Treatment of neonatal seizures

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INTRODUCTION — The occurrence of neonatal seizures may be the first, and perhaps the only, clinical sign of a central nervous system (CNS) disorder in the newborn infant. Seizures may indicate the presence of a potentially treatable etiology and should prompt an immediate evaluation to determine cause and to institute etiology-specific therapy. In addition, seizures themselves may require emergent therapy, since they can adversely affect the infant's homeostasis or they may contribute to further brain injury. Some types of neonatal seizures are associated with a relatively high incidence of early death and, in survivors, a high incidence of neurologic impairment, developmental delay, and postneonatal epilepsy.

Management of neonatal seizures involves accurate diagnosis of seizures, expedited evaluation and targeted treatment for their etiology, and medication to abolish the electrographic seizures. This topic will discuss the approach to treatment of neonatal seizures. The etiology, clinical features and diagnosis of neonatal seizures are discussed separately. (See "Etiology and prognosis of neonatal seizures" and "Neonatal epilepsy syndromes" and "Clinical features, evaluation, and diagnosis of neonatal seizures".)

ETIOLOGIC THERAPY — Treatment directed at the cause of neonatal seizures is critical since it may prevent further brain injury. This is particularly true for seizures associated with some metabolic disturbances (eg, hypoglycemia, hypocalcemia, and hypomagnesemia) and with central nervous system (CNS) or systemic infections. Furthermore, neonatal seizures may not be effectively controlled with antiseizure drugs unless their underlying cause is treated.

The most common etiologies of neonatal seizures are reviewed in the Table (table 1).

Neonatal encephalopathy — Neonatal encephalopathy (and associated hypoxic-ischemic encephalopathy) is the most common cause of neonatal seizures. Even with therapeutic hypothermia for neuroprotection, about 50 percent of newborns with hypoxic ischemic encephalopathy have electrographic seizures [1].

The treatment of neonatal encephalopathy is discussed separately. (See "Clinical features, diagnosis, and treatment of neonatal encephalopathy".)

CNS infection — Neonates with seizures should be presumed to have an infectious etiology until proven otherwise. Thus, a sepsis evaluation is mandatory. Infection of the central nervous system is a relatively common cause of neonatal seizures and should be treated with broad spectrum antibiotics at doses sufficient to treat meningitis.

Treatment of infection and meningitis in neonates is discussed separately. (See "Febrile infant (younger than 90 days of age): Outpatient evaluation" and "Bacterial meningitis in the neonate: Treatment and outcome" and "Group B streptococcal infection in neonates and young infants", section on 'Management'.)

Metabolic disturbances — Metabolic disturbances are a treatable common cause of neonatal seizures.

Hypoglycemia — Hypoglycemia should be corrected immediately with a 10 percent glucose solution given intravenously at 2 mL/kg. Maintenance glucose infusion can be given to a maximum of 8 mg/kg per
A detailed review of the evaluation and treatment of hypoglycemia in infants is discussed separately. (See "Pathogenesis, screening, and diagnosis of neonatal hypoglycemia").

**Hypocalcemia** — Hypocalcemia associated with severe neuromuscular irritability or seizures is treated with 10 percent calcium gluconate (100 mg/kg or 1 mL/kg IV). The solution is infused over 5 to 10 minutes while the heart rate and infusion site are monitored. The dose can be repeated in 10 minutes if no response occurs. Alternatively, calcium chloride (20 mg/kg or 0.2 mL/kg) can be given. After acute treatment, maintenance calcium gluconate should be added to the intravenous solution. The etiology, evaluation and treatment of hypocalcemia in neonates are discussed in detail separately. (See "Neonatal hypocalcemia", section on 'Management'.)

**Hypomagnesemia** — Neonatal hypomagnesemia is often associated with hypocalcemia, although it can occur alone. The treatment is 50 percent solution of magnesium sulfate given by intramuscular injection at 0.25 mL/kg or 125 mg/kg. The same dose can be repeated every 12 hours until normomagnesemia is achieved. (See "Neonatal hypocalcemia", section on 'Correction of hypomagnesemia'.)

**Pyridoxine or PLP responsive seizures** — Although inborn errors of metabolism are rare, seizures are a common manifestation of many of them, especially in the neonatal period. It is important to recognize such disorders early, since cofactor or vitamin supplementation and other disease-modifying therapies are available for some. (See "Etiology and prognosis of neonatal seizures", section on 'Inborn errors of metabolism'.)

In particular, pyridoxine-dependent epilepsy (PDE) due to antiquitin (ATQ) deficiency and the related disorder, pyridoxamine 5'-phosphate oxidase (PNPO) deficiency, are rare but treatable genetic causes of medically refractory neonatal seizures. The approach to recognition and treatment of PDE is summarized in the algorithm (algorithm 1). Sequential therapeutic trials of pyridoxine (100 mg IV injections, repeated every 5 to 15 minutes up to a maximum of 500 mg with continuous EEG monitoring, or 15-30 mg/kg/day orally divided t.i.d.) and pyridoxal 5'-phosphate (PLP, the active form of pyridoxine [vitamin B6]) should be given to neonates with seizures unresponsive to conventional anticonvulsants, particularly if the cause of the seizures is not known.

Trials should be performed with electroencephalographic and close cardiopulmonary monitoring, as there is a risk of apnea with pyridoxine, particularly when given IV. If there is no response to pyridoxine or PLP, folic acid (leucovorin, 2.5 mg IV) may be administered, since some cases of antiquitin deficiency respond better to folic acid than pyridoxine [2].

The results of one case series caution that EEG-response alone to pyridoxine IV does not definitively identify (nor does lack of initial response exclude) PDE [3,4]. Individuals with pyridoxine or folic acid responsive seizures should undergo further biochemical evaluation including measurement of urine alpha-aminoisocaproic semialdehyde (alpha-AASA) and/or plasma pipicolic acid [5]. Elevation of alpha-AASA is informative in both treated and untreated states [6,7]. Mutation analysis of the ALDH7A1 gene is recommended in patients with abnormal biochemical screening and/or clear evidence of pyridoxine or folic acid responsiveness [6,7]. PNPO mutation analysis is suggested in patients with either pyridoxine or PLP-responsive seizures who have normal alpha-AASA levels.

Patients with antiquitin deficiency should receive chronic supplementation with pyridoxine and/or folic acid and may also benefit from a lysine-restricted diet supplemented with lysine-free amino acid formula [5,8-10]. Long-term treatment doses of pyridoxine vary between 15 and 30 mg/kg/day for infants [5]. Some commercially available lysine-free formulas are also free of tryptophan, in which case tryptophan should be supplemented. Long-term treatment with high doses of pyridoxine can result in peripheral neuropathy. Infants with PNPO deficiency should receive chronic oral PLP supplementation [5].

**Biotinidase deficiency** — Biotinidase deficiency due to mutations in the biotinidase gene may result in medically refractory neonatal seizures that are responsive to oral biotin supplementation. In states where
biotinidase enzyme activity is not included in the newborn screening panel, a trial of biotin may be considered in addition to pyridoxine, PLP, and/or folic acid (algorithm 1).

ANTISEIZURE DRUG THERAPY — The use of antiepileptic drug therapy for neonates with seizures will be reviewed. Initiating therapy, selecting appropriate agents, and stopping or continuing therapy are the main decisions involved. There are no evidence-based or broadly-accepted guidelines for medical management of neonatal seizures, and the approach below is based on clinical experience, observational studies, and a limited number of randomized trials [11,12].

Decision to institute drug therapy — After initial management of airway and cardiovascular support and the identification and institution of etiologic-specific therapy, the next decision is whether to initiate antiepileptic drug therapy. Factors that must be considered include seizure duration and severity as well as seizure etiology. For example, neonates with brief seizures due to transient, reversible electrolyte or glucose abnormalities do not require immediate treatment with antiepileptic drugs, while seizures due to other etiologies, particularly if they are prolonged, are properly treated with antiepileptic drugs.

A common approach has been to treat clinically-evident seizures, with or without EEG confirmation of the diagnosis. The approach is problematic because it does not accurately or adequately treat true seizures; infants whose clinical events have no EEG correlate (ie, are not truly seizures) will be exposed unnecessarily to potentially harmful medication, while neonates with clinically-subtle or truly subclinical seizures will be insufficiently treated [13]. EEG is therefore critical in the diagnosis and treatment of neonatal seizures. (See "Clinical features, evaluation, and diagnosis of neonatal seizures", section on 'Diagnosis'.)

Drug selection — An approach to first-line and second-line antiepileptic drug selection and dosing based on seizure frequency and individual patient characteristics is summarized in the algorithm (algorithm 2). The traditional strategy is to acutely treat seizures with a medication that can be subsequently given as maintenance therapy.

First-line therapy — Phenytoin has long been used as first-line therapy for seizures in neonates, and international survey data indicate that it remains the most commonly used agent in this setting [14-16]. The next most frequently used first-line agent is fosphenytoin. Enteral absorption of phenytoin is limited for newborns, however, and maintenance dosing of phenytoin is very challenging. Neither agent appears to be more effective than the other and neither is completely effective.

This was demonstrated in the only randomized trial of first-line therapy in neonates with seizures, in which 59 infants with EEG-confirmed seizures were randomized to receive either phenobarbital or phenytoin [17]. Seizures were controlled by first-line therapy in less than half of the infants (43 versus 45 percent), and seizure severity was a better predictor of treatment success than the assigned treatment.

The initial dose of phenobarbital is 20 to 30 mg/kg IV, followed by a maintenance dose of 4 to 6 mg/kg per day in two divided doses. If seizures do not resolve after the first loading dose, repeat boluses of 10 to 20 mg/kg should be given with a goal phenobarbital level of approximately 50 micrograms/mL or a total 24-hour dose of 50 mg/kg (algorithm 2). The use of both phenobarbital and phenytoin in the neonate requires additional knowledge concerning their pharmacologic characteristics [18-22]. (See 'Phenobarbital' below and 'Phenytoin' below.)

Acute treatment can also be initiated with a short-acting benzodiazepine, particularly if a delay is likely prior to availability and administration of a longer-acting medication. Other antiepileptic drugs that can be given intravenously, such as levetiracetam, are being increasingly used for treatment of neonatal seizures but are not yet considered evidence-based first-line agents. (See 'Refractory seizures' below.)

Endpoint of acute therapy — The decision to initiate acute therapy should come with a predefined, expected end point of treatment. Experts advocate the treatment of both clinical and subclinical electrographic seizures, since the only difference between the two types may be their cortical distribution.
It should be noted that neonates with electroclinical seizures may have electroclinical dissociation, or uncoupling, after treatment initiation. In this scenario, the clinical signs vanish but the electrographic seizures persist [23,24]. Ideal management therefore includes EEG confirmation of treatment response, which is defined most precisely by resolution of electrographic seizures.

The role of continuous EEG monitoring in directing treatment is highlighted in a guideline from the American Clinical Neuropysiology Society [25]. Since most abnormal movements are not neonatal seizures and most neonatal seizures are subclinical, using EEG to guide treatment of neonatal seizures limits unnecessary exposure to antiseizure drugs for those whose events are not seizures and avoids undertreatment of those with subtle or subclinical seizures. However, it is acknowledged that no clinical data prove definitively that this approach improves long-term outcomes.

Current practice consists of acute antiseizure drug therapy until seizures are controlled, with the first medication given in sufficient doses to achieve seizure-freedom and/or serum levels in the high therapeutic range and/or the maximum tolerated dose. This is followed by additional medications, titrated to effect. (See 'Refractory seizures' below.)

In some cases, seizures cannot be completely controlled with standard treatment and the risks of adverse effects must be weighed against the potential benefit of complete seizure control. The etiology of the seizures is a major factor in this level of decision-making (eg, a target of complete seizure control may be appropriate for a neonate with hypoxic ischemic encephalopathy, but might be unreasonable for a newborn with lissencephaly).

**Refractory seizures** — Neonatal seizures refractory to phenobarbital often respond poorly to second-line antiseizure drugs. This observation is illustrated by results of a small trial that randomly assigned neonates whose seizures failed to respond to phenobarbital (11 of 22) to second line therapy with either clonazepam (n=3), midazolam (n=3), or lidocaine (n=5) [26]. No response was seen in the neonates treated with clonazepam or midazolam. Three of five responded to lidocaine; two neonates became seizure-free with 4 mg/kg per hour of lidocaine, and one had an 80 percent reduction in seizure burden. All of the 11 neonates whose seizures failed to respond to phenobarbital had a poor neurodevelopmental outcome at one year.

Choice of a second-line drug in infants who continue to seize despite first-line therapy must be individualized, as efficacy data are derived primarily from case series and not from randomized trials. The most commonly used drugs in this setting are phenytoin/fosphenytoin, levetiracetam, lidocaine, and midazolam. Factors to consider when selecting an agent include seizure severity, the side effect profile of the drug, respiratory and cardiovascular stability of the patient, and the presence of cardiac, renal, or hepatic dysfunction (algorithm 2). Suggested dosing is provided in the algorithm and discussed in more detail below. (See 'Dosing considerations in neonates' below.)

Newer anticonvulsants are increasingly prescribed for neonatal seizures, despite the fact that this is an off-label indication [27,28]. This trend has been driven by incomplete efficacy of more standard agents and concerns about their potential neurotoxicity. However, there is little supporting evidence, and none from randomized controlled trials, that support a greater efficacy and lower adverse event rate with these agents in neonates. The published literature is limited by the lack of standardized medication dosing, variable timing of administration of the newer anticonvulsants, limited EEG monitoring to confirm diagnosis and treatment response, and absence of a placebo arm.

Levetiracetam in particular has been used with increasing frequency, likely due to its readily available intravenous formulation and favorable side effect profile among older children and adults. It can be a good option in neonates with cardiac or liver dysfunction. Additionally, levetiracetam does not appear to enhance neuronal apoptosis in the developing brain [29,30] and might have neuroprotective effects [31]. Despite these encouraging observations, the pharmacokinetic and safety profile, and even the efficacy of levetiracetam for neonatal seizure treatment are not fully understood and may differ from older children and adults [32-35]. (See 'Levetiracetam' below.)
Intravenous **lidocaine** is an effective agent for neonatal seizures in selected patients, with reported response rates ranging from 60 to 90 percent in mostly small, single-center studies [26,36-41]. In cases of continued, EEG-confirmed status epilepticus despite high doses of **phenobarbital**, lidocaine may be the preferred second-line drug, provided there are no contraindications to its use (eg, congenital heart disease, pretreatment with fosphenytoin/phenytoin) (algorithm 2). In a retrospective study of over 400 full-term (n=319) and preterm (n=94) infants with neonatal seizures diagnosed by amplitude-integrated EEG who received lidocaine as a second or third-line agent, the overall response rate was 71 percent [37]. Response rates were higher in full term than preterm infants (76 versus 55 percent). In full term infants, lidocaine was associated with a higher response rate compared with **midazolam** in the second-line setting (21 versus 13 percent). Dosing considerations are reviewed below. (See 'Lidocaine' below.)

Continuous infusion of **midazolam** is also an option in neonates with status epilepticus, provided a secure airway has been established. A nonrandomized retrospective study found that midazolam was rapidly effective in 13 neonates (10 with status epilepticus [SE]) who had electrographic seizures refractory to **phenobarbital** and **phenytoin** [42]. Midazolam was given as a bolus of 0.15 mg/kg followed by continuous infusion beginning at 1 mcg/kg per minute and increasing by 0.5 to 1 mcg/kg per minute every two minutes to electrographic seizure control or to a maximum of 18 mcg/kg per minute. Neonates with SE were given a repeat bolus of midazolam 0.10 to 0.15 mg/kg if SE persisted 15 to 30 minutes after the initial bolus. While these results appear promising, randomized clinical trial data are needed to confirm that midazolam is effective for neonatal seizures, especially since midazolam was ineffective in a small randomized clinical trial [26].

Pyridoxine and pyridoxal-5'-phosphate (PLP) trials should also be considered in neonates with seizures that are refractory to conventional antiseizure drugs, particularly if the cause of the seizures is not known (algorithm 1). (See 'Pyridoxine or PLP responsive seizures' above.)

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**Dosing considerations in neonates**

**Phenobarbital** — **Phenobarbital** is eliminated by the liver and kidney; thus, infants with impaired hepatic or renal function, such as those with HIE, will have a reduced rate of elimination and potential for toxicity with standard dosing. Although therapeutic hypothermia treatment may reduce clearance of phenobarbital marginally, no a priori change in loading or initial maintenance dosing is required [22]. The half-life of phenobarbital is greater in premature compared with term infants, and longer in the first month of life compared with older ages in term infants.

Thus, standard **phenobarbital** dosing in premature infants has the potential for higher serum levels and resultant toxicity. As the infant becomes older, identical daily maintenance doses may result in lower serum levels and create the potential for breakthrough seizures with no other change in the infant's clinical condition. Overall, monitoring trends of serum levels rather than day-to-day fluctuations are more useful in management of phenobarbital therapy [43-45].

A growing body of research on neuronal chloride homeostasis explains, at least in part, why **phenobarbital** is often incompletely effective in newborns [46,47]. The neuronal chloride gradient in mature neurons is maintained by KCC2 co-transporters, which decrease resting intracellular chloride concentrations. When gamma-aminobutyric acid (GABA) receptors are activated (eg, by medications such as phenobarbital), the cell is hyperpolarized. In immature neurons, KCC2 is underexpressed and NKCC1 co-transporters are prevalent. The result is a reversed neuronal chloride gradient, such that activation of GABA receptors can paradoxically depolarize the neuron.

These observations have led to interest in **bumetanide** as a potential adjuvant treatment for neonatal seizures. Bumetanide is a diuretic that acts on NKCC1 channels and could, in theory, be used as rationale polytherapy in combination with **phenobarbital**. In animal models [48,49] and a human case study [50], co-treatment with bumetanide and phenobarbital appeared to enhance treatment effects. However, a multicenter phase II/III trial of bumetanide combined with phenobarbital was closed early due to limited efficacy and
important safety concerns, including 3 of 11 surviving infants with significant hearing impairment [51]. Another clinical trial is underway (NCT00830531). Until further data are available, use ofbumetanide as an adjuvant treatment for neonatal seizures is not recommended.

Phenytoin — The prodrug fosphenytoin is the preferred formulation of phenytoin for rapid intravenous loading based on a lower risk of side effects, including a reduced risk oflocal irritation at the site of infusion. Hypotension and cardiac arrhythmias remain a risk, however, and cardiac monitoring is required. The typical loading dose of fosphenytoin is 20 mg phenytoin equivalents (PE) per kg, at a rate of 3 mg PE/kg/minute. (See "Management of convulsive status epilepticus in children", section on 'Fosphenytoin and phenytoin'.)

Pharmacologic characteristics of phenytoin include its nonlinear pharmacokinetics, variable rate ofhepatic metabolism, decreased elimination rates during the first weeks of life, and variable bioavailability of the drug with various generic preparations [52,53]. In addition, a redistribution of phenytoin results in a drop in brain concentrations after the first dose. Finally, phenytoin has poor oral bioavailability in infants. Thus, phenytoin use requires individualization of dosing after initiation of therapy and should generally be avoided as a chronic maintenance medication for newborns.

Levetiracetam — The pharmacokinetic and safety profile of levetiracetam for neonatal seizure treatment is not fully understood and may differ from older children and adults [32-35]. It follows that the doses of levetiracetam reported in the literature are very broad (10 to 60 mg/kg/day) [32,33,54]. We suggest a loading dose of 40 mg/kg IV, followed by a maintenance dose of 40-60 mg/kg/day IV in two or three divided doses [34,35]. Ongoing clinical trials (eg, NCT01720667) may soon address some of these important unknown factors [26,42].

Lidocaine — Lidocaine is typically administered as an initial bolus dose (2 mg/kg over 10 minutes), followed by a continuous infusion of 7 mg/kg/hour for 4 hours and decreasing the dose by 50 percent every 12 hours for the next 24 hours (ie, 3.5 mg/kg/hour for 12 hours, then 1.75 mg/kg/hour for 12 hours) (table 2) [37]. In order to minimize the risk of iatrogenic arrhythmia, the maximum lidocaine infusion time is 48 hours, but the most recent publications indicate that less than 30 hours is preferable [37,55].

Intravenous lidocaine administration may be arrhythmogenic and requires continuous noninvasive monitoring of ECG, heart rate, and blood pressure. Additionally, lidocaine is contraindicated in infants with congenital heart disease and in those who have already received phenytoin/fosphenytoin, due to the heightened risk for arrhythmia [56].

The continuous infusion must be adjusted for neonates treated with therapeutic hypothermia, as hypothermia decreases lidocaine clearance [37]. In this setting, and in infants with low body weight (<2.5 kg), slightly lower doses of lidocaine should be used, although optimal approach has not been established. Proposed dosing of lidocaine under both normothermic and hypothermic conditions is presented in the table (table 2) [37].

Midazolam — Midazolam it typically given as a bolus of 0.15 mg/kg followed by continuous infusion beginning at 1 mcg/kg per minute and titrated upward to effect [42]. Aside from sedation and the need for assisted ventilation, midazolam is associated with minimal cardiovascular effects.

Duration of therapy — There are no well-defined criteria to determine which neonates require chronic anticonvulsant therapy after acute neonatal seizures are controlled or the duration of such treatment.

Since acute symptomatic seizures usually resolve within two to three days, and most often do not recur, there has been an increasing trend toward early discontinuation of antiseizure drugs, before or shortly after discharge from the hospital [57]. However, no study has compared long-term effects or outcomes of chronic versus short-term antiseizure drug therapy, and there is wide variability in practice [58]. In contrast with acute symptomatic seizures, newborns with epilepsy will have ongoing risk for recurrent seizures after the neonatal period and should be maintained on antiseizure medication.
When chronic therapy is considered, maintenance doses of phenobarbital are typically given (3 to 6 mg/kg per day), and serum levels are monitored. Reported schedules for chronic anticonvulsant treatment range from one week up to 12 months after the last seizure [59,60].

Weaning the medication is often done after the recording of an EEG that demonstrates no seizures and a normalizing inter-ictal background. Decisions about discontinuing medication should take into consideration the seizure etiology (eg, an infant with HIE may not require ongoing therapy while a child with a malformation of cortical development is likely to require ongoing therapy) and the seizure severity. If seizures were difficult to control, then reducing the number of chronic medications to one or two drugs is reasonable in the neonatal period, with subsequent tapering during infancy if the seizures do not recur.

SUMMARY AND RECOMMENDATIONS

- In the neonate, seizures may indicate the presence of a potentially treatable etiology and should prompt an immediate evaluation to determine cause and to institute etiology-specific therapy. (See "Clinical features, evaluation, and diagnosis of neonatal seizures", section on 'Etiologic evaluation'.)

- Treatment of the underlying cause of neonatal seizures (for metabolic disorders, central nervous system or systemic infection, or hypoxic ischemic encephalopathy) is critical since it may prevent further brain injury. Also, neonatal seizures may not be effectively controlled with antiseizure drugs unless their underlying cause is treated. (See 'Etiologic therapy' above.)

- Factors that must be considered in deciding upon anticonvulsant therapy include seizure etiology, seizure duration, and seizure severity. (See 'Decision to institute drug therapy' above.)

- When a decision is made to initiate antiseizure drug therapy, we suggest first-line treatment with phenobarbital rather than phenytoin (Grade 2C). Phenobarbital and phenytoin were equally effective in a randomized trial, but maintenance oral dosing of phenytoin in the newborn is very challenging. Dosing schedules are listed in the figure (algorithm 2). (See 'Drug selection' above and 'First-line therapy' above.)

- Neonatal seizures refractory to phenobarbital often respond poorly to second-line antiseizure drugs. The most commonly used drugs in this setting are phenytoin/fosphenytoin, levetiracetam, lidocaine, and midazolam. Factors to consider when selecting an agent include seizure severity, the side effect profile of the drug, respiratory and cardiovascular stability of the patient, and the presence of cardiac, renal, or hepatic dysfunction (algorithm 2). (See 'Refractory seizures' above.)

- Pyridoxine (100 mg IV in repeated doses with continuous EEG monitoring or 15-30 mg/kg/day orally divided t.i.d.) and pyridoxal 5'-phosphate (PLP, 60 mg/kg/day orally divided t.i.d.) should be given sequentially to neonates with seizures unresponsive to conventional anticonvulsants, particularly if the cause of the seizures is unknown (algorithm 1). If there is no response to pyridoxine or PLP, folinic acid (leucovorin, 2.5 mg IV) may be administered for possible folinic acid responsive seizures. (See 'Pyridoxine or PLP responsive seizures' above.)

- Current best practice consists of continuing acute medication therapy until all seizures (clinical and EEG seizures) are controlled, with the first medication given in doses sufficient to achieve serum levels in the high therapeutic range or to the maximum tolerated dose before additional medications are added, unless the risks of treatment outweigh the potential benefit. (See 'Endpoint of acute therapy' above.)

- There are no well-defined criteria that predict which neonates will require chronic anticonvulsant therapy. Anticonvulsants are withdrawn on a case-by-case basis, with decision-making guided by seizure etiology, difficulty in controlling the initial seizures, and expected prognosis of the infant. (See 'Duration of therapy' above.)

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### Common etiologies of neonatal seizures

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<td>Hypoxic-ischemic encephalopathy</td>
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Graphic 73867 Version 11.0
Diagnostic and treatment algorithm for cofactor-responsive neonatal seizures

Neonatal seizures unresponsive to conventional antiepileptic drugs

- Pyridoxine trial* (100 mg IV or 15-30 mg/kg/day orally divided three times per day x 2-3 days)

- No

- Yes

  - Clinical or EEG response?

    - Yes

    - Test urine alpha-AASA and/or plasma piperolic acid

    - Normal

    - Elevated

    - PLP trial (60 mg/kg/day orally divided three times per day x 2-3 days)

    - Clinical or EEG response?

    - Yes

    - Confirm with PNPO mutational analysis

    - Possible PNPO deficiency

    - No

    - Folinic acid trial (leucovorin 2.5 mg IV)

    - Clinical or EEG response?

    - Yes

    - Consider biotin trialΔ (10 mg orally)

    - No

    - Confirm with ALDH7A1 mutational analysis

    - Possible antithin deficiency

Alpha-AASA: alpha-aminoacidipic semialdehyde; EEG: electroencephalography; PLP: pyridoxal 5'-phosphate; PNPO: pyridoxamine 5'-phosphate oxidase.

* Risk of apnea, particularly when pyridoxine is given IV.

† Repeated every 5 to 15 minutes with continuous EEG monitoring.

Δ If biotinidase deficiency has not been excluded by newborn screen.

ο alpha-AASA is also elevated in molybdenum cofactor/sulfite oxidase deficiency.

Graphic 97078 Version 3.0
Antiseizure drug therapy for neonatal seizures

Phenobarbital loading dose
20-30 mg/kg IV

Seizures resolve?

Yes

• Begin maintenance phenobarbital 12 hours after loading (4-6 mg/kg/day IV or oral in 2 divided doses)
• Continue EEG monitoring until patient is seizure-free for 24 hours

Repeat 10-20 mg/kg IV
bring phenobarbital level or maximum of 50 mg/kg
• Begin or continue EEG monitoring

Ongoing seizures*

Frequent seizures, including status epilepticus

Cardiac abnormalities and/or cardiovascular instability?

Yes

Has patient already received phenytoin/fosphenytoin?

• Midazolam 0.15 mg/kg IV bolus, then 0.06 mg/kg/hour infusion, titrating upward to effect (maximum 0.4 mg/kg/hour). Wean gradually after 24 hours of seizure freedom.
• Levetiracetam 40 mg/kg IV bolus, then 40-60 mg/kg/day IV or oral in 2 or 3 divided doses.

No

Yes

• Lidocaine infusion 1.2 mg/kg bolus, then 7 mg/kg/hour for 4 hours, then 3.5 mg/kg/hour for 12 hours, then 1.75 mg/kg/hour for 12 hours (28 hours total); continue phenobarbital
• Levetiracetam 40 mg/kg IV bolus, then 40-60 mg/kg/day IV or oral in 2 or 3 divided doses
• Fosphenytoin begin (5-10 mg/kg IV bolus), reassess (target 1-2 mg/kg/hour)

Cardiac abnormalities

EEG: electroencephalography; IV: intravenous; PE: phenytoin equivalents.

* There are limited data on comparative efficacy and best dosing strategies for second-line therapies.

† Low body weight (<2.5 kg) and newborns undergoing hypothermia treatment are at risk for accumulation of lidocaine. Adjust concurrent therapeutic hypothermia[1]. Refer to accompanying text and separate table of lidocaine dosing for neonatal seizures.

Reference:


Graphic 100337 Version 5.0
## Lidocaine dosing for neonatal seizures

<table>
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<tr>
<th>Weight (kg)</th>
<th>Bolus (mg/kg) given over 10 minutes</th>
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<tbody>
<tr>
<td>&lt;2.5 kg</td>
<td>2</td>
<td>6 mg/kg/h x 4 hours</td>
<td>3 mg/kg/h x 12 hours</td>
<td>1.5 mg/kg/h x 12 hours</td>
<td>28</td>
<td>80</td>
</tr>
<tr>
<td>≥2.5 kg</td>
<td>2</td>
<td>7 mg/kg/h x 4 hours</td>
<td>3.5 mg/kg/h x 12 hours</td>
<td>1.75 mg/kg/h x 12 hours</td>
<td>28</td>
<td>93</td>
</tr>
</tbody>
</table>

### Therapeutic hypothermia

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Bolus (mg/kg) given over 10 minutes</th>
<th>1st infusion</th>
<th>2nd infusion</th>
<th>3rd infusion</th>
<th>Total infusion duration (hours)</th>
<th>Total dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.5 kg</td>
<td>2</td>
<td>6 mg/kg/h x 3.5 hours</td>
<td>3 mg/kg/h x 12 hours</td>
<td>1.5 mg/kg/h x 12 hours</td>
<td>27.5</td>
<td>77</td>
</tr>
<tr>
<td>≥2.5 kg</td>
<td>2</td>
<td>7 mg/kg/h x 3.5 hours</td>
<td>3.5 mg/kg/h x 12 hours</td>
<td>1.75 mg/kg/h x 12 hours</td>
<td>27.5</td>
<td>89.5</td>
</tr>
</tbody>
</table>

This table is provided as an example of a lidocaine dosing protocol that includes dose adjustments for infants with low body weight and those undergoing therapeutic hypothermia who are at increased risk of drug accumulation; it was used in a cohort of infants who received lidocaine as a second- or third-line antiseizure drug for neonatal seizures unresponsive to first-line therapy (eg, phenobarbital).

The optimal dosing regimen in these infants is unknown. Intravenous lidocaine administration may be arrhythmogenic and requires continuous noninvasive monitoring of ECG, heart rate, and blood pressure; it is contraindicated in congenital heart disease or in infants pretreated with phenytoin/fosphenytoin.

**ECG:** electrocardiography.


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