5):731–735 e1.
72. McBride MC, Laroia N, Guillet R. Electrographic seizures in neonates correlate with poor neurodevelopmental outcome. *Neurology*. 2000;**55**(4):506–13.
73. van Rooij LG, de Vries LS, Handryastuti S, et al. Neurodevelopmental outcome in term infants with status epilepticus detected with amplitude-integrated electroencephalography. *Pediatrics*. 2007;**120**(2):e354–63.
74. Painter MJ, Sun Q, Scher MS, Janosky J, Alvin J. Neonates with seizures: what predicts development? *J Child Neurol*. 2012;**27**(8):1022–6.
75. Maartens IA, Wassenberg T, Buijs J, et al. Neurodevelopmental outcome in full-term newborns with refractory neonatal seizures. *Acta Paediatr*. 2012;**101**(4):e173–8.
76. Shah DK, Wusthoff CJ, Clarke P, et al. Electrographic seizures are associated with brain injury in newborns undergoing therapeutic hypothermia. *Arch Dis Child Fetal Neonatal Ed*. 2014;**99**(3):F219–24.
77. Glass HC, Glidden D, Jeremy RJ, et al. Clinical neonatal seizures are independently associated with outcome in infants at risk for hypoxic-ischemic brain injury. *J Pediatr*. 2009;**155**(3):318–23.

https://doi.org/10.1017/9781316536001.001 Published online by Cambridge University Press

78. Dunne JM, Wertheim D, Clarke P, et al. Automated electroencephalographic discontinuity in cooled newborns predicts cerebral MRI and neurodevelopmental outcome. *Arch Dis Child Fetal Neonatal Ed*. 2017;**102**(1): F58–64.

79. Meyn DF, Jr., Ness J, Ambalavanan N, Carlo WA. Prophylactic phenobarbital and whole-body cooling for neonatal hypoxic-ischemic encephalopathy. *J Pediatr*. 2010;**157**(2):334–6.

80. van Rooij LG, Toet MC, van Huffelen AC, et al. Effect of treatment of subclinical neonatal seizures detected with aEEG: randomized, controlled trial. *Pediatrics*. 2010;**125**(2):e358–66.

81. Srinivasakumar P, Zempel J, Trivedi S, et al. Treating EEG seizures in hypoxic ischemic encephalopathy: a randomized controlled trial. *Pediatrics*. 2015;**136**(5):e1302–9.

82. Topjian AA, Gutierrez-Colina AM, Sanchez SM, et al. Electrographic status epilepticus is associated with mortality and worse short-term outcome in critically ill children. *Crit Care Med*. 2013;**41**(1):215–23.

83. Wagenman KL, Blake TP, Sanchez SM, et al. Electrographic status epilepticus and long-term outcome in critically ill children. *Neurology*. 2014;**82** (5):396–404.

84. WHO, *Guidelines on Neonatal Seizures*. World Health Organization; 2011.

85. Glauser TA, Clancy RR. Adequacy of routine EEG examinations in neonates with clinically suspected seizures. *J Child Neurol*. 1992;**7**(2):215–20.

86. Wusthoff CJ, Dlugos DJ, Gutierrez-Colina A, et al. Electrographic seizures during therapeutic hypothermia for neonatal encephalopathy. *J Child Neurol*. 2011;**26**(6):724–728.

87. Lynch NE, Stevenson NJ, Livingstone V, et al. The temporal evolution of electrographic seizure burden in neonatal hypoxic ischemic encephalopathy. *Epilepsia*. 2012;**53** (3):549–57.

88. Clancy RR, Sharif U, Ichord R, et al. Electrographic neonatal seizures after infant heart surgery. *Epilepsia*. 2005;**46** (1):84–90.

89. Shah DK, Zempel J, Barton T, Lukas K, Inder TE. Electrographic seizures in preterm infants during the first week of life are associated with cerebral injury. *Pediatr Res*. 2010;**67**(1):102–6.

90. Herman ST, Abend NS, Bleck TP, et al. Consensus statement on continuous EEG in critically ill adults and children, part II: personnel, technical specifications, and clinical practice. *J Clin Neurophysiol*. 2015;**32**(2):96–108.

91. Scheuer ML, Wilson SB. Data analysis for continuous EEG monitoring in the ICU: seeing the forest and the trees. *J Clin Neurophysiol*. 2004;**21**(5):353–78.

92. Wusthoff CJ, Shellhaas RA, Clancy RR. Limitations of single-channel EEG on the forehead for neonatal seizure detection. *J Perinatol*. 2009;**29**(3):237–42.

93. de Vries, LS, Hellstrom-Westas L. Role of cerebral function monitoring in the newborn. *Arch Dis Child Fetal Neonatal Ed*. 2005;**90**(3):F201–7.

94. Clancy RR, Dicker L, Cho S, et al. Agreement between long-term neonatal background classification by conventional and amplitude-integrated EEG. *J Clin Neurophysiol*. 2011;**28** (1):1–9.

95. van Rooij LG, de Vries LS, van Huffelen AC, Toet MC. Additional value of two-channel amplitude integrated EEG recording in full-term infants with unilateral brain injury. *Arch Dis Child Fetal Neonatal Ed*. 2010;**95**(3):F160–8.

96. Shah DK, Mackay MT, Lavery S, et al. Accuracy of bedside electroencephalographic monitoring in comparison with simultaneous continuous conventional electroencephalography for seizure detection in term infants. *Pediatrics*. 2008;**121**(6):1146–54.

97. Shellhaas RA, Soaita AI, Clancy RR. Sensitivity of amplitude-integrated electroencephalography for neonatal seizure detection. *Pediatrics*. 2007;**120** (4):770–7.

98. Shellhaas RA, Clancy RR. Characterization of neonatal seizures by conventional EEG and single-channel EEG. *Clin Neurophysiol*. 2007;**118**(10):2156–61.

99. Rennie JM, Chorley G, Boylan GB, et al. Non-expert use of the cerebral function monitor for neonatal seizure detection. *Arch Dis Child Fetal Neonatal Ed*. 2004;**89**(1):F37–40.

100. Stewart CP, Otsubo H, Ochi A, et al. Seizure identification in the ICU using quantitative EEG displays. *Neurology*. 2010;**75**(17):1501–8.

101. Pensirikul AD, Beslow LA, Kessler SK, et al. Density spectral array for seizure identification in critically ill children. *J Clin Neurophysiol*. 2013;**30** (4):371–5.

102. Akman CI, Micic V, Thompson A, Riviello JJ, Jr. Seizure detection using digital trend analysis: Factors affecting utility. *Epilepsy Res*. 2011;**93** (1):66–72.

103. Topjian AA, Fry M, Jawad AF, et al. Detection of electrographic seizures by critical care providers using color density spectral array after cardiac arrest is feasible. *Pediatr Crit Care Med*. 2015;**16**(5):461–7.

https://doi.org/10.1017/9781316536001.001 Published online by Cambridge University Press