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Guideline Brief

Clinical practice guideline on perinatal hypoxic-ischaemic encephalopathy on newborns.

Guideline ID: 88 2015

Agency for Health Quality and Assessment of Catalonia (AQuAS) | GuiaSalud | Ministry of Health (Spain)

Guideline Development Group of the Clinical Practice Guideline on Perinatal Hypoxic-Ischaemic Encephalopathy in Newborns. Clinical practice guidelines on perinatal hypoxic-ischaemic encephalopathy on newborns. Barcelona (Spain): Agency for Health Quality and Assessment of Catalonia (AQuAS); 2015. 263 p. [272 references]

View Original Guideline

Overview

Guideline Topic

Hypoxic-ischaemic encephalopathy

Note: The guideline development group understands encephalopathy during the first days of life to be a neurological syndrome that is present as from birth and is characterised by difficulties to initiate or maintain respiration and by alterations in the ability to wake up or remain awake (alert) and alterations in muscle tone and in excitability, with or without convulsions.

The perinatal hypoxic-ischaemic origin of the encephalopathy will be defined by: 1.) The presence of an obstetric background of risk (sentinel event, non-reassuring foetal status or labour dystocia), and/or 2.) An altered perinatal status defined by an Apgar of less than 5 at 5 or 10 minutes and/or an umbilical artery pH or a pH in the first hour of life of the newborn of less than 7.00 and/or a base deficit of greater than 12 mmol/L.

Patient Population

Newborns with a gestational age of greater than or equal to 35 weeks with perinatal hypoxic-ischaemic encephalopathy

Note: This clinical practice guideline (CPG) does not cover:

- Either the handling or the consequences of perinatal hypoxic-ischaemic injury in newborns ≤35 weeks of gestation.
- Neonatal encephalopathy whose primary origin is of a haemorrhagic, infectious, metabolic or toxic pathology.
- Newborns with encephalopathy but with congenital malformations of the central nervous system or severe genetic anomalies.
- Newborns with a focal ischaemic injury in the tributary region of a specific vessel (perinatal stroke).
- Neonatal encephalopathy due to potential postnatal hypoxic-ischaemic injury in full-term newborns, such as the so-called neonatal collapse.
- Organisational aspects or care models that are required to put the recommendations into practice.

Recommendations

Recommendation Statements

Risk/Comorbidity Factors

Does the administration of 21% oxygen versus the administration of 100% oxygen during the resuscitation of newborns with a gestational age of greater than or equal to 35 weeks with asphyxia reduce neurological morbidity and mortality?

Weak: In newborns with a gestational age of greater than or equal to 35 weeks that require ventilation due to apnea and bradycardia at birth, the guideline development group (GDG) suggests not beginning the administration of 100% O2.

√: In newborns with a gestational age of greater than or equal to 35 weeks that require ventilation due to apnea and bradycardia at birth, the GDG suggests beginning resuscitation with ambient air or intermediate concentrations of oxygen and suggest that the concentration of O2 be adjusted according to the patient's clinical response and saturation.

Is an Apgar score of 0 at 10 minutes in newborns with a gestational age of greater than or equal to 35 weeks that develop hypoxic-ischaemic encephalopathy (HIE) always related to neurological mortality or morbidity?

Weak: Given that an Apgar score of 0 at 10 minutes is not always related to death or moderate/severe neurological disability, the GDG suggests not using this data by itself to make the decision to limit the therapeutic effort and interrupt resuscitation measures at 10 minutes of life.

√: In newborns with a gestational age of greater than or equal to 35 weeks that show an Apgar score of 0 at 10 minutes of life, the GDG suggests considering a delay in the decision to limit the therapeutic effort. Delaying this decision from 10 minutes of life (Apgar at 10 minutes) to making it in the first hours of life (72 hours) could allow having the results of diagnostic tests that have greater prognostic value and knowing the preferences of the parents.

Which of the following factors occurring in newborns with perinatal HIE during the first 72 hours of life (hyperthermia, hypo/hypercapnia, hypo/hyperglycaemia) are associated with greater neurological morbidity and mortality?

Strong: In newborns with a gestational age of greater than or equal to 35 weeks with HIE, the GDG recommends avoiding hyperthermia in the first 72 hours of life.

Strong: In newborns with a gestational age of greater than or equal to 35 weeks with HIE, the GDG recommends avoiding severe hypocapnia (pCO2 <20 mm Hg) in the first 24 hours of life.

√: In newborns with a gestational age of greater than or equal to 35 weeks with HIE, the GDG suggests avoiding hypercapnia in the first 24 hours of life.

Strong: In newborns with a gestational age of greater than or equal to 35 weeks with HIE, the GDG recommends avoiding hypoglycaemia in the first 72 hours of life.

√: In newborns with a gestational age of greater than or equal to 35 weeks with HIE, the GDG suggests avoiding hyperglycaemia in the first 72 hours of life.

Treatment

In newborns with a gestational age of equal to or greater than 35 weeks with perinatal HIE, does therapeutic hypothermia, in comparison with normothermia, reduce the risk of death or neurological morbidity in the long term?

Strong: The GDG recommends the use of hypothermia in newborns with a gestational age of greater than or equal to 35 weeks with perinatal HIE, both moderate and severe, to reduce the risk of death or severe disability in neurodevelopment at 18 to 24 months of age.

Weak: The GDG recommends the use of hypothermia in newborns with a gestational age of greater than or equal to 35 weeks with perinatal HIE, both moderate and severe, to reduce the risk of death or severe disability in neurodevelopment at 6 to 8 years.

√: The GDG recommends that children with moderate or severe HIE be cared for at hospitals with level III neonatal or paediatric intensive care units with the availability of controlled hypothermia and the capacity to respond to the healthcare complexity of these patients, as

well as the availability of proven diagnostic-prognostic tests to establish the severity of the brain damage.

In newborns with a gestational age of greater than or equal to 35 weeks with perinatal HIE, does the clinical severity of the encephalopathy determine the effectiveness of treatment with hypothermia?

Strong: The GDG recommends the use of hypothermia in newborns with a gestational age of greater than or equal to 35 weeks with perinatal HIE, both moderate and severe, to reduce the risk of death or severe disability in neurodevelopment at 18 to 24 months of age.

In newborns with a gestational age of greater than or equal to 35

weeks, is the clinical severity of perinatal HIE during the first 6 hours of life correlated to the risk of death or neurological morbidity in the long term?

Strong: In newborns with a gestational age of greater than or equal to 35 weeks with HIE, the GDG recommends, during the first 6 hours of life, that clinical grading systems based on Sarnat's scale be applied to classify the severity of the encephalopathy and to identify candidates for therapeutic hypothermia (patients with moderate or severe encephalopathy).

In newborns with a gestational age of greater than or equal to 35 weeks with HIE, has therapeutic hypothermia changed the capacity of the clinical grading of encephalopathy to predict the risk of death or neurological morbidity in the long term?

Strong: In newborns with a gestational age of greater than or equal to 35 weeks with HIE, whether or not they are treated with hypothermia, the GDG recommends that the clinical grading of the encephalopathy at 72 hours be used as a tool for predicting the risk of death or severe disability.

Are there pharmacological treatments that, initiated in the first hours of life of newborns with a gestational age of greater than or equal to 35 weeks with moderate or severe perinatal HIE, might decrease neurological morbidity and mortality?

√: In newborns with a gestational age of greater than or equal to 35 weeks with moderate or severe HIE, the GDG suggests not using allopurinol in the first 6 hours of life to reduce death or disability in the short or medium term.

Weak: In newborns with a gestational age of greater than or equal to 35 weeks with moderate or severe HIE, the GDG suggests not using phenobarbital in the first 6 hours of life to reduce death or disability in the short or medium term.

Does the combination of hypothermia with other pharmacological treatments such as topiramate, erythropoietin (EPO), allopurinol or xenon reduce the risk of death or disability at 18 to 24 months in newborns with moderate or severe HIE versus treatment with hypothermia alone in these patients?

√: In newborns with a gestational age of greater than or equal to 35 weeks with moderate or severe perinatal HIE, the GDG currently suggests not using any pharmacological treatment in conjunction with hypothermia to reduce death or disability.

Does the treatment of electrical seizures in newborns with a gestational age of greater than or equal to 35 weeks with HIE, treated or not with therapeutic hypothermia, have an influence on the risk of death or disability at 18 to 24 months?

Weak: In newborns with a gestational age of greater than or equal to 35 weeks with HIE and not treated with therapeutic hypothermia and in the presence of electrical seizures, the GDG suggests that anticonvulsant drugs be administered.

√: In newborns with a gestational age of greater than or equal to 35 weeks with significant HIE treated with therapeutic hypothermia, the GDG suggests that anticonvulsant drugs be administered if there are maintained electrical seizures.

Does sedation with opioid derivatives in newborns with HIE (with or without hypothermia) decrease the risk of death or disability at 18 to 24 months?

√: The GDG suggests routine sedation with opioid derivatives, such as morphine or fentanyl, in newborns with a gestational age of greater than or equal to 35 weeks with HIE treated with hypothermia to decrease the stress and discomfort associated with body cooling and to possibly increase the neuroprotective effect of the hypothermia.

Prognostic Studies

In patients with HIE, treated or not with hypothermia, what is the prognostic value of amplitude-integrated electroencephalography (aEEG)?

Weak: The GDG suggests the use of aEEG within the first 6 hours of life as a prognostic tool in newborns with HIE. The diagnostic odds ratio (OR) is 30.69 (95% confidence interval [CI]; 10.09 to 93.31) for death/disability in patients not treated with hypothermia and 12.74 (95% CI; 3.24 to 50.16) in patients treated with hypothermia.

Strong: The GDG recommends the use of aEEG as a prognostic tool of death or severe disability in newborns with HIE as from 6 hours of life. This prognostic value in hours of life is delayed in newborn treated with hypothermia versus those not treated with this therapy: the maximum value was obtained at 24 hours in children not treated with hypothermia (97.5% posttest probability for death/disability; 95% CI, 93.3% to 99.1%) and at 48 hours in children treated with hypothermia (96.9% posttest probability; 95% CI, 81.7 to 99.6%).

In patients with HIE, treated or not with hypothermia, what is the prognostic value of brain magnetic resonance imaging (MRI)?

Strong: The GDG recommends conducting a cerebral MR study during the first month of life as a prognostic tool in newborns with moderate or severe HIE, whether or not they are treated with therapeutic hypothermia (diagnostic OR of 29.5; 95% CI; 12.12 to 72.25%, and diagnostic OR of 29.80; 95% CI; 17.09 to 51.95%, respectively).

Strong: In newborns with HIE, whether or not they are treated with therapeutic hypothermia, the GDG recommends conducting a cerebral MRI at between 8 and 30 days to establish the prognosis of death or severe disability.

Strong: In those patients in which there are prognostic doubts or testing is necessary to orient medical decisions, such as adapting the therapeutic effort, the GDG suggests conducting an early cerebral MRI in the first week of life. The diagnostic OR is 31.05 (95% CI; 10.69 to 90.84) for death/disability in patients not treated with hypothermia and 48.34 (95% CI; 1.85 to 1246.90) in children treated with hypothermia.

What is the prognostic value of the biomarkers in blood, urine or cerebral spinal fluid (CSF) to predict death or neurodevelopmental problems in newborns with moderate or severe HIE, treated or not with hypothermia?

Strong: In newborns with a gestational age of greater than or equal to 35 weeks with HIE, and who are stable and without refractory coagulopathy, the determination of neuron-specific enolase (NSE) in CSF in the first 72 hours of life should be considered, particularly if additional information is required to establish the prognosis or make decisions about limiting the therapeutic effort.

Follow-up

Do the current data for predicting neurological damage based on both clinical data and/or the pattern of involvement in the neuroimaging MRI (NMRI) allow establishing differentiated and effective programmes of neurodevelopmental follow-up?

√: The follow-up on newborns with perinatal HIE and the duration thereof should be planned individually according to both biological risk factors (severity of the encephalopathy, type of brain injury) and family and social factors.

√: Children with moderate or severe HIE must be cared for at a hospital centre with access to treatment using hypothermia and to the various prognostic tests indicated in this CPG.

√: Assessments should be scheduled considering the age of appearance of each one of the complications and the specific risk that such complications could appear in each child

complications and the specific risk that such complications could appear in each child.

√: Given the diversity and complexity of the problems that appear after being discharged from the hospital, caring for these children requires a multidisciplinary approach.

√: Both children with a high risk of death after being discharged from the hospital and their families require special care targeted at anticipating the complications that lead to death, at optimising care at the end of life and at taking care of family needs related to grief.

Evidence Rating Scheme

Classification of the Quality of Evidence in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) System

Quality of the Scientific Evidence	Design of the Study	Decrease the Quality If	Increase the Quality If
High	RCT	Limitation in the design: Important (**-1**) Very important (**-2**) Inconsistency (**-1**) Direct evidence: Some (**-1**) uncertainty Major (**-2**) Uncertainty about whether or not the evidence is direct Inaccurate data (**-1**)	Association: scientific evidence of a strong association (RR greater than 2 or less than 0.5 based on observation studies without confusion factors) (**+1**) Scientific evidence of a very strong association (RR greater than 5 or less than 0.2 based on studies without the possibility of bias) (**+2**)
Moderate			
Quality of the Scientific Evidence	**Design of the Study**	**Decrease the Quality If**	**Increase the Quality If**
Low	Observational studies	Notification bias: High probability of (**-1**)	Dose-response gradient (**+1**) All the possible confusion factors could have reduced the observed effect (**+1**)
Very low	Other types of design		

Recommendation Rating Scheme

Implications of the Grades of Recommendations in the GRADE System

Implications of a Strong Recommendation

Patients	Clinicians	Managers/Planners
The vast majority of people would agree with the recommended action, and only a small proportion would not.	The majority of patients should receive the recommended intervention.	The recommendation can be adopted as a health policy in the majority of situations.

Implications of a Weak Recommendation

Patients	Clinicians	Managers/Planners
The majority of people would agree with the recommended action, but a considerable number of people would not.	It recognises that various options will be appropriate for different patients and that the health professional has to help each patient reach a decision that is the most consistent with their values and preferences.	Considerable debate is necessary, in addition to participation by stakeholders.

Note: Likewise, 'guidelines of good clinical practice' (√) have been formulated, based on the clinical experience of the coordination team regarding important practical aspects that we have wanted to emphasise and about which there is no supporting scientific evidence.

Benefits

Refer to the "Balance Between Benefits and Risks" sections of the original guideline for further discussion of potential benefits of individual recommendations.

Risks

Refer to the "Balance Between Benefits and Risks" sections of the original guideline for further discussion of potential harms of individual recommendations.

Methods

Methodology

The methodology used to prepare this clinical practice guideline (CPG) is included in the *Preparation of Clinical Practice Guidelines in the National Health System. Update of the Methodological Manual* (see the "Supporting Documents" field).

The steps below have been followed:

- Formation of the guideline development group, integrated by professionals: specialists in paediatrics (neonatologists), clinical psychology, nursing and methodology (evidence-based medicine, CPG drafting, qualitative research and economic evaluation). To incorporate the values and preferences of the parents, relatives and caregivers of newborns with perinatal hypoxic-ischaemic encephalopathy (HIE) when formulating the recommendations of the CPG and to prepare information for parents, relatives and caregivers (refer to Appendix 1 of the original guideline), a qualitative study was conducted.

- The formulation of clinical questions following the Patient-Intervention-Comparison-Outcome (PICO) format.

- A bibliographical search in: CMA Infobase, DARE (only systematic reviews), Clearinghouse, Cochrane, Fisterra, Google, Guidelines International Network, Pubmed,

  CINHAL, Scopus, Tripdatabase, Web of Knowledge Center of Review and Dissemination, Eguidelines, Doc's CISMEf, GuiaSalud, NHR Health Technology Assessment Programme, NHS Evidence, Scottish Intercollegiate Network, UK Health Centre, UptoDate, Web Hospital, Web Rafa Bravo, Clinical Trials, Clinical Trials Register, Current Controlled Trials and NHSEED. Searches were conducted between February 2012 and April 2012, with alerts that were maintained until January 2013. The language was only an excluding factor at the time when the complete text of observational studies written in Chinese, Japanese and Russian were obtained. In the first phase, a preliminary search of CPGs (used as secondary sources of evidence) and of systematic reviews was conducted in the aforementioned databases. In a second phase, an expanded search of original studies (RCTs) was conducted in Pubmed, Cochrane and CINHAL. The search was expanded to observational studies (third phase) when the clinical question was not answered with the documents identified in the previous phases. Searches of qualitative studies (in Pubmed, PsycINFO and CINHAL) and of economic evaluations (Pubmed and NHSEED) were

conducted. Alerts were activated in Pubmed until January 2013. The search strategy is presented in Appendix 2 of the original guideline.

- Synthesis and evaluation of the quality of the evidence. The two CPGs on perinatal CPG that were found, were independently evaluated by two components of the development group using the AGREE II instrument.54 Systematic reviews were evaluated using the broken-down criteria of AMSTAR.55 For the economic evaluations, the criteria described by López-Bastida et al. were used.53 The group agreed upon a series of aspects for evaluating the quality of primary studies, which varied depending on whether they were evaluation studies of diagnostic tests or predictive strategies of interventions or of risk factors (refer to Appendix 2 of the methodological manual).

- Final evaluation of the quality of studies and a summary of the evidence for each question, therefore following the Grading of Recommendations Assessment, Development and Evaluation (GRADE).

- The formulation and grading of recommendations was done according to the GRADE system. Controversial recommendations or those with an absence of evidence were resolved by consensus in a meeting attended in person by members of the development group.

- The expert collaborators reviewed both the questions and the selected studies, the tables of evidence and the recommendations. The outside reviewers participated in the review of the first draft of the guideline. Various scientific societies were contacted (Spanish Society of Neonatology, Spanish Society of Paediatrics, Spanish Society of Obstetrics and Gynaecology, Spanish Society of Neonatal Nursing, Spanish Society of Paediatric Intensive Care, Spanish Society of Paediatric Anaesthesiology, Hipo SEN and Cat), as well as the most relevant experts at the state level who take part in the treatment and care of these patients. Given that there are no associations of parents of children with HIE established in Spain, none could be contacted.

Guideline Funder

This CPG has been funded through the agreement signed by the Institute of Health Carlos III (ISCIII), an autonomous body of the Ministry of Economy and Competitiveness, and the AQuAS, within the framework of developing activities by the Spanish Network of Agencies for Health Technology Assessment and National Health Service (NHS) benefits, financed by the Ministry of Health, Social Services and Equality.

Guideline Development Group

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External Review

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Conflicts of Interest (COIs)

All members of the Development Group, as well as those who participated in the expert collaboration and external review, made the declaration of interest below.

Declaration of Interests

Guideline Development Group of the CPG on Perinatal Hypoxic-Ischaemic Encephalopathy

Thais Agut Quijano, Ana Alarcón Allen, Gemma Arca Díaz, Juan Arnáez Solís, Albert Balaguer Santamaría, Mireia Espallargués Carreras, M. Dolors Estrada Sabadell, Alfredo García-Alix Pérez, Javier González de Dios, Ana Martín Ancel, Miriam Martínez-Biarge, Ana María Merino Márquez, Carlos Ochoa Sangrador, Ruth del Río Florentino, Silvia Semaan Llurba and Verónica Violant Holz declared no conflict of interests.

Albert Balaguer Santamaría received aid from the pharmaceutical industry in 2010, managed from his service to attend a national conference on paediatrics. In 2011, he received financing from the Instituto Carlos III to work on a research project not related to this CPG.

Nuria Herranz Rubia received professional fees as a speaker for Abbot in 2008 regarding a conference on the Hera project.

Dorotea Blanco Bravo received professional fees as a speaker for Covidien in 2011.

Others Collaborations

Marta Camprubí Camprubí, Y. Castilla Fernández, A. Alberola Pérez, H. Boix Alonso, S. Caserío, G. Ginovart Galiana, S. Lubián, Violeta Tenorio Romojaro and E. Valverde Núlez declared no conflict of interests.

External Review

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Related Content

Supporting Documents

- Original guideline in Spanish; 2015.
- Quick Reference Guides and Summary Versions (in Spanish).
- Methodological Material Clinical Practice Guideline Hypoxic-Ischemic Encephalopathy Perinatal in the Newborn (in Spanish).
- Preparation of Clinical Practice Guidelines in the National Health System. Update of the Methodological Manual (in Spanish); 2016 Mar.

- Updating Clinical Practice Guidelines in the Spanish National Health System: Methodology Handbook; 2009 Mar.

- Original Guideline via Mobile Application (in Spanish).

Patient Education

- Appendix 1 of Original Guideline; 2015. Also available in Spanish.

Note: This patient information has been derived and prepared from the original clinical practice guideline for health care professionals. It is intended to help patients better understand their health and their diagnosed disorders. Patients and their representatives should still consult with a licensed health care professional for evaluation of treatment options as well as answers to their personal medical questions.

Disclaimer

ECRI's Guideline Briefs are designed to provide information and assist decision-making. Variations in practice will inevitably, and appropriately, occur when clinicians take into account the needs and preferences of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional using these Guideline Briefs is responsible for evaluating the appropriateness of applying them in a clinical setting.

TRUST Scorecard

Composition of Guideline Development Group (GDG)

Yes	Multidisciplinary GDG Members
Yes	Methodologist Involvement
★★★★★	Incorporation of Patient and Public Perspectives

Systematic Review of Evidence

★★★★☆	Literature Search

Study Selection

Evidence Synthesis

Foundations for Recommendations

Strength of Evidence Grade

Description of Benefits and Harms of Recommendations

Summary of Evidence Supporting Recommendations

Strength of Recommendations Rating

Clear Articulation of Recommendations

Yes **Funding Source Disclosure**

Disclosure and Management of Financial COIs

External Review

Updating