Neonatal Seizures

Hannah C. Glass, MDCM, MAS, FRCPC
Joseph E. Sullivan, MD

Corresponding author
Joseph E. Sullivan, MD
Pediatric Epilepsy Center, Box 0138, 400 Parnassus Avenue,
University of California, San Francisco, San Francisco, CA 94143, USA.
E-mail: Joseph.sullivan@ucsf.edu

Current Treatment Options in Neurology 2009, **11:**405–413
Current Medicine Group LLC ISSN 1092-8480

Opinion statement

Seizures in neonates are common and often suggest a serious underlying brain injury such as hypoxia-ischemia, stroke, or hemorrhage. There is a lack of evidence regarding optimal monitoring, evaluation, and treatment for newborns with seizures. Prolonged video-electroencephalogram (EEG) is the gold standard for detecting seizures, whereas amplitude-integrated EEG may be a convenient and useful screening tool. Evaluation involves a thorough search for the etiology of the seizures and includes detailed clinical history, routine chemistries, neuroimaging (preferably MRI), and specialized testing such as screening for inborn error of metabolism if no structural cause is readily apparent. There is a lack of consensus regarding the relative risk versus benefit for aggressive medical treatment of neonatal seizures. Evidence is increasing that seizures themselves impair brain development, but there is evidence in animal models that commonly used medications are potentially neurotoxic. We believe that medical management with a goal of eliminating electrographic and electroclinical seizures is probably warranted.

Introduction

The estimated rate of seizures in term newborns is 1 to 3 per 1000 live births [1–3]. The first year of life represents the highest risk for seizures (especially acute symptomatic seizures) [4], which may reflect the developmental stage–specific mechanisms that lead to relative excitability in the neonatal brain [5••], as well as the high risk for perinatal brain injury.

Seizures in the neonatal period are often the first sign of neurologic dysfunction and frequently reflect serious underlying brain injury. Therefore, a suspicion of seizures in a newborn should prompt a rapid and thorough evaluation. Neonatal seizures may be caused by a variety of underlying conditions (Table 1). The most common cause is hypoxic-ischemic brain injury due to perinatal asphyxia [6]. In a Canadian population-based study by Ronen et al. [7], 42% of newborns with seizures had encephalopathy (mostly following hypoxia-ischemia), 19% had infections, and 10% had cerebral dysgenesis. Additional important causes of neonatal seizures include intracranial hemorrhage, perinatal stroke, and transient metabolic disturbances such as hypoglycemia and hypocalcemia [8]. Epilepsy syndromes are a rare but important cause of seizures in the newborn period. Benign familial neonatal seizures and benign idiopathic neonatal seizures are characterized by seizure onset in the first week of life in an otherwise well-appearing child and a favorable outcome [8,9]. Early myoclonic epilepsy and early infantile epileptic encephalopathy (Ohtahara syndrome) are rare epileptic encephalopathies with frequent refractory seizures, characteristic burst-suppression patterns on electroencephalography (EEG), and poor neurodevelopmental prognosis [10,11].

Neonates with seizures are at risk for early death, and survivors have a high incidence of adverse neurodevelopmental outcome, including motor or cognitive disability [6,7]. The outcome depends largely on the underlying disease process, with the best prognosis seen in infants with late-onset hypocalcemia and subarachnoid hemorrhage, and the worst outcome in infants with intraventricular hemorrhage or brain malformation [8].

The topic of neonatal seizures has gained increasing interest over the past years in light of accumulating evidence from animal studies that seizures may impair brain development and lead to long-term deficits in learning, memory, and behavior (reviewed in [12•]). Although the exact mechanisms are unknown, work in

animal models of seizure have shown reduced density of dendritic spines in hippocampal pyramidal neurons [13], decreased neurogenesis [14], delayed neuronal loss [15], and changes in hippocampal plasticity such as decreased capacity for long-term potentiation, reduced susceptibility to kindling, and enhanced paired-pulse inhibition [16]. Human studies in children with hypoxic-ischemic injury show an independent association between seizures and impaired brain metabolism [17], as well as poor long-term neurodevelopmental outcome [18•].

There are currently no evidence-based guidelines for evaluation and management of neonatal seizures. There has been a paucity of high-quality studies in this area, so considerable uncertainty remains regarding optimal monitoring, investigation, and treatment of neonatal seizures. There is also a strong need for well-conducted randomized controlled trials of the newer seizure medications in newborns. In 2007, the members of a National Institute of Neurological Disorders and Stroke workshop focusing on "Improving the Treatment of Neonatal Seizures" highlighted several important themes to guide future trials. First, since the developmental stage contributes to the pathophysiology of seizures and the response to therapy, dedicated trials in newborns are essential. Second, conventional EEG should remain the gold standard for seizure monitoring. Finally, the underlying cause of the seizures should be considered in the clinical trial design [19].

Treatment

Evaluation

History and physical examination

The initial history should focus on the details of the pregnancy, delivery, and resuscitation. In encephalopathic infants, risk factors for birth asphyxia and infection should be sought. In well-appearing newborns, the maternal medical history, as well as family history of thrombosis and seizures, should be detailed. The general physical examination should be comprehensive, including an evaluation of vital signs, cardiac and respiratory function and organ size, and fetal growth, dysmorphisms, and neurocutaneous stigmata. The neurologic examination should include detailed assessments of mental status, the cranial nerves, motor findings, and primitive and deep tendon reflexes.

Laboratory tests

Initial laboratory tests should include evaluation of serum glucose and lumbar puncture, as hypoglycemia and bacterial meningitis can lead to permanent injury if left untreated [8, Class III]. Additional tests should include serum calcium, sodium, potassium, phosphorus, and magnesium. Further evaluation that may be warranted on a case-by-case basis could include serum amino acids, urine organic acids, very long chain fatty acids, and cerebrospinal fluid studies for glucose, glycine, lactate, ammonia, and neurotransmitters. Such evaluations should definitely be performed in the setting of medically refractory seizures of unknown etiology, especially in the setting of a burst-suppression pattern on EEG.

Imaging

Neuroimaging using cranial ultrasound, CT, or (preferably) MRI is essential to the evaluation of neonatal seizures, both to identify underlying injury or developmental abnormalities and to help clinicians and the family to better understand the prognosis.

Cranial **ultrasound** is readily available in most units and is important for rapid initial assessment of a sick neonate to identify large space-occupying lesions such as hemorrhage, arteriovenous malformations, or hydrocephalus. Ultrasound may be insensitive for hypoxic-ischemic injury, and serial ultrasound is more sensitive than a single study.

Ultrasound should be followed by **MRI**, where available, to help identify the full extent of the injury. **CT scans** have higher resolution

Table 1. Etiology of seizures in newborns

Global hypoxia-ischemia
Focal hypoxia-ischemia
Arterial stroke
Venous stroke
Intracranial hemorrhage
Intraventricular
Parenchymal
Subarachnoid
Subdural
Transient metabolic deficit
Hypoglycemia
Hypocalcemia and hypomagnesemia
Hyponatremia
Infection
Inborn error of metabolism
Amino acidopathy
Organic acidopathy
Mitochondrial disease
Peroxisomal disorders
Pyridoxine-dependent seizures
Folinic acid–responsive seizures
Glucose transporter deficiency
Molybdenum cofactor deficiency (sulfite oxidase/xanthine oxidase deficiency)
Epileptic syndromes
Benign familial neonatal seizures (KCNQ2, KCNQ3)
Benign idiopathic neonatal seizures
Early myoclonic epilepsy
Early infantile epileptic encephalopathy (Ohtahara syndrome)
Central nervous system malformations

than ultrasound, but they expose the infant to ionizing radiation and have been replaced by MRI in many centers. MRI has higher resolution than cranial ultrasound and CT, so it is now considered the gold standard for evaluating brain injury or developmental abnormalities in newborns [20, Class III]. It is important to consider the timing of the MRI when evaluating newborns with seizures. In newborns with stroke or hypoxic-ischemic brain injury, conventional T1-weighted and T2-weighted sequences may be normal in the first 48 hours. Reduced water motion on diffusion-weighted imaging (DWI) sequences is apparent shortly after the injury but becomes falsely negative (pseudonormalizes) within about 7 days [21,22]. Therefore, when imaging newborns between the second and fifth days of life, DWI is an essential part of the evaluation, whereas in the second week of life, the extent of injury should be apparent on T1-weighted and T2-weighted sequences [23••]. If stroke is suspected, vascular imaging (MR venography) with or without gadolinium contrast is essential to accurately diagnose and follow venous thrombosis [23••].

Electroencephalography and long-term monitoring

EEG in the neonatal period is often performed for two reasons: to evaluate for background abnormalities to aid in prognosis and to monitor for seizures. It is widely known and accepted that neonatal seizures are often subtle and may go undetected by clinical observation alone. Furthermore, even when seizures are noted clinically, once treatment has been initiated, many neonates may undergo electroclinical dissociation, in which overt clinical seizure activity ceases, but subclinical seizures on EEG are ongoing [24]. At minimum, neonates at high risk for seizures and those with suspicious clinical events should be monitored with a full neonatal electrode array and concurrent video monitoring for 30 to 60 minutes in an attempt to record wakefulness, quiet, and active sleep. A more prolonged recording is more sensitive for detecting subclinical seizures, and 24 hours of long-term monitoring is recommended, especially when severe background abnormalities are present, as it has been shown that neonates with severely abnormal background patterns have a higher incidence of status epilepticus [25]. In the presence of documented seizures, long-term monitoring should be continued until the infant has been seizure-free for at least 24 hours. If continuous EEG recording is not available, serial/sequential EEGs may be an appropriate compromise.

When interpreting a neonatal EEG, the reader should be systematic and always evaluate the overall background to assess for the expected patterns seen at different gestational ages, including the presence or absence of state changes. In the neonatal ICU, many infants are severely ill and receive medications (eg, benzodiazepines, barbiturates, or narcotics) that may affect the EEG background. Documentation, preferably directly on the EEG recording, of when such medications are administered is extremely important, as these agents may alter the background; therefore the EEG activity may not necessarily be an accurate representation of the true cerebral physiology.

Amplitude-integrated EEG is less accurate than video-EEG for detecting seizures in newborns, especially when seizures are brief, low-voltage, or focal [26••, Class II]. However, amplitude-integrated EEG is often more readily available and may be a useful tool, especially when there may be a delay until video-EEG can be applied and interpreted.

Medical therapy

- There are no evidence-based guidelines for the management of neonatal seizures. Expert opinion supports treating clinical and electrographic seizures [27••, Class III], although there is no good evidence regarding the relative benefit and harm of the anticonvulsants currently used to treat seizures in neonates.
- According to international survey data, phenobarbital is widely used as the first anticonvulsant (82% in US centers) [28–30, Class III].
- A single randomized controlled trial of phenytoin versus phenobarbital as a first-line agent for term infants with seizures found no difference in seizure cessation between these medications (RR, 0.97; 95% CI, 0.54–1.72; $P = 0.91$). Both agents had poor efficacy, with seizure control (defined by the study parameters as an 80% reduction in the severity of seizures), in less than half of the infants [31, Class I].
- In North America, phenytoin (or, preferably, fosphenytoin) is commonly used in refractory cases, although erratic pharmacokinetics and drug interactions make dosing a challenge. Lorazepam and midazolam may also be used as an alternative to or in addition to phenobarbital in refractory cases. Lidocaine is widely used for refractory neonatal seizures in Europe [32].
- If the underlying etiology of medically refractory seizures is unknown, a trial of pyridoxine, together with folinic acid, should be considered, and a screening metabolic evaluation should be performed as outlined above.

- When evaluating the efficacy of a medication in a given child, it is important to remember that phenobarbital and other drugs frequently result in electroclinical dissociation (ie, ongoing electrographic seizures in spite of termination of clinical events), making medication appear effective unless the infant is monitored with EEG [24]. In addition, seizures due to acute symptomatic causes such as hypoxic-ischemic brain injury and stroke rarely persist beyond a few days, making any add-on agent appear more effective than the initial therapy.
- The risk versus benefit for aggressive treatment of neonatal seizures (especially seizures that are electrographic only) is complicated by the potentially neurotoxic effects of antiseizure medications, as shown in animal studies [33]. In humans, the impact of therapeutic doses of these agents on neurodevelopmental outcome in newborns with seizures is not known. In our opinion, all seizure types, including subclinical, electroclinical, and subtle, should be treated. Multicenter neonatal seizure trials with long-term developmental follow-up are necessary to definitively answer the question of whether neonatal seizures affect outcomes independent of underlying etiology.
- Most experts suggest early termination of seizure medications, to minimize side effects and because neonatal seizures typically abate within days, independent of the therapeutic intervention, and have a low risk of early recurrence [8,34–36, Class III]. The natural history of seizures due to various etiologies may be used to guide duration of therapy [8, Class III]. For seizures due to moderate hypoxic-ischemic brain injury, subarachnoid hemorrhage, or treatable and reversible metabolic disorders, medical therapy can be discontinued early, preferably within 7 days of seizure treatment or prior to discharge. Newborns with seizures due to severe hypoxic-ischemic brain injury, intraparenchymal hemorrhage, or ischemic stroke may need longer treatment. Neonates with a history of status epilepticus have a higher risk of developing postnatal epilepsy than those with repetitive seizures, but there is no evidence that treatment with medication has an effect on the natural history and outcome [25]. Ongoing treatment should be reassessed within 3 months, given the potential negative effects on the infant brain of ongoing therapy.

Pharmacologic treatment

Lorazepam

Standard dosage	0.05–0.1 mg/kg intravenously.
Contraindications	Inability to provide cardiorespiratory support, hypersensitivity.
Main drug interactions	None applicable to acute therapy.
Main side effects	Respiratory depression, depressed level of consciousness, hypotension.
Special points	May cause myoclonus in very-low-birth-weight infants.

Midazolam

Standard dosage	Bolus 0.15–0.2 mg/kg intravenously, followed by continuous infusion (1 mcg/kg/min) increasing by 0.5–1 mcg/kg per minute every 2 minutes until favorable response or a maximum of 18 mcg/kg per minute [37].
Contraindications	Inability to provide cardiorespiratory support, hypersensitivity.
Main drug interactions	None applicable to acute therapy.
Main side effects	Respiratory depression, depressed level of consciousness, hypotension.

Phenobarbital

Standard dosage	Bolus 20 mg/kg intravenously, repeated once as needed; daily dosing 5 mg/kg per day (target level 40–60 mcg/mL).
Contraindications	Hypersensitivity, porphyria, severe liver dysfunction, inability to provide cardiorespiratory support.
Main drug interactions	Multiple interactions with other drugs metabolized by the liver.
Main side effects	Respiratory depression, depressed level of consciousness, hypotension, hypotonia. Idiosyncratic skin rash, hepatotoxicity, blood dyscrasia.
Special points	Prolonged half-life in first week of life (43–217 hours) limits need for weaning phenobarbital in the case of short-term therapy.

Phenytoin and fosphenytoin

Standard dosage	Bolus 20 mg/kg intravenously; daily dosing 5 mg/kg per day (target level 10–20 mcg/mL).
Contraindications	Hypersensitivity.
Main drug interactions	Multiple interactions with other drugs metabolized by the liver.
Main side effects	Infusion site reaction and arrhythmia with intravenous phenytoin. Idiosyncratic skin rash, hepatotoxicity, blood dyscrasia.
Special points	Fosphenytoin is a water-soluble phenytoin prodrug that has fewer cardiovascular, central nervous system, and local cutaneous side effects than phenytoin. Because of saturable metabolism, small increases in phenytoin dose may produce disproportionate increases in concentration. Significant variability and changes in pharmacokinetics over the first weeks of life may lead to inconsistent drug levels.

Pyridoxine

Standard dosage	100 mg intravenously, preferably with EEG monitoring, followed by 10–100 mg orally per day. (Doses as high as 400 mg/d may be necessary in pyridoxine dependency.)
Contraindications	None.
Main drug interactions	None.
Main side effects	Sedation, restlessness, crying, neuropathy, hypotonia, hemorrhagic gastritis, rash, respiratory distress, folic acid deficiency.
Special points	Peripheral neuropathies can occur with relatively low doses (50 mg/d) after prolonged use. If pyridoxine-dependent seizures are suspected, should co-administer folinic acid (see below).

Folinic acid

Standard dosage	5–20 mg/d.
Contraindications	Megaloblastic anemia.
Main drug interactions	None.
Main side effects	None.

Emerging therapies

Newer pharmacologic agents

- Although there are few data on their safety or pharmacokinetics in neonates, newer antiseizure agents are increasingly used off-label [38]. The use of **levetiracetam** in several newborns with refractory seizures has been reported, with no noted side effects [39,40]; a safety and pharmacokinetics study is enrolling newborns. **Topiramate** is an interesting option because it also has neuroprotective effects in animal models of brain injury [41], and early studies using an intravenous formulation are under way.

- An in vitro study of **bumetanide** in a rat hippocampal slice preparation showed a significant reduction in seizure frequency and duration when combined with phenobarbital, compared with phenobarbital alone [42]. This effect is attributed to alterations in chloride transport resulting in improved efficacy of phenobarbital in an immature brain. Bumetanide is widely used as a diuretic in humans and preterm infants, and a recent case report demonstrated a drastic reduction in seizures when bumetanide was administered for fluid management [43]. Larger studies are being developed to determine optimal dosing and efficacy in the treatment of neonatal seizures.
- **Retigabine** is a novel antiepileptic drug that has been shown to act at neuronal KCNQ2/3 and KCNQ3/5 potassium channels [44]. Mutations in the *KCNQ2/3* gene have been found to be a major cause of benign familial neonatal seizures [45], and other modulators of KCNQ opening have been shown to be effective in preventing and suppressing seizures in an animal model of neonatal seizures [46]. Because of this unique mechanism of action, retigabine has excellent potential for the treatment of neonatal seizures and warrants further study in treatment trials for human neonatal seizure.

Automated seizure detection and trending

- Amplitude-integrated EEG is one method of displaying a simplified rendering of a limited EEG tracing as a means of real-time screening for background abnormalities and electrographic seizure activity. Other methods of automated seizure detection and trending of digital EEG data may also give valuable real-time bedside information for non–EEG-trained personnel, and these packages are becoming more readily available as add-on software from many EEG vendors.
- One method uses compressed spectral array and envelope trending. For a small cohort of neonates, experienced users of this method were able to identify 88% of prolonged seizures, and inexperienced users were able to identify 55% [47]. The ability to identify brief or slowly evolving seizures was not as high, but the authors suggested that the absolute seizure count may not be as clinically relevant as the presence or absence of seizures in response to treatment.
- More complex automated algorithms lack the sensitivity and specificity to be used in clinical practice [48]. Algorithm development is a topic of ongoing research, and it is likely that a combination of algorithms will be necessary to reliably detect the full range of highly variable neonatal seizure patterns. Like any automated algorithm or compressed trending of a complex data set, these are subject to false positive and false negative results due to common artifacts. When decisions are made on the basis of any trending algorithm, one should always have access to the raw data and be able to determine whether common artifacts could be causing a misleading trend.

Acknowledgments

This project was supported by NIH/NCRR/OD UCSF-CTSI Grant Number KL2 RR024130 (HCG). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. 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:**24–28.e1.
2. Lanska MJ, Lanska DJ, Baumann RJ, et al.: **A population-based study of neonatal seizures in Fayette County, Kentucky.** *Neurology* 1995, **45:**724–732.
3. Saliba RM, Annegers JF, Waller DK, et al.: **Incidence of neonatal seizures in Harris County, Texas 1992–1994.** *Am J Epidemiol* 1999, **150:**763–769.
4. Annegers JF, Hauser WA, Lee JR, et al.: **Incidence of acute symptomatic seizures in Rochester, Minnesota, 1935–1984.** *Epilepsia* 1995, **36:**327–333.
5.•• Jensen FE: **Developmental factors regulating susceptibility to perinatal brain injury and seizures.** *Curr Opin Pediatr* 2006, **18:**628–633.

This comprehensive review examines the developmental aspects of susceptibility to brain injury and seizures in preterm and term neonates.

6. Tekgul H, Gauvreau K, Soul J, et al.: **The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants.** *Pediatrics* 2006, **117:**1270–1280.
7. Ronen GM, Buckley D, Penney S, et al.: **Long-term prognosis in children with neonatal seizures: a population-based study.** *Neurology* 2007, **69:**1816–1822.
8. Volpe JJ: **Neonatal seizures.** In *Neonatal Neurology.* Edited by Volpe JJ. Philadelphia: WB Saunders; 2008:203–244.
9. Soldovieri MV, Miceli F, Bellini G, et al.: **Correlating the clinical and genetic features of benign familial neonatal seizures (BFNS) with the functional consequences of underlying mutations.** *Channels (Austin)* 2007, **1:**228–233.
10. Ohtahara S, Yamatogi Y: **Ohtahara syndrome: with special reference to its developmental aspects for differentiating from early myoclonic encephalopathy.** *Epilepsy Res* 2006, **70(Suppl 1):**S58–S67.
11. Djukic A, Lado FA, Shinnar S, et al.: **Are early myoclonic encephalopathy (EME) and the Ohtahara syndrome (EIEE) independent of each other?** *Epilepsy Res* 2006, **70(Suppl 1):**S68–S76.
12.• Silverstein FS, Jensen FE: **Neonatal seizures.** *Ann Neurol* 2007, **62:**112–120.

This comprehensive and well-written review examines the developmental mechanisms that underlie seizure generation and response to anticonvulsants in the developing brain.

13. Jiang M, Lee CL, Smith KL, et al.: **Spine loss and other persistent alterations of hippocampal pyramidal cell dendrites in a model of early-onset epilepsy.** *J Neurosci* 1998, **18:**8356–8368.
14. McCabe BK, Silveira DC, Cilio MR, et al.: **Reduced neurogenesis after neonatal seizures.** *J Neurosci* 2001, **21:**2094–2103.
15. Montgomery EM, Bardgett ME, Lall B, et al.: **Delayed neuronal loss after administration of intracerebroventricular kainic acid to preweanling rats.** *Brain Res Dev Brain Res* 1999, **112:**107–116.
16. Lynch M, Sayin U, Bownds J, et al.: **Long-term consequences of early postnatal seizures on hippocampal learning and plasticity.** *Eur J Neurosci* 2000, **12:**2252–2264.
17. Miller SP, Weiss J, Barnwell A, et al.: **Seizure-associated brain injury in term newborns with perinatal asphyxia.** *Neurology* 2002, **58:**542–548.
18.• 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:**318–323.

This well-conducted study shows that seizures are independently associated with worse long-term outcome in children with perinatal asphyxia.

19. Silverstein FS, Jensen FE, Inder T, et al.: **Improving the treatment of neonatal seizures: National Institute of Neurological Disorders and Stroke workshop report.** *J Pediatr* 2008, **153:**12–15.
20. Bonifacio SL, Miller SP: **Neonatal seizures and brain imaging.** *J Pediatr Neurol* 2009, **7:**61–67.
21. Mader I, Schoning M, Klose U, et al.: **Neonatal cerebral infarction diagnosed by diffusion-weighted MRI: pseudonormalization occurs early.** *Stroke* 2002, **33:**1142–1145.
22. Kuker W, Mohrle S, Mader I, et al.: **MRI for the management of neonatal cerebral infarctions: importance of timing.** *Childs Nerv Syst* 2004, **20:**742–748.
23.•• Barkovich AJ, Miller SP, Bartha A, et al.: **MR imaging, MR spectroscopy, and diffusion tensor imaging of sequential studies in neonates with encephalopathy.** *AJNR Am J Neuroradiol* 2006, **27:**533–547.

This well-conducted study examines the timing of the evolution of brain injury on various MR sequences in newborns with encephalopathy.

24. Weiner SP, Painter MJ, Geva D, et al.: **Neonatal seizures: electroclinical dissociation.** *Pediatr Neurol* 1991, **7:**363–368.
25. Pisani F, Cerminara C, Fusco C, et al.: **Neonatal status epilepticus vs recurrent neonatal seizures: clinical findings and outcome.** *Neurology* 2007, **69:**2177–2185.
26.•• Shellhaas RA, Soaita AI, Clancy RR: **Sensitivity of amplitude-integrated electroencephalography for neonatal seizure detection.** *Pediatrics* 2007, **120:**770–777.

This well-conducted study compares EEG and amplitude-integrated EEG for seizure detection in newborns.

27.•• Clancy RR: **Prolonged electroencephalogram monitoring for seizures and their treatment.** *Clin Perinatol* 2006, **33:**649–665.

This comprehensive review examines the utility of prolonged EEG monitoring in newborns.

28. Bartha AI, Shen J, Katz KH, et al.: **Neonatal seizures: multicenter variability in current treatment practices.** *Pediatr Neurol* 2007, **37:**85–90.
29. Wheless JW, Clarke DF, Arzimanoglou A, et al.: **Treatment of pediatric epilepsy: European expert opinion 2007.** *Epileptic Disord* 2007, **9:**353–412.
30. Bassan H, Bental Y, Shany E, et al.: **Neonatal seizures: dilemmas in workup and management.** *Pediatr Neurol* 2008, **38:**415–421.
31. Painter MJ, Scher MS, Stein AD, et al.: **Phenobarbital compared with phenytoin for the treatment of neonatal seizures.** *N Engl J Med* 1999, **341:**485–489.
32. Malingre MM, Van Rooij LG, Rademaker CM, et al.: **Development of an optimal lidocaine infusion strategy for neonatal seizures.** *Eur J Pediatr* 2006, **165:**598–604.
33. Bittigau P, Sifringer M, Genz K, et al.: **Antiepileptic drugs and apoptotic neurodegeneration in the developing brain.** *Proc Natl Acad Sci U S A* 2002, **99:**15089–15094.
34. Hellstrom-Westas L, Blennow G, Lindroth M, et al.: **Low risk of seizure recurrence after early withdrawal of antiepileptic treatment in the neonatal period.** *Arch Dis Child Fetal Neonatal Ed* 1995, **72:**F97–F101.
35. Levene M: **The clinical conundrum of neonatal seizures.** *Arch Dis Child Fetal Neonatal Ed* 2002, **86:**F75–F77.
36. Guillet R, Kwon J: **Seizure recurrence and developmental disabilities after neonatal seizures: outcomes are unrelated to use of phenobarbital prophylaxis.** *J Child Neurol* 2007, **22:**389–395.
37. Castro Conde JR, Hernandez Borges AA, Domenech Martinez E, et al.: **Midazolam in neonatal seizures with no response to phenobarbital.** *Neurology* 2005, **64:**876–879.

38. Silverstein FS, Ferriero DM: **Off-label use of antiepileptic drugs for the treatment of neonatal seizures.** *Pediatr Neurol* 2008, **39:**77–79.
39. Hmaimess G, Kadhim H, Nassogne MC, et al.: **Levetiracetam in a neonate with malignant migrating partial seizures.** *Pediatr Neurol* 2006, **34:**55–59.
40. Shoemaker MT, Rotenberg JS: **Levetiracetam for the treatment of neonatal seizures.** *J Child Neurol* 2007, **22:**95–98.
41. Liu Y, Barks JD, Xu G, et al.: **Topiramate extends the therapeutic window for hypothermia-mediated neuroprotection after stroke in neonatal rats.** *Stroke* 2004, **35:**1460–1465.
42. Dzhala VI, Brumback AC, Staley KJ: **Bumetanide enhances phenobarbital efficacy in a neonatal seizure model.** *Ann Neurol* 2008, **63:**222–235.
43. Kahle KT, Barnett SM, Sassower KC, et al.: **Decreased seizure activity in a human neonate treated with bumetanide, an inhibitor of the Na(+)-K(+)-2Cl(-) cotransporter NKCC1.** *J Child Neurol* 2009, **24:**572–576.
44. Tatulian L, Delmas P, Abogadie FC, et al.: **Activation of expressed KCNQ potassium currents in native neuronal M-type potassium currents by the anti-convulsant drug retigabine.** *J Neurosci* 2001, **21:**5535–5545.
45. Castaldo P, del Giudice EM, Coppola G: **Benign familial neonatal convulsions caused by altered gating of KCNQ2/KCNQ3 potassium channels.** *J Neurosci* 2002, **22:**RC199.
46. Rao YH, Lapides DA, Keating JG, et al.: **A KCNQ channel opener for experimental neonatal seizures and status epilepticus.** *Ann Neurol* 2009, **65:**326–336.
47. Abend NS, Dlugos D, Herman S: **Neonatal seizure detection using multichannel display of envelope trend.** *Epilepsia* 2008, **49:**349–352.
48. Faul S, Boylan G, Connolly S, et al.: **An evaluation of automated neonatal seizure detection methods.** *Clin Neurophysiol* 2005, **116:**1533–1541.