Amplitude-Integrated Electroencephalography: The Child Neurologist’s Perspective

Hannah C. Glass, MDCM1, Courtney J. Wusthoff, MD2, and Renée A. Shellhaas, MD3

Abstract
Neurologists increasingly recognize that critically ill patients are at high risk for seizures, particularly nonconvulsive seizures, and that neuromonitoring is a useful tool for diagnosing seizures and assessing brain function in these patients. Amplitude-integrated electroencephalography (EEG) is a simplified bedside neurophysiology tool that has become widely used in neonates over the past decade. Despite widespread interest by both neurologists and neonatologists in continuous brain monitoring, amplitude-integrated EEG has been largely ignored by neurologists, forcing neonatologists to “go it alone” when interpreting data from this bedside tool. Although amplitude-integrated EEG cannot replace conventional EEG for background monitoring and detection of seizures, it remains a useful instrument that complements conventional EEG, is being widely adopted by neonatologists, and should be supported by neonatal neurologists.

Keywords
seizure, electroencephalogram, neonatal seizures, hypoxic-ischemic encephalopathy, status epilepticus, neurocritical, neurointensive care, epilepsy

Neurologists increasingly recognize that critically ill patients of all ages are at high risk for seizures, particularly nonconvulsive seizures, and that neuromonitoring can provide useful information about brain function for assessment and prognostication. With the advent of effective neuroprotective therapy and advances in safe neuroimaging methods for neonates, neonatologists have increasingly incorporated continuous, real-time, bedside monitoring of neonatal brain function into their management strategies.

The gold standard for neonatal brain monitoring is continuous video electroencephalography (EEG), with electrodes placed according to the International 10-20 system, modified for neonates. However, there are barriers to implementation of this technology: recording and interpretation require specialized training, it is expensive, and access to equipment is variable, often depending on the time of day or day of the week. Amplitude-integrated EEG is a bedside neurophysiology tool that uses a limited number of channels to record raw EEG data that are then filtered, rectified, processed, and displayed on a semilogarithmic amplitude and time-compressed scale (Figure 1). In most instances, neonatologists, nurses, or other intensive care nursery staff apply the electrodes and interpret the amplitude-integrated EEG recording independently, without input from a neurologist. Due to its ease of application and interpretation, as well as the obstacles to conventional EEG monitoring, amplitude-integrated EEG has been in widespread use in the intensive care nurseries of European centers for more than 2 decades and has been increasingly used in North American intensive care nurseries over the past several years.

The dramatic increase in amplitude-integrated EEG use has largely occurred independent of pediatric neurologists. Despite shared interest in continuous brain monitoring among both neurologists and neonatologists, neonatologists have primarily adopted amplitude-integrated EEG. Pediatric neurologists have been less enthusiastic (and in some cases reluctant) to accept its use due to amplitude-integrated EEG’s limited sensitivity for

1 Departments of Neurology and Pediatrics, University of California, San Francisco, San Francisco, CA, USA
2 Division of Child Neurology, Stanford University, Stanford, CA, USA
3 Division of Pediatric Neurology, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA

Corresponding Author:
Hannah C. Glass, MDCM, Department of Neurology, University of California, San Francisco, 505 Parnassus Avenue, M793, Box 0114, San Francisco, CA 94143.
Email: Hannah.Glass@ucsf.edu
seizure detection and the lack of evidence that such monitoring improves outcomes.4

As pediatric neurologists, we advocate that amplitude-integrated EEG is a useful tool that can complement, although not replace, continuous video EEG. Neurologists working in the intensive care nursery should become familiar with the advantages and limitations of this technology and be prepared to interpret bedside amplitude-integrated EEG recordings. The particular expertise of the pediatric neurologist in amplitude-integrated EEG interpretation adds important data to management decisions. Skill in the use of amplitude-integrated EEG benefits neurologists in many ways: amplitude-integrated EEG can be used to evaluate changes in encephalopathy over time and provides useful prognostic information for many neonates, in addition to identifying many seizures. Neurologists will find amplitude-integrated EEG fairly easy to interpret at the bedside, even without formal training in neurophysiology. Finally, neurologists’ involvement in amplitude-integrated EEG use and bedside interpretation can improve communication and coordination of care with the neonatology team.

**Evaluation of Amplitude-Integrated EEG Background**

The amplitude-integrated EEG background is categorized by features similar to those used in conventional neonatal EEG interpretation: amplitude criteria, continuity and discontinuity, and presence of sleep-wake cycling. The 2 most widely used classification schemes are illustrated in Figure 1. The system described by al Naqeeb and colleagues5 classifies amplitude-integrated EEG as normal, moderately abnormal, or suppressed using voltage-based criteria. An alternate system, proposed by

![Figure 1. Two-channel (4-electrode) amplitude-integrated EEG display. The upper 2 panels display single-channel EEG recorded from the left (top) and right (second from top) centroparietal leads. The y-axis shows amplitude on a logarithmic scale; the x-axis shows time in seconds. The bottom 2 panels show the corresponding amplitude-integrated EEG for each side. Note the rectification of voltages (with all values >0) and the time compression on the x-axis (this screen shows 3.5 hours of amplitude-integrated EEG). The vertical bar indicates the segment of EEG displayed across the amplitude-integrated EEG panels. (A) Normal or continuous normal voltage: upper margin >10 μV and lower margin >5 μV. (B) Moderately abnormal or discontinuous normal voltage: upper margin >10 μV and lower margin <5 μV. The tracing is discontinuous, and there is no sleep-wake cycling. (C) Burst suppression is a pattern of mixed inactivity with bursts of higher amplitude. (D) Suppressed activity or flat tracing is defined by low voltage/inactive amplitude-integrated EEG with an amplitude <5 μV; it can be called continuous low voltage when the background is approximately 5 μV.5,6](image-url)
Toet and colleagues, relies on pattern recognition in combination with voltage criteria to distinguish between 5 categories: continuous normal voltage, discontinuous normal voltage, burst suppression, continuous low voltage, and flat trace. A study comparing interrater reliability of the 2 amplitude-integrated EEG classification systems found more consistent interpretation with the simple voltage criteria system than the pattern recognition system, and both systems had equivalent agreement with classification criteria of the conventional EEG background.

Overall, the amplitude-integrated EEG background has been shown to have fair to good agreement with EEG background classification when studied in term newborns with encephalopathy. Given the prognostic value of the EEG background appearance in neonates with encephalopathy, an abnormal amplitude-integrated EEG background pattern during the first 3 to 6 postnatal hours was reported to be highly predictive of adverse outcome, and the combination of amplitude-integrated EEG background assessment with the clinical neurological examination was more predictive than either alone. The amplitude-integrated EEG background remains predictive of outcome in neonates treated with therapeutic hypothermia. Although an abnormal amplitude-integrated EEG result in the first 6 hours of life in a cooled patient has a lower positive predictive value for poor outcome than before hypothermia therapy, a normal, early amplitude-integrated EEG result is reassuring for a high likelihood of good outcome, and delayed recovery beyond 48 hours is highly predictive of later neurodevelopmental disability (positive predictive value, ~90%).

Failure to develop sleep-wake cycling in the first 72 hours of life is also strongly predictive of later disability.

As with continuous video EEG in the setting of hypothermia, amplitude-integrated EEG is most useful in showing evolution of the background over several days. The compressed time scale of the amplitude-integrated EEG display is ideal for evaluating the evolution of the background quickly and accurately at the bedside since several hours of monitoring data can be viewed on a single screen.

Because of the high sensitivity and specificity of early amplitude-integrated EEG to predict outcome after neonatal encephalopathy, 2 large trials of therapeutic hypothermia used an abnormal amplitude-integrated EEG background as an inclusion criterion “to improve the specificity of case selection [and] to control for severity of injury” beyond what was considered possible with clinical neurological examination alone. Following that precedent, many intensive care nurseries use amplitude-integrated EEG to determine the degree of encephalopathy when selecting patients for therapeutic hypothermia. Similarly, amplitude-integrated EEG is widely used in prognostication for neonates with encephalopathy. Given these high stakes, it is particularly important that the neurologist provides perspective on amplitude-integrated EEG, particularly to help avoid common amplitude-integrated EEG pitfalls.

For example, as in EEG, artifacts can contaminate the amplitude-integrated EEG background, leading to the potential for misinterpretation (Figure 2). In a study of 200 hours of amplitude-integrated EEG, 12% of recordings were significantly affected by artifacts. Preliminary evidence shows that artifacts can be even more common in amplitude-integrated EEG of preterm infants. Such artifacts are commonly recognized by those familiar with EEG but cannot be immediately obvious if relying only on the amplitude-integrated EEG trace. Electrocardiography (ECG) artifacts can elevate the amplitude-integrated EEG’s voltage and make the amplitude-integrated EEG background appear falsely normal (Figure 2). Similarly, in some tracings, electrographic seizures can falsely elevate the overall voltage of the amplitude-integrated EEG background. Both of these types of artifacts can lead inexperienced users to mistakenly read the amplitude-integrated EEG as “normal,” which could exclude an infant from hypothermia therapy (Figure 3). The neurologist’s expertise in identifying seizures, both clinically and on EEG, and knowledge of common extracerebral EEG artifacts can prevent such errors, with potentially significant treatment implications.

Neonatologists recognize the challenges of amplitude-integrated EEG interpretation, and many report limited confidence in being the sole reader of amplitude-integrated EEG. The neurologist familiar with the amplitude-integrated EEG background can better anticipate early concerns (or early positive signs) that the neonatologist can already have identified.
based on this technique. At the same time, the neurologist can complement this single indicator with a comprehensive clinical evaluation and review of continuous video EEG and neuroimaging data. Overall, amplitude-integrated EEG has proven utility in rapidly identifying normal and abnormal background patterns, with defined validity for prognostication. Neurologists can take advantage of this utility, while also providing a complementary perspective to optimize amplitude-integrated EEG background interpretation.

Amplitude-Integrated EEG for Seizure Detection

In contrast to seizures among older children and adults, the majority of neonatal seizures are subclinical; they have no external manifestations. Many authors have described this phenomenon, with rates of subclinical seizures typically exceeding 50% and often approaching 80% or more of all neonatal seizures.21-23 Conversely, many unusual neonatal movements have no electrographic correlate, but based on bedside observation, they can easily be misdiagnosed as seizures.24 Therefore, clinical observation alone is inadequate for the diagnosis, quantification, and management of neonatal seizures. For these reasons, continuous bedside monitoring is recommended for all neonates with clinical suspicion and/or high risk for seizures.1

While there is considerable debate about the use of amplitude-integrated EEG for seizure detection, as detailed below, scientific evidence and clinical experience suggest that amplitude-integrated EEG is useful to detect many seizures and can lead to improved real-time diagnosis and treatment (Figure 4).

Continuous video EEG remains the gold standard for neonatal seizure detection and quantification, with electrodes placed according to the International 10-20 system, modified for neonates.1 An electrographic seizure, as seen on conventional EEG, must have a sudden, evolving, repetitive, and stereotyped electrographic pattern with a clear beginning, middle, and end and a minimum duration of 10 seconds. The advantages of conventional EEG include its detailed information about the interictal background, seizures, seizure burden, and response to anticonvulsant medication as well as the differential diagnosis of paroxysmal clinical events, many of which are found not to be seizures.
Several studies have evaluated the accuracy of amplitude-integrated EEG for seizure detection, as summarized in Table 1. A typical neonatal seizure is of low to moderate amplitude (which can be less obvious on amplitude-integrated EEG display) and quite brief; 60% are less than 90 seconds in duration (90 seconds corresponds to ~1.4 mm on a typical amplitude-integrated EEG display).\textsuperscript{25} Neonatal seizures are also often of very low frequency and could be filtered out of the amplitude-integrated EEG trace (which filters frequencies <2 Hz and >15 Hz). These inherent features of neonatal seizures can render them difficult to detect with precision on amplitude-integrated EEG (Figure 5).

When reviewing the amplitude-integrated EEG literature, it is critical to distinguish the sensitivity reported for individual seizure detection from the sensitivity for seizure-positive amplitude-integrated EEG records. The former applies to each individual seizure, while the latter indicates only that at least 1 seizure was detected on the amplitude-integrated EEG record.

Multivariate analyses indicated that neonatologists’ expertise with amplitude-integrated EEG interpretation, increasing individual seizure duration, higher seizure amplitude, and larger number of seizures per hour improve the odds of seizure detection on single-channel amplitude-integrated EEG.\textsuperscript{26} Electrode location is also important, as frontal or forehead electrode...
positioning is likely to decrease the sensitivity for seizure detection because these electrodes are subject to myogenic and extracerebral artifacts, and neonatal seizures rarely originate in the frontal lobes. Shah et al demonstrated that the use of dual-channel amplitude-integrated EEG, in addition to the availability of raw EEG data from which the amplitude-integrated EEG was derived (a feature available on most modern amplitude-integrated EEG monitors), improved the sensitivity for seizure detection significantly. Neurologists should note that the “raw” EEG trace is not identical to a conventional single-channel EEG since many devices still subject the “raw” trace to amplitude-integrated EEG filters and integration.

Given the concern about adverse effects of anticonvulsant medications, neurologists also have concerns about the possibility of overtreating neonates for seizures based on the inaccurate interpretation of amplitude-integrated EEG. It is reassuring that most of the published studies report fairly high specificity for seizure detection with amplitude-integrated EEG, although this is not a universal finding. Overall, the literature suggests that if a seizure is identified by amplitude-integrated EEG, the diagnosis is correct. False-positive findings are relatively rare. Reasons for false-positive seizure detection include the ubiquitous extracerebral artifacts in the intensive care nursery. For example, rocking or patting a neonate, or using a bag for assisted ventilation, can create rhythmic artifacts that are easily mistaken for seizures. Mistaking patting for an ictal discharge is rare when time-locked video is recorded with the continuous video EEG, but video is not available with most amplitude-integrated EEG machines. Electrode malfunction and ECG artifacts are also very common and can be difficult to distinguish from abnormal (cerebral) EEG or amplitude-integrated EEG patterns.

Because of the potential for overdiagnosis (based on artifacts on the amplitude-integrated EEG or raw EEG trace) and underdiagnosis (due to the time-compressed amplitude-integrated EEG trace and also inherent features of neonatal seizure detection), continuous video EEG remains the gold standard for neonatal seizure detection. However, amplitude-integrated EEG, especially when rapidly applied and reviewed by an experienced clinician, can provide reassurance that paroxysmal clinical events are not seizures and can identify many seizures, allowing the prompt administration of antiseizure medications. Expedited continuous video EEG monitoring, to confirm a seizure diagnosis, quantify the seizure burden, and guide treatment, must back up the use of amplitude-integrated EEG for seizure detection.

**Optimizing Use of Concurrent Amplitude-Integrated EEG/EEG**

Amplitude-integrated EEG has been traditionally recorded on a separate bedside machine often called a cerebral function

Figure 5. Brief seizures can be difficult to detect on amplitude-integrated EEG, but they can be revealed upon review of the raw EEG data. The arrow points to the amplitude-integrated EEG at the time of the seizure displayed above, in the raw EEG channels.
monitor. Several bedside monitors with similar features are commercially available: most include a standardized amplitude-integrated EEG display for 1 or more channels and have the ability to annotate events, such as clinically apparent seizures or medication administration. While these machines have the advantage of being easy to use, we have found that having both an amplitude-integrated EEG machine and a separate continuous video EEG machine at the bedside is clumsy, costly, and can lead to challenges in communication between the bedside team and neonatal neurologist as they look at different tracings.

Bedside display of amplitude-integrated EEG with concurrent continuous video EEG recording is a potentially good solution (Figure 6). Using this system, the same machine is used to record amplitude-integrated EEG (with limited electrodes placed at the time of admission or of initial clinical concern by the bedside nurse or neonatologist and displayed as amplitude-integrated EEG at the bedside), followed by full electrode placement for conventional EEG when possible (and displayed remotely as continuous video EEG for the neurologist and neurophysiologist). With this system, the bedside intensive care nursery clinician can monitor for changes on amplitude-integrated EEG, and the neonatal EEG reader, who has access to continuous video EEG, can review any areas of concern upon request as well as according to guidelines for care.1

The advantages to this system are many. First, the hospital supports and maintains a single type of machine that can be used both in the intensive care setting and the neurophysiology laboratory. Second, while most hospitals support remote access for continuous video EEG from the intensive care unit, many amplitude-integrated EEG stand-alone systems do not have this capacity. Third, annotated events (either at the bedside or in the neurophysiology laboratory) are displayed for all viewers. For example, the neonatologist can see that the neurologist has reviewed a section of tracing, and the neurologist can see where the bedside nurse has noted a suspicious clinical event or administered a medication. Finally, we have found that communication between the neurologist and neonatologist is improved and education is facilitated when all are looking at the same tracing.

Conclusions

An editorial in 2011 noted that amplitude-integrated EEG has “become the standard technology” for brain monitoring in term neonates: “many neonatologists would like to have continuous access to EEG monitoring but often this is not achievable as neurophysiology departments cannot provide an ‘out of hours service.’”4,32 A recent survey of specialists primarily in Europe and North America found that 65% used amplitude-integrated EEG in their intensive care nursery, either alone or in conjunction with EEG.4 Eighty percent of those surveyed reported that the neonatologist alone, without neurologist or neurophysiologist input, interpreted amplitude-integrated EEG. When neurologists fail to support amplitude-integrated EEG, intensive care nursery staff has no alternative but to “go it alone.”4

Pediatric neurologists will find that their perspective is uniquely valuable in assessing amplitude-integrated EEG and that neonatologists are usually appreciative of the support. Indeed, in Boylan et al’s4 survey regarding amplitude-integrated EEG use, only 28% of respondents felt confident in their own skills in amplitude-integrated EEG interpretation.

Figure 6. In this example, a single machine is used to acquire the same data, which are displayed differently for different users, optimizing the advantages of both amplitude-integrated EEG and EEG. The bedside team sees the display at left, showing overall trends and allowing a quick review of suspicious segments of EEG. The neurophysiologist can confirm these abnormalities through the review of conventional, neonatal montage EEG.
Amplitude-integrated EEG is here to stay, with the benefit of bringing convenient and timely neuromonitoring to the forefront of intensive care nursery care. For too long, infants’ brain function has not been a focus in the intensive care nursery. Rather than resisting change, we encourage neurologists to embrace amplitude-integrated EEG, learn to interpret the amplitude-integrated EEG background, and use amplitude-integrated EEG as a springboard to optimal neuromonitoring and improved collaboration in the care of neonates at high risk for cerebral dysfunction.

Acknowledgments
Amy J. Markowitz, JD, provided editorial support. The authors thank Dr John Barks for his assistance with figures.

Author Contributions
HCG drafted portions of the article, edited the article, and approved the final draft. CJW drafted portions of the article, edited the article, and approved the final draft. RAS drafted portions of the article, edited the article, and approved the final draft.

Declaration of Conflicting Interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This work was supported by the National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (5K23NS066137) and the NIH/National Institute of Child Health and Human Development (5K23HD068402) (to RAS).

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