EPNS endorsement of the Treatment of Seizures in the Neonate: Guidelines and Consensus-based Recommendations Special Report from the ILAE Task Force on Neonatal Seizures

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Abbreviations

AGREE II	Appraisal of Guidelines for Research & Evaluation II
HIE	Hypoxic-ischaemic encephalopathy
ILAE	International League Against Epilepsy
WHO	World Health Organisation

Background

The International League against Epilepsy (ILAE) is a global organization focused on advancing research, improving clinical care, and promoting education related to epilepsy. The ILAE includes clinicians, researchers, healthcare providers and individuals with epilepsy. The ILAE aims to improve the understanding, diagnosis, treatment and prevention of epilepsy.

Neonatal seizure is defined as a seizure occurring in an infant less than 28 days. The neonatal period is the highest risk for seizures with an incidence of 1-5/1000 live births. (1–6) There is a higher prevalence among premature infants, with seizures affecting 10-130/1000 live premature births. Neonatal seizures are associated with a higher risk of death and adverse neurodevelopmental outcomes. (7–9)

There are many causes of seizures in the newborn period. In term and late preterm newborns (> 33 weeks gestational age), the most frequent causes are acute/symptomatic seizures in the setting of hypoxic-ischaemic encephalopathy (HIE), stroke, intracranial haemorrhage or infection. However, in 10-15%, neonatal seizures are related to an underlying cortical malformation, genetic/epileptic syndrome or inborn error of metabolism.(5) (10) In infants <32 weeks gestational age, the most common cause is intracranial haemorrhage, with a strong correlation between gestational age and seizure occurrence. (11) (8)

The last international guideline about the management of neonatal seizure was published in 2011 by the World Health Organization (WHO), ILAE and the International Bureau of Epilepsy. (12) In recent years, new evidence has emerged to inform updated recommendations on the monitoring, investigations and treatment of seizures. Therefore, the ILAE reviewed the literature, to provide an evidence-based guideline on the treatment of seizures in the neonatal population.(13) (14)

The guideline and consensus-based recommendation addressed six distinct questions relating to the management of neonatal seizures:

1. First-line anti-seizure medication
2. Second-line anti-seizure medication
3. Duration of anti-seizure medication treatment
4. Impact of therapeutic hypothermia on seizure burden in neonates with HIE
5. Impact of electrographic seizure treatment on outcome
6. Administration of pyridoxine

Aim:

To evaluate the methodological rigour and recommendations as outlined in *"Treatment of Seizures in the Neonate: Guidelines and Consensus-based Recommendations – Special Report from the ILAE Task Force on Neonatal Seizures"*(14)

Methods:

Appraisal Criteria:

AGREE II Instrument

Background
The Appraisal of Guidelines for Research and Evaluation (AGREE) instrument was developed to address the issue of variability in guideline quality. (15)(16) The AGREE instrument is an internationally validated tool that assesses the methodological rigour and transparency in which a guideline is developed. The quality standards for evaluating existing guidelines based on the AGREE II instrument have been utilized in other paediatric diseases, neonatal conditions and rare diseases (17)(18) The AGREE-II instrument is applicable regardless of the small patient numbers, potentially small volume of evidence, and other limitations typically encountered in rare disease guidelines.

Methodology
The purpose of the AGREE II instrument is to provide a framework to:

1. Assess the quality of guidelines
2. Provide a methodological strategy for the development of guidelines
3. Inform what information and how information ought to be reported in guidelines.

The AGREE II Instrument consists of a set of 23 items organised into six domains: Each domain captures a unique dimension of guideline quality. The six domains' scores are judged as independent factors; they cannot be aggregated into a single quality score. The rating system of AGREE II (**Appendix 1**) uses a 7-point scale for each item (1- strongly disagree to 7- strongly agree).

Domain 1. Scope and Purpose is concerned with the overall aim/objectives of the guideline, the specific health questions, the clarity of the guideline's objective and the target population *(items 1-3).*
Domain 2. Stakeholder Involvement focuses on the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users (*items 4-6).*
Domain 3. Rigour of Development relates to the process used to gather and synthesise the evidence, the methods to formulate the recommendations, and to update them (*items 7-14).*
Domain 4. Clarity of Presentation deals with the language, structure, and format of the guideline *(items 15- 17).*
Domain 5. Applicability pertains to the likely barriers and facilitators to implementation, strategies to improve uptake, and resource implications of applying the guideline *(items 18-21).*
Domain 6. Editorial Independence is concerned with the guideline development process being free from biases or conflicts of interest *(items 22-23).*
Upon completing the 23 items, an overall guideline assessment is needed. Overall assessment requires the AGREE II user to make a conclusion as to the quality of the guideline, considering the criteria considered in the assessment process. (16) The interpretation of the domain scores can be used to identify strengths and limitations of guidelines or to select high-quality guidelines for adaptation, endorsement, or implementation.

Review Group and role of members
The AGREE-II developers recommend that a guideline be assessed by at least two appraisers and preferably four as this will increase the reliability of the assessment. (16)

Four clinicians (experts) working in the field of paediatric neurology and neonatology were recruited for participation as appraisers.
Dr Lena-Luise Becker, Consultant Neurologist, Charité–Universitätsmedizin Berlin, Germany
Prof Mike Boyle, Consultant Neonatologist, Rotunda Maternity Hospital, Dublin and Honorary Clinical Associate Professor, Royal College of Surgeons, Dublin, Ireland.
Dr Kathleen Gorman, Consultant Neurologist, Children's Health Ireland at Temple Street, Dublin, Ireland and Associate Clinical Professor, University College Dublin, Ireland
Prof Agnese Suppiej, Consultant Neurologist, and Professor of Paediatrics, University of Ferrara, Ferrara Italy

Dr Gorman coordinated the review group and drafting of the final document.

Guideline Assessment using AGREE II instrument

All four assessors completed the AGREE II guideline and endorsed the "*Treatment of Seizures in the Neonate: Guidelines and Consensus-based Recommendations – Special Report from the ILAE Task Force on Neonatal Seizures".*

Strengths of Guideline

1. **Scope and Purpose**:
   - The scope is well-defined and focused on evidence-based recommendations and consensus expert opinion for the management of neonatal seizures.
   - The document identified key clinical questions/issues and provided an approach for the clinical treatment of neonatal seizures.
2. **Stakeholder Involvement**:
   - The guideline development process involved a multidisciplinary group with expertise in neonatology, neurology, epilepsy and electrophysiology.
   - Individuals from all over the world (Africa, Asia, Australia, Europe, North America and South) were included in the working group to ensure the guidelines are applicable and relevant in all regions and resource settings.
3. **Rigour of Development**:
   - The document includes a clear description of the process for developing the recommendations.
   - The methodology for selecting and evaluating evidence is transparent, and the strength of the evidence is clearly indicated.
   - Consensus-based recommendations were developed when there were gaps in the published literature/evidence.
4. **Clarity of Presentation**:
   - The guidelines are presented in a clear format, with specific recommendations that are easy to interpret.
   - Each section is well-organized, with distinct headings (questions) and subheadings, making it easy for clinicians to read/follow.
   - A summary table for pharmacological agents (**Table 2**) and a flowchart of suggested treatment pathway (**Figure 3**) allow for quick reference in the clinical setting.
5. **Applicability**:
   - The guidelines were generally applicable across different healthcare settings, though certain recommendations may require adaptation depending on resources available in specific regions.
   - Considerations for the feasibility of implementing the recommendations in various healthcare settings were acknowledged in the discussion.
6. **Editorial Independence**:
   - The task force disclosed any potential conflicts of interest among the panel members.
   - The guideline is not influenced by funding from the pharmaceutical or medical device industries.

Limitations

1. **Scope and Purpose**
   - No issues highlighted.
2. **Stakeholder Involvement:**
   - Only medical professionals (19 child neurologists and clinical neurophysiologists, three neonatologists) were involved in the working group. There was no inclusion of other multi-disciplinary team members such as neonatal nurses or pharmacists.
   - Only a single parent representative was involved and unclear of their role in the process of developing guidelines.
3. **Rigour of Development:**
   - Some recommendations (e.g. Recommendation 2: Second-line anti-seizure medication) were based on expert opinion rather than high-quality evidence.

- External review of the guideline was via the ILAE website. This is an open-access website and therefore individuals not necessarily experts in neonatal seizures could have provided feedback. Also, the ILAE website is primarily utilised and accessed by neurologists/ epileptologists rather than neonatologists.
- No information was provided on auditing of the guidelines.

4. **Clarity of Presentation:**
   - Additional explanations or references in the main document to supporting data would have been helpful, especially for clinicians less familiar with the topic.
5. **Applicability:**
   - The guidelines did not adequately address how to apply the guidelines in settings with limited resources or different healthcare infrastructure.
   - The feasibility of implementing some recommendations—particularly around monitoring, may be challenging in certain healthcare settings/resources. No discussion regarding the cost of implementing this guideline.
6. **Editorial Independence:**
   - There were minor concerns regarding potential conflicts of interest among task force members, particularly if the members have strong ties to pharmaceutical companies involved in the development of seizure medications.

Overall Assessment: Endorse

Conclusion: To endorse the *Treatment of Seizures in the Neonate: Guidelines and Consensus-based Recommendations – Special Report from the ILAE Task Force on Neonatal Seizures*. The guidelines received favourable ratings from the AGREE-II assessment.

Review date: 5 years. However, this should be reviewed sooner if there are significant new guidelines, international consensus statements or new evidence/treatments become available.

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