Practical Approaches to The Treatment of Neonatal Seizures

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Abstract

Purpose of review: This paper critically reviews the current literature and evidence on diagnosis, classification, clinical approach, and management of neonatal seizures. A step wise approach for the treatment of neonatal seizures is presented. *Recent findings:* In a recent randomized controlled trial comparing phenobarbital to levetiracetam as a first-choice anti-seizure medication with primary outcome seizure free for 24 hours, the former was found superior (80% vs 28%, $p<0.001$). *Summary*: Neonatal seizures require immediate diagnostic and therapeutic interventions. Phenobarbital is the first line anti-seizure drug for neonatal seizures, but there is little evidence regarding second line pharmacotherapy. There is a need for more randomized controlled trials for the use of other existing anti-seizure drugs, yet unlicensed in neonates, and the development of new drugs specifically for neonates.

Introduction

Seizures are the most frequent neurological emergency in the neonatal period, occurring in 1.5 to 3 per 1,000 term live births and 10 to 130 per 1,000 preterm live births (1). Neonatal seizures are mostly acute provoked, attributed to an underlying brain insult, such as hypoxic ischemic encephalopathy (HIE). Diagnosis cannot be based on clinical observation alone, since there is poor association between clinical observation and EEG (2). Therefore, the gold standard for diagnosis and confirmation of neonatal seizures is multi-channel video EEG, which due to limited resources is only available in few neonatal units. To avoid under- and over-diagnosis of neonatal seizures and thus correctly guide treatment, one must aim to correctly detect and classify neonatal seizures, whilst considering underlying causes and effects of seizures.

The American Clinical Neurophysiology Society defines a neonatal seizure as ‘a sudden, abnormal electrographic event, characterized by a repetitive and evolving pattern of discharges with a minimum 2 μV peak-to-peak voltage and duration of at least 10 seconds. The term ’evolving’ is defined as an unequivocal evolution in frequency, voltage, morphology, or location (3). This definition does not preclude any clinical component. Seizure burden is defined as ictal electrographic activity in a set period of EEG recording and expressed as summed electrographic seizure in seconds per hour (4). High seizure burden is associated with poor outcome (5-7). There is no consensus on a definition for neonatal status epilepticus. For the purposes of this review, a neonate is considered in status epilepticus if there is continuous seizure activity for ≥30 minutes or a summed electrographic seizures burden of ≥30 min in any one hour period (hourly seizure burden range: ≥ 50%) (8, 9).

Neonatal seizures are associated with 7% to 33% mortality (1). Up to 40% to 60% of surviving neonates will have a form of long term sequelae, such as cerebral palsy, learning difficulties, and/or epilepsy (6). Whilst the underlying cause of neonatal seizures may

determine rate of mortality and long-term neurodevelopmental outcome, there is growing evidence that neonatal seizures and seizure burden are associated with poor outcome independent of the severity of the underlying cause, especially in cases related to perinatal asphyxia (7, 10-12). A study looking into neonates with HIE prior to and after the era of therapeutic hypothermia, identified that an abnormal outcome at 24 to 48 months of age was associated to seizure burden rather than severity of HIE or treatment with hypothermia. A neonate would have nine times more chance of an abnormal neurodevelopmental outcome if the seizure burden as >40 minutes per hour and eight times more if the seizure burden was >13 minutes per hour. The incidence of an abnormal neurodevelopmental outcome would (11). The use of anti-seizure medications in neonates may be non-efficacious and even harmful for the developing brain, as shown in animal studies (13-15). It is, therefore, essential that the diagnostic approach and overall clinical management for neonatal seizures is optimized.

Diagnostic evaluation

Etiology

Neonatal seizures may present at any point in the first 28 days with highest incidence in the first week of life (16, 17). In most cases, neonatal seizures are acute provoked events secondary to an acute insult, such as HIE (35-45%), cerebral infarction or intracranial hemorrhage (20-30%), infection (5-20%), and/or electrolyte imbalances (16, 18-21). The regular use of genetic testing, in recent years has enabled the detection of IEM and neonatal onset genetic epilepsies early in the life (20), leading to an increased appreciation of such disorders; responsible for approximately up to 13% of cases (see **Fig. 1**).

Clinical manifestation

Neonatal seizures are often subtle and difficult to discern from spontaneous movements or non-epileptic, paroxysmal events, such as jitteriness and myoclonus. Multiple studies have highlighted the difficulty in the clinical assessment of neonatal seizures (2, 22-24). Murray et

al., showed that only one third of term neonates with EEG-confirmed seizures had associated clinical manifestations, of which only one third was accurately detected by experienced neonatal staff (24). Malone et al., demonstrated a poor interobserver agreement amongst neonatal health care professionals in discriminating between clinical seizures and non-epileptiform paroxysmal events (2).

Neonates who are at elevated risk of seizures, are often critically ill, sedated and not infrequently muscle relaxed, thus explaining the high incidence of electrographic-only seizures (20, 22, 25-31). In addition, it is recognized that some anti-seizure medications (particularly phenobarbital and phenytoin) can cause 'uncoupling'; a phenomenon which describes the fact that electrographic seizures persist despite the suppression of the clinical manifestation. There is also some evidence that therapeutic hypothermia, a gold standard treatment in moderate to severe forms of HIE (32), despite overall reducing seizure burden, may contribute to uncoupling (30, 33).

Role of EEG

As the clinical diagnosis of neonatal seizures is not dependable, neonates at risk or with clinical suspicion of seizures, should undergo at least one routine video EEG, or preferably EEG monitoring. Continuous video EEG (cEEG) is considered the gold standard for the detection of seizures. It also allows detection, quantification (including the calculation of seizure burden) and classification of neonatal seizures. The latter also aids recognition of status epilepticus and monitoring treatment success (34, 35).

Certain features and EEG patterns may help determine the underlying etiology. Bursts of monophasic negative activity, known as comb-like activity, in the central and centro-parietal regions have been described in maple syrup urine disease (MSUD) (36). Unilateral amplitude suppression together with focal clonic electro-clinical seizures are highly associated with

perinatal stroke (37). Alternating burst suppression pattern during sleep with a multifocal attenuation pattern during wakefulness, together with sequential seizures (focal, tonic seizures with head deviation, sometimes followed by asymmetrical clonic jerks, eye flickering, and tachypnea) have been described in neonatal epileptic encephalopathy due to variants of KCNQ2 (38).

Following a therapeutic intervention, EEG is used to monitor changes in the ongoing activity, seizure burden and seizure frequency, especially in cases of electrographic-only seizures or electroclinical dissociation. Additionally, these changes can aid prognostication in terms of mortality and morbidity. A recent comprehensive review of the literature has shown that burst suppression, low amplitude EEG or flat trace are the key features of the ongoing activity in neonates that determine neurodevelopmental outcome at 12 months of age (39).

Access to cEEG is limited in most countries (40). In most neonatal units this gap has been bridged by amplitude integrated EEG (aEEG) which can be easily applied by trained neonatal staff. One to two channels of EEG are displayed in a filtered and time-compressed manner. Although interpretation is quicker and easier, a high proportion of seizures may be missed (41), especially if seizures are of low amplitude or brief. Detection of seizure frequency can be increased by using two aEEG channels and adding the display of raw EEG channels (42).

Classification

A task force of the International League Against Epilepsy (ILAE) has recently published a new classification of neonatal seizures (43). In contrast to the previous neonatal classification, diagnosis is based on EEG or aEEG thus including both electrographic-only and electro-clinical seizures. The latter are divided in motor (clonic, tonic, myoclonic, epileptic spasms, and automatisms) non-motor, (autonomic seizures and behavioral arrest), sequential

seizures and unclassified. In contrast to the classification of seizures in adults or children, the classification is based on the most dominant element of the seizure and not necessarily the seizure onset. It is worth highlighting that in the motor seizures, the term 'subtle' seizures from Volpe's classification (44) is not used. The term 'sequential' seizure has been introduced as an extra type of motor seizure. This is characterized by a sequence of clinical features with no predominant manifestation, often with changing lateralization (43).

Classifying neonatal seizures is an important part of reaching to a diagnosis. For example, tonic seizures may be associated to underlying genetic disorders (45), sequential seizures have been described in specific neonatal onset familial and non-familial epilepsies, such as KCNQ2 and SCN2A (38, 46, 47) and focal clonic seizures have a strong association to perinatal stroke.

Other investigations

Figure 2 illustrates a series of investigations in establishing the underlying cause of neonatal seizures. Initial investigations can be performed at the cot-side and may lead to a treatable cause, such as hypoglycemia or an electrolyte disturbance. Second-line investigations are undertaken, in the instance of intractable seizures; not responding to first and/or second line treatment. If neonatal seizures are not responding to first line treatment, other underlying causes need to be excluded such as genetic epilepsies or IEM.

Treatment

Indications to treat

There is as yet no unified international consensus on when and how to treat neonatal seizures. The World Health Association (WHO) guideline on neonatal seizures was published in 2011 (48) and is currently being revised by an ILAE task force.

The current recommendation in a neonate at risk of seizures is to confirm seizure detection on EEG or aEEG prior to commencing treatment (48, 49). The Brighton collaboration has produced an algorithm, which defines distinct levels of diagnostic certainties according to availability of tests (21, 43). More specifically, when the assessment is entirely based on clinical evaluation, only focal clonic or focal tonic movements can be diagnosed with adequate certainty and considered 'probable' seizures. Clinical events such as motor automatisms (e.g., mouthing, eye flickering), autonomic changes and/or behavioral arrest are considered as 'possible seizures' and would warrant confirmation with EEG, particularly if they occur in isolation.

Clinically, it is recommended to commence treatment for neonatal seizures that are prolonged (longer than 1-2 minutes), and/or frequent (3 or more in one hour). However, if aEEG or video-EEG monitoring is available, it is ideally recommended to calculate the seizure burden and treat accordingly. The threshold for treatment does remain low based on a recent trial design by Soul et al., which recommends initiation of treatment for seizure burden >1 minute per hour (50). Practically, this suggests that one would not necessarily treat a single or multiple very brief seizures of a summed duration of < 60 seconds per hour. Where possible, EEG monitoring should continue for at least 24 hours after cessation of seizures to ensure treatment efficacy (4, 35).

Treatment options

Only a limited number of anti-seizure medications is used in the neonatal period (51). Phenobarbital is commonly used as a first line drug. Recently, off-label drugs, such as levetiracetam and topiramate have been increasingly used (52). Treatment for neonatal seizures varies across the globe but also within countries with little unified consensus. Therapeutic hypothermia is now used as standard of care in high income countries for neuroprotection in moderate and severe HIE. It has been shown to reduce seizure burden and reduce the risk of

later epilepsy (32, 33). Based on the authors' expertise and clinical experience, a proposed algorithm for the treatment of neonatal seizures can be seen in **figure 3** and the choices of treatment are described below.

First-line Pharmacotherapy: Phenobarbital

Phenobarbital is the most used first line anti-seizure drug in neonates, despite concerns regarding impaired longer-term neurodevelopment and apoptotic effects (14, 53, 54). A randomized controlled trial (23) and systematic reviews indicate that phenobarbital is efficacious in 50% of cases (48, 55, 56). However, a recent, multi-center, randomized, controlled trial cEEG monitoring evaluated the safety and efficacy of levetiracetam versus phenobarbital in near-term and term neonates with seizures and found a much better efficacy of the latter. After 24 hours there was 80% resolution of seizures (n=24/30) with phenobarbital versus 28% (n=15/53) with levetiracetam (57). These results differ from uncontrolled studies that have indicated good efficacy of levetiracetam and often better to the one of phenobarbital (58-60). Studies without EEG-confirmed seizures should not be considered as adequate for evaluation of drug efficacy (50).

In summary, phenobarbital is recommended as the first line drug of choice for neonatal seizures. Treatment should be started with a loading dose of 20 mg/kg. As it can cause electroclinical dissociation, EEG monitoring should be performed for at least 24 hours. If there is insufficient response or seizures reappear, the loading dose may be repeated at 20 mg/kg or in two divided doses 10 and 10 mg/kg (in the space of 1 to 2 hours) (maximum total loading dose 40mg/kg) (61). A multi-center study in the Netherlands also showed that the changes in phenobarbital levels did not alter significantly when given during therapeutic hypothermia, concluding that a total of 40 mg/kg can safely be administered prior to initiation of second line anti-seizure drugs (62). Close and continuous monitoring of vital signs is required. If the neonate is not intubated and ventilated, need for further respiratory support should be

considered especially if a second loading dose is likely to be needed. The recommended maintenance dose, if required, is 3 to 5 mg/kg/day in two divided doses according to response with regular monitoring of plasma drug levels (61).

Second line pharmacotherapy

If seizures persist despite adequate doses of first line treatment or reemerge, second line drugs should be given without delay, such as phenytoin, levetiracetam, benzodiazepines, and lidocaine. Of note, most anti-seizure drugs are used as off-license in neonates and only few studies have addressed superiority or inferiority of either drug. Until there is higher level evidence to support the use of specific medications, one should employ a practical approach considering different scenarios of neonatal seizures and aiming to minimize adverse events. At present, there is no evidence to support the choice of certain second-line pharmacotherapy in relation to potential underlying causes, other than in cases of suspected IEM or neonatal onset epilepsies.

Levetiracetam

Levetiracetam is a well-tolerated drug for neonates with a favorable pharmacokinetic profile, few adverse effects, and little interaction with other medications (63, 64). Unlike phenobarbital, it does not cause respiratory suppression and unlike phenytoin, it is not reported to cause any hemodynamic instabilities (59). Levetiracetam has been shown to be effective as second line pharmacotherapy in adults and pediatric patients with status epilepticus (65), however, in neonates treated with adequate doses of phenobarbital, add-on treatment with levetiracetam has not been equally effective (57). Animal studies have demonstrated a possible neuroprotective effect of levetiracetam (66, 67). In contrast, Griesmaier et al., found that levetiracetam induces neurotoxicity in the early phases of HIE, whereas this was not observed when the drug was administered during established therapeutic hypothermia (68). Another animal study comparing low (7 mg/kg) versus high dose (70 mg/kg) of levetiracetam in HIE,

showed that exposure to the high dose, alone or with hypothermia induced neuronal apoptosis, but this was not seen in lower doses (69).

Levetiracetam may be an ideal second-line treatment for seizures in neonates post cardiac surgery, neonates with observed or known cardiac arrhythmias and/or those with hemodynamic instability (e.g., on inotropes), where phenytoin is contraindicated. The variability in dosage for levetiracetam, in the literature, spans from 10 to 40 mg/kg for loading and from 10 to 80 mg/kg/day divided twice daily for maintenance (70, 71). The recommended loading dose is 40 mg/kg IV. A second dose of 20 mg/kg may be given in the same 24-hour period. The suggested maintenance dose is 30 to 60 mg/kg/day in three divided doses (58, 71).

Phenytoin

In many counties, phenytoin is the preferred second line drug. If the neonate exhibits a high seizure burden and/or is in status epilepticus, phenytoin has been shown to be efficacious as an add-on therapy after phenobarbital (23, 72, 73). In a recent pediatric open-label randomized trial in children with status epilepticus aged 6 months -18 years, levetiracetam and phenytoin were equally effective as second line treatment, neonatal seizures (65) but no data for neonatal status epilepticus exist and the findings of the NeoLev2 study are discouraging (57). As with phenobarbital it has been reported to produce similar levels of electroclinical dissociation, up to 58% (29), therefore cEEG monitoring is highly advised to exclude ongoing electrographic seizures. Adverse effects include irritation at infusion site, apnea, hemodynamic instability, cardiac arrhythmias. Hence, it is important to consider the neonate's respiratory and hemodynamic status as well as any previous history of cardiac arrhythmias. There are some indications from pediatric studies, that phenytoin during therapeutic hypothermia may decrease its metabolism (74) and consequently increase the risk of bradycardia (75); therefore extra precautions should be taken if given during therapeutic hypothermia. The recommended loading dose is 20 mg/kg over 20-minute and the recommended maintenance dose is 2.5-5

mgs/kg/day in 2 divided doses; regular monitoring plasma drug levels are necessary due to a narrow therapeutic window and the relationship between dose and serum phenytoin concentration is non-linear (61).

Third line pharmacotherapy

As a third line treatment option midazolam or lidocaine may be considered. This should be evaluated based on the clinical scenario, local pharmacy policies and clinical expertise, but also the choice of previous drugs as lidocaine is contraindicated in neonates which have received phenytoin.

Midazolam

Several studies have evaluated midazolam as a second- and third- line drug with variable efficacy (55, 76, 77). In studies using aEEG monitoring, midazolam has been reported up to 50% effective as a second line anti-seizure drug with its efficacy (78, 79). Midazolam is administered as a bolus of 150 to 200 micrograms/kg (over 10 minutes), followed by a continuous intravenous infusion at 60 micrograms/kg/hour, increased in steps of 60 micrograms/kg/hour every 15 minutes until seizure controlled (61). Higher doses (at a maximum infusion rate of 300 micrograms/kg/hour) may be considered in refractory seizures where some effect has been noted in reduction of seizure frequency and seizure burden (80). It is recommended to wean Midazolam gradually over a day or two.

Lidocaine

Lidocaine is used in some European countries as second- or third-line drug. There is some evidence that in refractory seizures in neonates with HIE, lidocaine is more effective than midazolam as a third-line drug (78, 81). The main concern is the narrow therapeutic window and the potential cardiac toxicity in the form of dysrhythmias, sinus bradycardia, and widening of the QRS complex. It is also reported to cause sino-atrial node suppression in combination

with other sodium channel blockers, such as phenytoin. Lidocaine is contraindicated in neonates with underlying cardiac conditions, hemodynamic instability, arrhythmias or having been on phenytoin in the last few days. A new dosing regimen has recently been published for preterm and term neonates (82). The recommended neonatal doses are the following: bolus of 2 mg/kg, over 10 minutes, followed by infusion at 6 mg/kg/hour for 6 hours and then reduced to 4 mg/kg/hour for 12 hours; then reduced to 2 mg/kg/hour for a further 12 hours (61). The dose needs to be adapted for preterm or small for gestational age neonates as well as for therapeutic hypothermia (83).

Considerations for channelopathies

It has been suggested that some neonates with seizures related to neonatal-onset genetic epilepsies respond well to sodium channel blockers such as phenytoin, carbamazepine, or lacosamide (84). Few studies have shown that oral carbamazepine is safe and effective at low does in neonates with self-limited (familial) neonatal epilepsy, KCNQ2 encephalopathy or SCN2A-related neonatal seizures (85-87). The dose is typically titrated to maintenance dosing of 10-20 mg/kg/day. However, no PK or safety studies have been conducted so far in this patient group. Intravenous phenytoin is preferable if the neonate is critically ill, or not tolerating oral feeds.

Considerations for inborn errors of metabolism

Acute metabolic disturbances like hypoglycemia, hypocalcemia or hyponatremia and inborn errors of metabolism (IEM) can be associated with neonatal seizures. Acute metabolic disturbances can easily be diagnosed by point of care techniques and treated. However, diagnosis of IEM still requires time consuming metabolic and genetic tests. Nevertheless, IEM presenting with neonatal encephalopathy and seizures may be treatable, thus making rapid recognition and initiation of treatment crucial.

Vitamin B6-dependent epilepsies comprise of genetically different disorders leading to a reduction of intracellular pyridoxal-5-phosphate and impaired amino acid and neurotransmitter metabolism (88). The most frequent genetic entities are Aldehyde Dehydrogenase 7A1 (ALDH7A1) deficiency, Pyridoxamine 5′- Phosphate Oxidase (PNPO) deficiency, and Pyridoxal Phosphate Binding Protein (PLPBP) deficiency. Neonates typically present with seizures, especially spasms and myoclonic seizures (43). Vitamin B6-dependent epilepsies may also present with fetal distress (89, 90). Other potentially treatable neonatal metabolic encephalopathies include biotinidase deficiency, molybdenum cofactor deficiency (MOCOD) type A, glucose transporter-1-deficiency (GLUT1D), urea cycle disorders, disorders of amino acid metabolism like MSUD, or organic acidurias.

In cases of neonatal seizures escalating to second line treatment, advice should be sought from the pediatric neurology and metabolic medicine teams. After the appropriate investigations (see **Fig. 2**) and advice, treatment with agents, such as pyridoxine (91), pyridoxal phosphate (PLP), biotin, and/or folinic acid may be considered. A trial of pyridoxine and PLP should be considered in all neonates with seizures not explained otherwise, and not responding to first line pharmacotherapy (92). The administration of intravenous pyridoxine is recommended at 100 mg IV or orally once a day, and should be continued for at least 3 days at 30 mg/kg/day in two divided doses (61). Its use in neonates has been associated with respiratory failure, when first administered, and, therefore, the neonate should be appropriately stabilized and monitored. Ideally, there should be cEEG monitoring during its administration to monitor response to treatment. Long term use of pyridoxine is associated with peripheral neuropathy and annual nerve conduction studies are required. If seizures persist, PLP should be considered as an alternative to pyridoxine. The use of PLP is recommended at 30 to 60 mg/kg/day in four to six divided doses (61). This is associated with raised liver enzymes which can be seen acutely

with high doses. It has also been associated with liver fibrosis and cirrhosis in relation to its long-term use (91, 93) and regular liver ultrasound scans are required.

Other drugs

Topiramate has been used off-label as anti-seizure medication in a few retrospective case review studies but not in any prospective studies or randomized controlled trials to provide evidence of its potential efficacy in neonates (94, 95). Its use is associated with significant adverse effects such as feeding difficulties, metabolic acidosis (52) and the development of necrotizing enterocolitis in preterm and near term neonates (96). In animal studies, bumetanide has been reported to enhance phenobarbital's efficacy on seizure freedom (97, 98), however, an open-label trial aiming to define dosage and feasibility was discontinued due to its association to a high incidence of hearing loss in neonates (99). A second randomized controlled trial with a single dose of bumetanide suggested possible short-lived efficacy, but there is no evidence that seizure control would be sustained. Without further safety studies bumetanide should not be used neonates as an anti-seizure medication (100). At present, there is no relevant safety data for neonates for these or other drugs, such as sodium valproate, paraldehyde and brivaracetam (although for the latter there is an ongoing study evaluating safety and efficacy).

Maintenance treatment

There is no evidence that continuing pharmacotherapy reduces the risk of subsequent epilepsy or improves long term neurodevelopmental outcome (101-103). In neonates with acute provoked seizures which responded well to first- or second-line treatment, pharmacotherapy should be discontinued before discharge from the neonatal unit. If the neonate is on more than one anti-seizure drugs, it is advisable to stop one drug at a time and repeat a standard video-EEG after all treatment has been discontinued. However, if seizures continue for over 7 days, despite treatment, and/or there is indication for early onset epilepsy

(e.g., due to IEM, cortical malformation, genetic causes, early onset epilepsy syndrome), pharmacotherapy should be continued with advice from the pediatric neurology team. The underlying cause, evidence of changes on brain imaging, and the frequency and type of seizures will guide the decision as to whether a period of maintenance anti-seizure treatment is required.

Conclusions

Neonatal seizures remain a clinical conundrum due to the complexity of their presentation, availability of EEG resources, limited options, and low-certainty evidence for the use of anti-seizure medication in this age group. Despite several, recent, high-quality studies with EEG, little has changed in terms of treatment. Hence, there is urgent need for multicenter randomized controlled trials evaluating exciting and new anti-seizure drugs.

Acknowledgements

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References

1. Vasudevan C, Levene M. Epidemiology and aetiology of neonatal seizures. Semin Fetal Neonatal Med. 2013;18(4):185-91.

2. Malone A, Ryan CA, Fitzgerald A, Burgoyne L, Connolly S, Boylan GB. Interobserver agreement in neonatal seizure identification. Epilepsia. 2009;50(9):2097-101.

3. Tsuchida TN, Wusthoff CJ, Shellhaas RA, Abend NS, Hahn CD, Sullivan JE, 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.

4. Shellhaas RA, Chang T, Tsuchida T, Scher MS, Riviello JJ, Abend NS, et al. The American Clinical Neurophysiology Society's Guideline on Continuous Electroencephalography Monitoring in Neonates. J Clin Neurophysiol. 2011;28(6):611-7.

5. Pisani F, Copioli C, Di Gioia C, Turco E, Sisti L. Neonatal seizures: relation of ictal video-electroencephalography (EEG) findings with neurodevelopmental outcome. J Child Neurol. 2008;23(4):394-8.

6. Uria-Avellanal C, Marlow N, Rennie JM. Outcome following neonatal seizures. Semin Fetal Neonatal Med. 2013;18(4):224-32.

7. Shah DK, Wusthoff CJ, Clarke P, Wyatt JS, Ramaiah SM, Dias RJ, 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.

8. Pisani F, Cerminara C, Fusco C, Sisti L. Neonatal status epilepticus vs recurrent neonatal seizures: clinical findings and outcome. Neurology. 2007;69(23):2177-85.

9. Payne ET, Zhao XY, Frndova H, McBain K, Sharma R, Hutchison JS, et al. Seizure burden is independently associated with short term outcome in critically ill children. Brain. 2014;137(Pt 5):1429-38.

10. van Rooij LG, Toet MC, van Huffelen AC, Groenendaal F, Laan W, Zecic A, et al. Effect of treatment of subclinical neonatal seizures detected with aEEG: randomized, controlled trial. Pediatrics. 2010;125(2):e358-66.

11. Kharoshankaya L, Stevenson NJ, Livingstone V, Murray DM, Murphy BP, Ahearne CE, et al. Seizure burden and neurodevelopmental outcome in neonates with hypoxic-ischemic encephalopathy. Dev Med Child Neurol. 2016;58(12):1242-8.

12. Glass HC, Glidden D, Jeremy RJ, Barkovich AJ, Ferriero DM, Miller SP. Clinical Neonatal Seizures are Independently Associated with Outcome in Infants at Risk for Hypoxic-Ischemic Brain Injury. J Pediatr. 2009;155(3):318-23.

13. Bittigau P, Sifringer M, Genz K, Reith E, Pospischil D, Govindarajalu S, et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. Proc Natl Acad Sci U S A. 2002;99(23):15089-94.

14. Forcelli PA, Janssen MJ, Vicini S, Gale K. Neonatal exposure to antiepileptic drugs disrupts striatal synaptic development. Ann Neurol. 2012;72(3):363-72.

15. Kaushal S, Tamer Z, Opoku F, Forcelli PA. Anticonvulsant drug-induced cell death in the developing white matter of the rodent brain. Epilepsia. 2016;57(5):727-34.

16. Ronen GM, Penney S, Andrews W. The epidemiology of clinical neonatal seizures in Newfoundland: a population-based study. J Pediatr. 1999;134(1):71-5.

17. Glass HC, Pham TN, Danielsen B, Towner D, Glidden D, Wu YW. 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.

18. Weeke LC, Groenendaal F, Toet MC, Benders MJ, Nievelstein RA, van Rooij LG, et al. The aetiology of neonatal seizures and the diagnostic contribution of neonatal cerebral magnetic resonance imaging. Dev Med Child Neurol. 2015;57(3):248-56.

19. Janackova S, Boyd S, Yozawitz E, Tsuchida T, Lamblin MD, Gueden S, et al. Electroencephalographic characteristics of epileptic seizures in preterm neonates. Clin Neurophysiol. 2016;127(8):2721-7.

20. Glass HC, Shellhaas RA, Wusthoff CJ, Chang T, Abend NS, Chu CJ, et al. Contemporary Profile of Seizures in Neonates: A Prospective Cohort Study. J Pediatr. 2016;174:98-103 e1.

21. Pellegrin S, Munoz FM, Padula M, Heath PT, Meller L, Top K, et al. Neonatal seizures: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2019;37(52):7596-609.

22. Mizrahi EM, Kellaway P. Characterization and classification of neonatal seizures. Neurology. 1987;37(12):1837-44.

23. Painter MJ, Scher MS, Stein AD, Armatti S, Wang Z, Gardiner JC, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med. 1999;341(7):485-9.

24. Murray DM, Boylan GB, Ali I, Ryan CA, Murphy BP, Connolly S. 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.

25. Clancy RR, Legido A, Lewis D. Occult neonatal seizures. Epilepsia. 1988;29(3):256-61.

26. Biagioni E, Ferrari F, Boldrini A, Roversi MF, Cioni G. Electroclinical correlation in neonatal seizures. Eur J Paediatr Neurol. 1998;2(3):117-25.

27. Boylan GB, Pressler RM, Rennie JM, Morton M, Leow PL, Hughes R, et al. Outcome of electroclinical, electrographic, and clinical seizures in the newborn infant. Dev Med Child Neurol. 1999;41(12):819-25.

28. Boylan GB, Rennie JM, Pressler RM, Wilson G, Morton M, Binnie CD. Phenobarbitone, neonatal seizures, and video-EEG. Arch Dis Child Fetal Neonatal Ed. 2002;86(3):F165-70.

29. 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.

30. Nash KB, Bonifacio SL, Glass HC, Sullivan JE, Barkovich AJ, Ferriero DM, et al. Video-EEG monitoring in newborns with hypoxic-ischemic encephalopathy treated with hypothermia. Neurology. 2011;76(6):556-62.

31. Nagarajan L, Ghosh S, Palumbo L. Ictal electroencephalograms in neonatal seizures: characteristics and associations. Pediatr Neurol. 2011;45(1):11-6.

32. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med. 2009;361(14):1349-58.

33. Boylan GB, Kharoshankaya L, Wusthoff CJ. Seizures and hypothermia: importance of electroencephalographic monitoring and considerations for treatment. Semin Fetal Neonatal Med. 2015;20(2):103-8.

34. Pavel AM, Rennie JM, de Vries LS, Blennow M, Foran A, Shah DK, et al. A machine-learning algorithm for neonatal seizure recognition: a multicentre, randomised, controlled trial. Lancet Child Adolesc Health. 2020;4(10):740-9.

35. Wusthoff CJ, Sundaram V, Abend NS, Massey SL, Lemmon ME, Thomas C, et al. Seizure Control in Neonates Undergoing Screening vs Confirmatory EEG Monitoring. Neurology. 2021;97(6):e587-e96.

36. Tharp BR. Unique EEG pattern (comb-like rhythm) in neonatal maple syrup urine disease. Pediatr Neurol. 1992;8(1):65-8.

37. Low E, Mathieson SR, Stevenson NJ, Livingstone V, Ryan CA, Bogue CO, et al. Early postnatal EEG features of perinatal arterial ischaemic stroke with seizures. PLoS One. 2014;9(7):e100973.

38. Serino D, Specchio N, Pontrelli G, Vigevano F, Fusco L. Video/EEG findings in a KCNQ2 epileptic encephalopathy: a case report and revision of literature data. Epileptic Disord. 2013;15(2):158-65.

39. Awal MA, Lai MM, Azemi G, Boashash B, Colditz PB. EEG background features that predict outcome in term neonates with hypoxic ischaemic encephalopathy: A structured review. Clin Neurophysiol. 2016;127(1):285-96.

40. Co JP, Elia M, Engel J, Jr., Guerrini R, Mizrahi EM, Moshe SL, et al. Proposal of an algorithm for diagnosis and treatment of neonatal seizures in developing countries. Epilepsia. 2007;48(6):1158-64.

41. Rakshasbhuvankar A, Paul S, Nagarajan L, Ghosh S, Rao S. Amplitude-integrated EEG for detection of neonatal seizures: a systematic review. Seizure. 2015;33:90-8.

42. Zhang L, Zhou YX, Chang LW, Luo XP. Diagnostic value of amplitude-integrated electroencephalogram in neonatal seizures. Neurosci Bull. 2011;27(4):251-7.

43. Pressler RM, Cilio, M. R., Mizrahi, E.M., Moshe, S.L., Lunes, M.L., Plouin, P., Vanhatalo, S., Yozawitz, E., de Vries, L.S., Vinayan, K., P., Triki, C., C., Wilmshurst, J.M., Yamatomo, H., Zuberi, S.M. . The ILAE Classification of Seizures & the Epilepsies: Modification for Seizures in the Neonate. Position paper by the ILAE Task Force on Neonatal Seizures. . Epilepsia. 2020.

44. Volpe JJ. Neurology of the Newborn: Neonatal Seizures. 5th ed. Philadelphia: Saunders Esevier; 2008. 203 p.

45. Nagarajan L, Palumbo L, Ghosh S. Classification of clinical semiology in epileptic seizures in neonates. Eur J Paediatr Neurol. 2012;16(2):118-25.

46. Milh M, Boutry-Kryza N, Sutera-Sardo J, Mignot C, Auvin S, Lacoste C, et al. Similar early characteristics but variable neurological outcome of patients with a de novo mutation of KCNQ2. Orphanet J Rare Dis. 2013;8:80.

47. Zara F, Specchio N, Striano P, Robbiano A, Gennaro E, Paravidino R, et al. Genetic testing in benign familial epilepsies of the first year of life: clinical and diagnostic significance. Epilepsia. 2013;54(3):425-36.

48. World Health Organisation W. Guidelines on neonatal seizures. Geneva 2011.

49. Evans DJ, Levene MI, Tsakmakis M. Anticonvulsants for preventing mortality and morbidity in full term newborns with perinatal asphyxia. Cochrane Database Syst Rev. 2007(3):CD001240.

50. Soul JS, Pressler R, Allen M, Boylan G, Rabe H, Portman R, et al. Recommendations for the design of therapeutic trials for neonatal seizures. Pediatr Res. 2019;85(7):943-54.

51. Sankar R, Painter MJ. Neonatal seizures: after all these years we still love what doesn't work. Neurology. 2005;64(5):776-7.

52. Silverstein FS, Ferriero DM. Off-label use of antiepileptic drugs for the treatment of neonatal seizures. Pediatr Neurol. 2008;39(2):77-9.

53. Bittigau P, Sifringer M, Ikonomidou C. Antiepileptic drugs and apoptosis in the developing brain. Ann N Y Acad Sci. 2003;993:103-14; discussion 23-4.

54. Forcelli PA, Kim J, Kondratyev A, Gale K. Pattern of antiepileptic drug-induced cell death in limbic regions of the neonatal rat brain. Epilepsia. 2011;52(12):e207-11.

55. Boylan GB, Rennie JM, Chorley G, Pressler RM, Fox GF, Farrer K, et al. Second-line anticonvulsant treatment of neonatal seizures: a video-EEG monitoring study. Neurology. 2004;62(3):486-8.

56. Booth D, Evans DJ. Anticonvulsants for neonates with seizures. Cochrane Database Syst Rev. 2004(4):CD004218.

57. Sharpe C, Reiner GE, Davis SL, Nespeca M, Gold JJ, Rasmussen M, et al. Levetiracetam Versus Phenobarbital for Neonatal Seizures: A Randomized Controlled Trial. Pediatrics. 2020;145(6).

58. McHugh DC, Lancaster S, Manganas LN. A Systematic Review of the Efficacy of Levetiracetam in Neonatal Seizures. Neuropediatrics. 2018;49(1):12-7.

59. Gowda VK, Romana A, Shivanna NH, Benakappa N, Benakappa A. Levetiracetam versus Phenobarbitone in Neonatal Seizures - A Randomized Controlled Trial. Indian Pediatr. 2019;56(8):643-6.

60. Loiacono G, Masci M, Zaccara G, Verrotti A. The treatment of neonatal seizures: focus on Levetiracetam. J Matern Fetal Neonatal Med. 2016;29(1):69-74.

61. National Institute for Health and Care of Excellence N. British National Formulary (BNF) for children. 2021.

62. de Haan TR, Bijleveld YA, van der Lee JH, Groenendaal F, van den Broek MP, Rademaker CM, et al. Pharmacokinetics and pharmacodynamics of medication in asphyxiated newborns during controlled hypothermia. The PharmaCool multicenter study. BMC Pediatr. 2012;12:45.

63. Ramantani G, Ikonomidou C, Walter B, Rating D, Dinger J. Levetiracetam: safety and efficacy in neonatal seizures. Eur J Paediatr Neurol. 2011;15(1):1-7.

64. Abend NS, Gutierrez-Colina AM, Monk HM, Dlugos DJ, Clancy RR. Levetiracetam for treatment of neonatal seizures. J Child Neurol. 2011;26(4):465-70.

65. Lyttle MD, Rainford NEA, Gamble C, Messahel S, Humphreys A, Hickey H, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet. 2019;393(10186):2125-34.

66. Hanon E, Klitgaard H. Neuroprotective properties of the novel antiepileptic drug levetiracetam in the rat middle cerebral artery occlusion model of focal cerebral ischemia. Seizure. 2001;10(4):287-93.

67. Kilicdag H, Daglioglu K, Erdogan S, Guzel A, Sencar L, Polat S, et al. The effect of levetiracetam on neuronal apoptosis in neonatal rat model of hypoxic ischemic brain injury. Early Hum Dev. 2013;89(5):355-60.

68. Griesmaier E, Stock K, Medek K, Stanika RI, Obermair GJ, Posod A, et al. Levetiracetam increases neonatal hypoxic-ischemic brain injury under normothermic, but not hypothermic conditions. Brain Res. 2014;1556:10-8.

69. Strasser K, Lueckemann L, Kluever V, Thavaneetharajah S, Hoeber D, Bendix I, et al. Dose-dependent effects of levetiracetam after hypoxia and hypothermia in the neonatal mouse brain. Brain Res. 2016;1646:116-24.

70. Mruk AL, Garlitz KL, Leung NR. Levetiracetam in neonatal seizures: a review. J Pediatr Pharmacol Ther. 2015;20(2):76-89.

71. Sharpe CM, Capparelli EV, Mower A, Farrell MJ, Soldin SJ, Haas RH. A seven-day study of the pharmacokinetics of intravenous levetiracetam in neonates: marked changes in pharmacokinetics occur during the first week of life. Pediatr Res. 2012;72(1):43-9.

72. Bye AM, Flanagan D. Spatial and temporal characteristics of neonatal seizures. Epilepsia. 1995;36(10):1009-16.

73. Ahrens S, Ream MA, Slaughter LA. Status Epilepticus in the Neonate: Updates in Treatment Strategies. Curr Treat Options Neurol. 2019;21(2):8.

74. Iida Y, Nishi S, Asada A. Effect of mild therapeutic hypothermia on phenytoin pharmacokinetics. Ther Drug Monit. 2001;23(3):192-7.

75. Bhagat H, Bithal PK, Chouhan RS, Arora R. Is phenytoin administration safe in a hypothermic child? J Clin Neurosci. 2006;13(9):953-5.

76. Sheth RD, Buckley DJ, Gutierrez AR, Gingold M, Bodensteiner JB, Penney S. Midazolam in the treatment of refractory neonatal seizures. Clin Neuropharmacol. 1996;19(2):165-70.

77. Slaughter LA, Patel AD, Slaughter JL. Pharmacological treatment of neonatal seizures: a systematic review. J Child Neurol. 2013;28(3):351-64.

78. Shany E, Benzaqen O, Watemberg N. Comparison of continuous drip of midazolam or lidocaine in the treatment of intractable neonatal seizures. J Child Neurol. 2007;22(3):255-9.

79. van den Broek MP, van Straaten HL, Huitema AD, Egberts T, Toet MC, de Vries LS, et al. Anticonvulsant effectiveness and hemodynamic safety of midazolam in full-term infants treated with hypothermia. Neonatology. 2015;107(2):150-6.

80. Castro Conde JR, Hernandez Borges AA, Domenech Martinez E, Gonzalez Campo C, Perera Soler R. Midazolam in neonatal seizures with no response to phenobarbital. Neurology. 2005;64(5):876-9.

81. Weeke LC, Toet MC, van Rooij LG, Groenendaal F, Boylan GB, Pressler RM, et al. Lidocaine response rate in aEEG-confirmed neonatal seizures: Retrospective study of 413 full-term and preterm infants. Epilepsia. 2015.

82. Favie LMA, Huitema ADR, van den Broek MPH, Rademaker CMA, de Haan TR, van Straaten HLM, et al. Lidocaine as treatment for neonatal seizures: Evaluation of previously developed population pharmacokinetic models and dosing regimen. Br J Clin Pharmacol. 2020;86(1):75-84.

83. van den Broek MP, Groenendaal F, Toet MC, van Straaten HL, van Hasselt JG, Huitema AD, et al. Pharmacokinetics and clinical efficacy of phenobarbital in asphyxiated newborns treated with hypothermia: a thermopharmacological approach. Clin Pharmacokinet. 2012;51(10):671-9.

84. Flor-Hirsch H, Heyman E, Livneh A, Reish O, Watemberg N, Litmanovits I, et al. Lacosamide for SCN2A-related intractable neonatal and infantile seizures. Epileptic Disord. 2018;20(5):440-6.

85. Pisano T, Numis AL, Heavin SB, Weckhuysen S, Angriman M, Suls A, et al. Early and effective treatment of KCNQ2 encephalopathy. Epilepsia. 2015;56(5):685-91.

86. Sands TT, Balestri M, Bellini G, Mulkey SB, Danhaive O, Bakken EH, et al. Rapid and safe response to low-dose carbamazepine in neonatal epilepsy. Epilepsia. 2016;57(12):2019-30.

87. Cornet MC, Morabito V, Lederer D, Glass HC, Ferrao Santos S, Numis AL, et al. Neonatal presentation of genetic epilepsies: Early differentiation from acute provoked seizures. Epilepsia. 2021;62(8):1907-20.

88. Wilson MP, Plecko B, Mills PB, Clayton PT. Disorders affecting vitamin B6 metabolism. J Inherit Metab Dis. 2019;42(4):629-46.

89. Mills PB, Footitt EJ, Mills KA, Tuschl K, Aylett S, Varadkar S, et al. Genotypic and phenotypic spectrum of pyridoxine-dependent epilepsy (ALDH7A1 deficiency). Brain. 2010;133(Pt 7):2148-59.

90. van Karnebeek CD, Tiebout SA, Niermeijer J, Poll-The BT, Ghani A, Coughlin CR, 2nd, et al. Pyridoxine-Dependent Epilepsy: An Expanding Clinical Spectrum. Pediatr Neurol. 2016;59:6-12.

91. Coughlin CR, 2nd, Tseng LA, Abdenur JE, Ashmore C, Boemer F, Bok LA, et al. Consensus guidelines for the diagnosis and management of pyridoxine-dependent epilepsy due to alpha-aminoadipic semialdehyde dehydrogenase deficiency. J Inherit Metab Dis. 2021;44(1):178-92.

92. Stockler S, Plecko B, Gospe SM, Jr., Coulter-Mackie M, Connolly M, van Karnebeek C, et al. Pyridoxine dependent epilepsy and antiquitin deficiency: clinical and molecular characteristics and recommendations for diagnosis, treatment and follow-up. Mol Genet Metab. 2011;104(1-2):48-60.

93. Cortes-Saladelafont E, Molero-Luis M, Hsjd Working G, Artuch R, Garcia-Cazorla A. Pyridoxal Phosphate Supplementation in Neuropediatric Disorders. Semin Pediatr Neurol. 2016;23(4):351-8.

94. Puri V, Ness S, Sattaluri SJ, Wang S, Todd M, Yuen E, et al. Long-term open-label study of adjunctive topiramate in infants with refractory partial-onset seizures. J Child Neurol. 2011;26(10):1271-83.

95. Glass HC, Poulin C, Shevell MI. Topiramate for the treatment of neonatal seizures. Pediatr Neurol. 2011;44(6):439-42.

96. Courchia B, Kurtom W, Pensirikul A, Del-Moral T, Buch M. Topiramate for Seizures in Preterm Infants and the Development of Necrotizing Enterocolitis. Pediatrics. 2018;142(1).

97. Dzhala VI, Brumback AC, Staley KJ. Bumetanide enhances phenobarbital efficacy in a neonatal seizure model. Ann Neurol. 2008;63(2):222-35.

98. Cleary RT, Sun H, Huynh T, Manning SM, Li Y, Rotenberg A, et al. Bumetanide enhances phenobarbital efficacy in a rat model of hypoxic neonatal seizures. PLoS One. 2013;8(3):e57148.

99. Pressler RM, Boylan GB, Marlow N, Blennow M, Chiron C, Cross JH, et al. Bumetanide for the treatment of seizures in newborn babies with hypoxic ischaemic encephalopathy (NEMO): an open-label, dose finding, and feasibility phase 1/2 trial. Lancet Neurol. 2015;14(5):469-77.

100. Soul JS, Bergin AM, Stopp C, Hayes B, Singh A, Fortuno CR, et al. A Pilot Randomized, Controlled, Double-Blind Trial of Bumetanide to Treat Neonatal Seizures. Ann Neurol. 2021;89(2):327-40.

101. Fitzgerald MP, Kessler SK, Abend NS. Early discontinuation of antiseizure medications in neonates with hypoxic-ischemic encephalopathy. Epilepsia. 2017;58(6):1047-53.

102. Jindal A, Angurana SK, Suthar R, Kumar P, Sundaram V. Effect of early withdrawal of phenobarbitone on the recurrence of neonatal seizures: An open-label randomized controlled trial. Epilepsy Behav. 2021;117:107875.

103. Glass HC, Soul JS, Chang T, Wusthoff CJ, Chu CJ, Massey SL, et al. Safety of Early Discontinuation of Antiseizure Medication After Acute Symptomatic Neonatal Seizures. JAMA Neurol. 2021;78(7):817-25.

104. Pressler RM, Cilio MR, Mizrahi EM, Moshe SL, Nunes ML, Plouin P, et al. The ILAE classification of seizures and the epilepsies: Modification for seizures in the neonate. Position paper by the ILAE Task Force on Neonatal Seizures. Epilepsia. 2021;62(3):615-28.

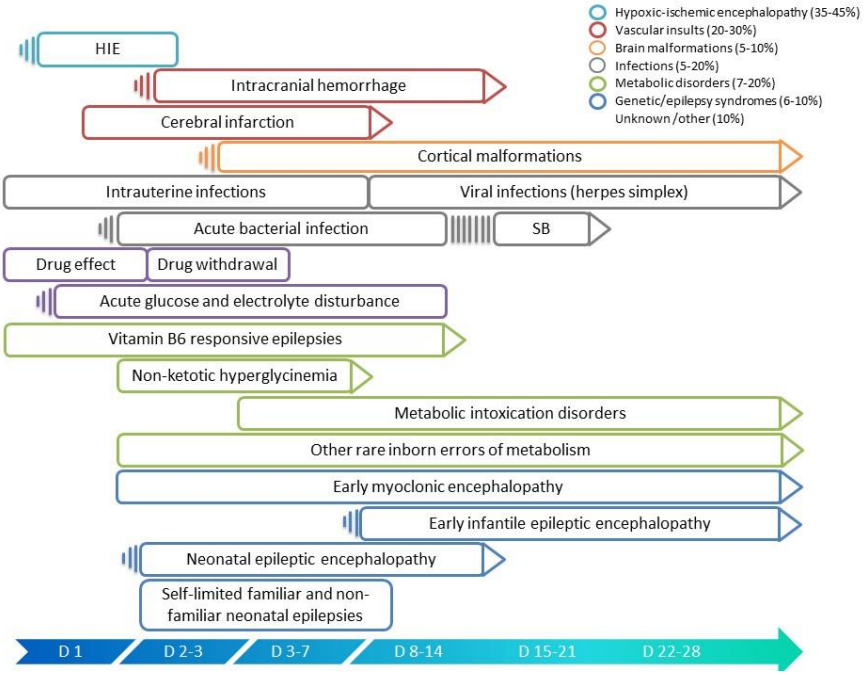

Figure 1: Commonest causes of seizures with respect to age of onset within the neonatal period (from day 1 to day 28 of life) (1).

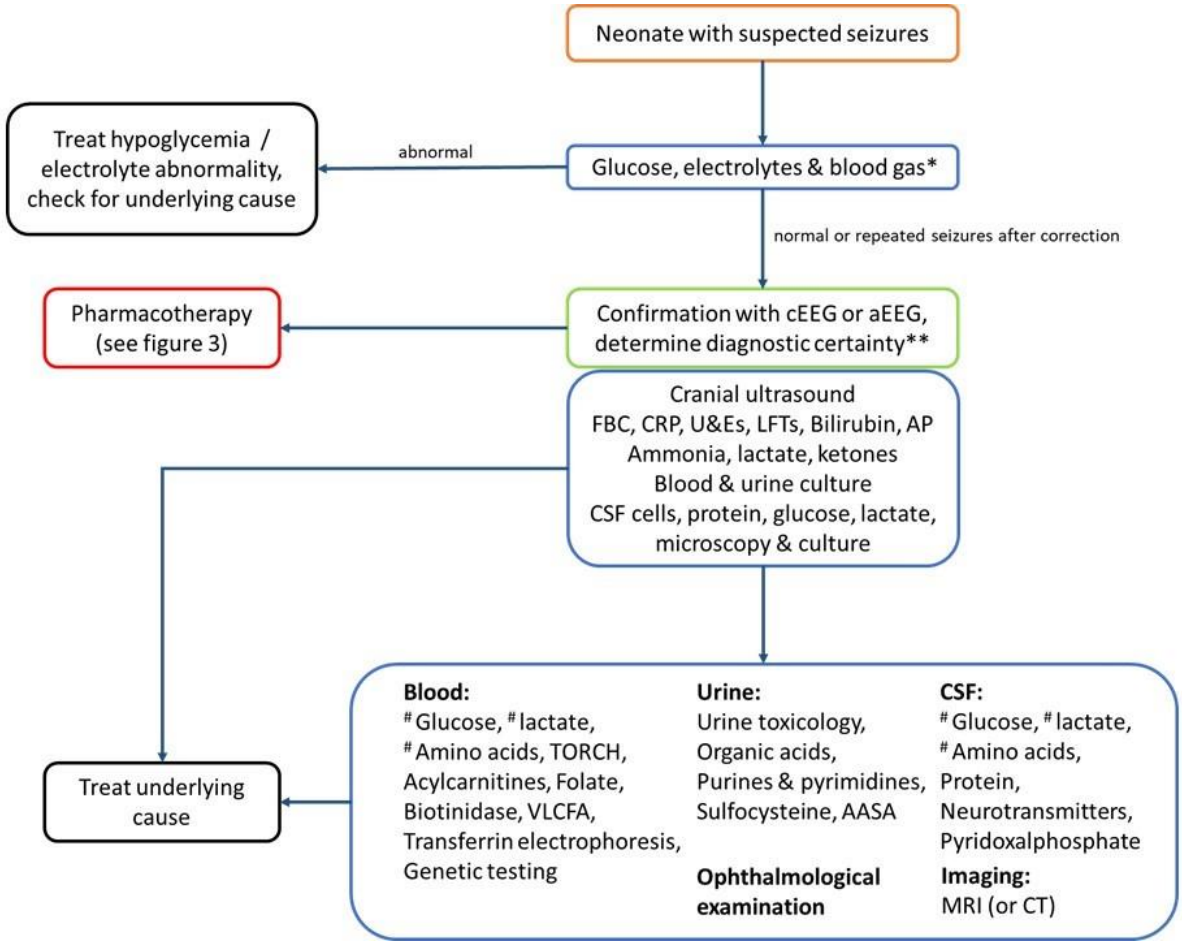

Figure 2: Stepwise approach in investigating neonatal seizures; first line; second line and advanced investigations in the instance of refractory seizures. Note that further tests may be requested by the local neurology and metabolic medicine teams as per case and local guidance. (FBC: full blood count, CRP: C-reactive protein, U&Es: urea and electrolytes, LFTs: liver function tests, CSF: cerebro-spinal fluid, CrUSS: cranial ultrasound scan, TORCH: Toxoplasma, Rubella, Cytomegalovirus, Herpes Simplex Virus, VLFCA: very low chain fatty acids, AASA: aminoadipic semialdehyde, CT: computed tomography, MRI: magnetic resonance imaging). *If available point of care blood gas with electrolyte and lactate reading. **Level 1: EEG (gold standard), Level 2: aEEG or clinical diagnosis of focal clonic or focal tonic (probable seizures)All other seizure types need confirmation according to GAIA case definition (21, 104). #Blood and CSF paired samples.

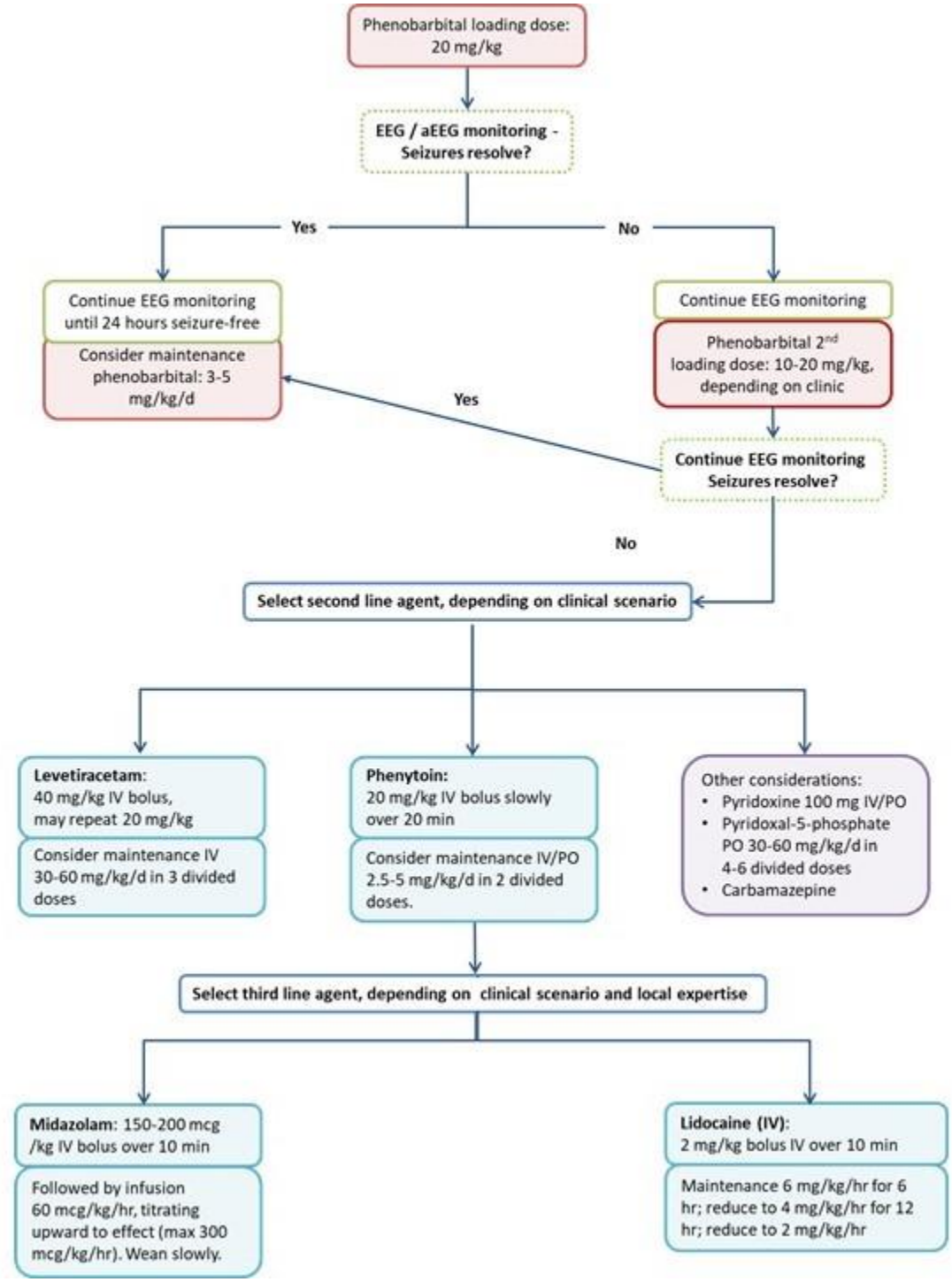

Figure 3: Algorithm for the treatment of neonatal seizures (IV: intravenous administration and PO: per os for oral administration). In case of status epilepticus use phenytoin as second line rather than levetiracetam if patient is hemodynamically stable. Do not use lidocaine as third line if phenytoin has been used as second line.