Clinical Practice Guidelines on Perinatal Hypoxic-Ischaemic Encephalopathy on Newborns

NOTE:

It has been 5 years since the publication of this Clinical Practice Guideline and it is subject to updating.

The recommendations included should be considered with caution taking into account that it is pending evaluate its validity.

CLINICAL PRACTICE GUIDELINES IN THE SPANISH NHS
MINISTRY OF HEALTH, SOCIAL SERVICES AND EQUALITY

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

RED ESPAÑOLA DE AGENCIAS DE EVALUACIÓN DE TECNOLOGÍAS Y PRESTACIONES DEL SISTEMA NACIONAL DE SALUD

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This CPG is an aid for decision making in health care. It is not mandatory, and it is not a substitute for the clinical judgement of heathcare personnel.

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Presentation

Documenting the variability in clinical practice, analysing the causes thereof and adopting strategies that are targeted at eliminating that variability have proved to be initiatives that promote effective and safe decision-making by health professionals that is focused on and shared by the people. Among such strategies, the preparation of Clinical Practice Guidelines (CPGs) is at the forefront, which are a "set of recommendations based on a systematic review of the evidence and on an assessment of the risks and benefits of the various alternatives, with the objective of optimising healthcare for patients".

One of the priorities of the Ministry of Health, Social Services and Equality is to continue fomenting the preparation and use of health technologies assessment reports and CPGs, thereby strengthening the Network of Agencies for the Assessment of Health Technologies and Services of the National Health System (SNS) and the GuíaSalud Project.

Neonatal encephalopathy due to a perinatal hypoxic-ischaemic injury represents a relevant social-health problem, because in addition to affecting a considerable number of newborns (approximately 1 out of every 1000), it involves a lifetime of serious and permanent consequences, with a huge impact on the functional capacity and the quality of life of these boys and girls, in addition to representing a high socio-economic cost for families and society.

Major advances have occurred over the last decade, not only in the diagnostic and prognostic approach, but also in the therapeutic handling of this entity. Despite the scientific evidence, there is considerable variability in the diagnostic and prognostic strategies and also in the therapeutic care, although to a lessor degree, given that at the current time, there are no alternatives to the use of therapeutic hypothermia, which is an effective and safe intervention that allows preventing or reducing the brain damage associated with hypoxic-ischaemic encephalopathy.

This guideline is the result of the work of a broad group of professionals linked directly to the care of newborns with hypoxic-ischaemic encephalopathy, and it attempts to establish recommendations based on the best scientific evidence in order to improve the healthcare that is given to these newborns and their families in the acute phase. To establish the recommendations, considerable effort was given to not only the systematic review and synthesis of the available knowledge, but also to conducting our own meta-analysis to answer many of the questions. In the review process, the guideline group relied on the collaboration of experts from different scopes and disciplines and from scientific societies related directly to the care of these children.

It should also be pointed out that this publication includes a guide for parents, relatives and caregivers, which has been established based on qualitative research on their own experiences and needs and expressed in their own words.

At the Directorate-General of Public Health, Quality and Innovation, we are pleased to present this guideline, and we hope that it allows finding the answers to many of the questions related to care for newborns with hypoxic-ischaemic encephalopathy, that it facilitates making safe and effective decisions and that it improves the quality of the healthcare given to these patients and their families.

José Javier Castrodeza Sanz
Director General of Public Health, Quality and Innovation

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Declaration of interests:

All members of the Development Group, as well as those who participated in the expert collaboration and external review, made the declaration of interest appearing in Appendix 5.

Key Questions

RISK / COMORBIDITY FACTORS

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

2. 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 HIE always related to neurological mortality or morbidity?

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

TREATMENT

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

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

6. 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?

7. 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 the encephalopathy to predict the risk of death or neurological morbidity in the long term?

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

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

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

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

PROGNOSTIC STUDIES

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

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

14. What is the prognostic value of the biomarkers in blood, urine or CSF to predict death or neurodevelopmental problems in newborns with moderate or severe HIE, whether or not treated with hypothermia?

FOLLOW-UP

15. Do the current data for predicting neurological damage based on both clinical data and/or the pattern of involvement in the NMR allow establishing differentiated and effective programmes of neurodevelopmental follow-up?

Levels of evidence and recommendations grades

Classification of the quality of evidence in the 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)** Notification bias: High probability of **(-1)**	Association: scientific evidence of a strong association (RR>2 or <0.5 based on observation studies without confusion factors) **(+1)** Scientific evidence of a very strong association (RR>5 or <0.2 based on studies without the possibility of bias) **(+2)** Dose-response gradient **(+1)** All the possible confusion factors could have reduced the observed effect **(+1)**
Moderate			
Low	Observational studies		
Very low	Other types of design		

RCT: randomised clinical trial

Implications of the grades if 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.

Likewise, "**guidelines of good clinical practice**" have been formulated (3), 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.

Recommendations of the CPG

Risk / comorbidity factors

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, we suggest not beginning the administration of O_2 at 100%.
√	In newborns with a gestational age of greater than or equal to 35 weeks that require ventilation due to apnea and bradycardia at birth, we suggest beginning resuscitation with ambient air or intermediate concentrations of oxygen and suggest that the concentration of O_2 be adjusted according to the clinical response and the saturation of the patient.
Weak	Given that an Apgar score of 0 at 10 minutes is not always related to death or moderate/severe neurological disability, we suggest not using this data by itself to make the decision to limit the therapeutic effort and to 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, we suggest 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 within the first hours of life (72 hours) could mean having the availability of the results of diagnostic tests that have greater prognostic value and knowing the preferences of the parents.
Strong	In newborns with a gestational age of greater than or equal to 35 weeks with HIE, we recommend 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, we recommend avoiding severe hypocapnia (pCO_2<20 mmHg) in the first 24 hours of life.
√	In newborns with a gestational age of greater than or equal to 35 weeks with HIE, we suggest 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, we recommend 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, we suggest avoiding hyperglycaemia in the first 72 hours of life.

Treatment

Strong	We recommend 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 18-24 months of age.
Weak	We recommend 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 6-8 years.
√	We recommend that children with moderate or severe HIE be cared for at hospitals with level III neonatal or paediatric intensive care units where controlled hypothermia is available and they have 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.
Strong	We recommend 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 18-24 months of age.
Strong	In newborns with a gestational age of greater than or equal to 35 weeks with HIE, we recommend, during the first 6 hours of life, the application of clinical grading systems based on the Sarnat scale to classify the severity of the encephalopathy and to identify candidates for therapeutic hypothermia (patients with moderate or severe encephalopathy).
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, we recommend that the encephalopathy be clinically graded at 72 hours as a tool for predicting the risk of death or severe disability.
√	In newborns with a gestational age of greater than or equal to 35 weeks with moderate or severe HIE, we suggest 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, we suggest not using phenobarbital in the first 6 hours of life to reduce death or disability in the short or medium term.
√	In newborns with a gestational age of greater than or equal to 35 weeks with moderate or severe perinatal HIE, we currently suggest not using any pharmacological treatment together with hypothermia to reduce death or disability.
Weak	In newborns with a gestational age of greater than or equal to 35 weeks with HIE and not treated with therapeutic hypothermia due to the presence of electrical seizures, we suggest that anticonvulsant drugs be administered.
√	In newborns with a gestational age of greater than or equal to 35 weeks with significant HIE and treated with therapeutic hypothermia, we suggest administering anticonvulsant drugs if electrical seizures are maintained.
√	We suggest 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 and 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

Weak	We suggest the use of aEEG within the first 6 hours of life as a prognostic tool in newborns with HIE. The diagnostic OR is 30.69 (95% 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	We recommend the use of aEEG as from 6 hours of life as a prognostic tool of death or severe disability in newborns with HIE. This prognostic value in hours of life is delayed in newborns 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%).
Strong	We recommend conducting a brain MRI 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; 16.09 to 51.95%, respectively).
Strong	In newborns with HIE, whether or not they are treated with therapeutic hypothermia, we recommend conducting a brain MRI between 8 and 30 days to establish the prognosis of death or severe disability.
Weak	In those patients in which there are prognostic doubts or testing is necessary to orient medical decisions, such as adapting the therapeutic effort, we suggest conducting an early brain 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.
Strong	In newborns with a gestational age of greater than or equal to 35 weeks with HIE and they are stable and without refractory coagulopathy, the determination of NSE in CSF in the first 72 hours of life must be considered, particularly if additional information is required to establish the prognosis or make decisions about limiting the therapeutic effort.

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 with hypothermia and to the various prognostic tests indicated in this CPG.
√	Evaluations 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.
√	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 the children at 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.

1. Introduction

The term perinatal asphyxia refers to the interruption of the gas exchange that takes place specifically around birth, which is manifested in the fetus or in the newborn as hypoxaemia, hypercapnia and lactic acidosis due to tissue hypoperfusion.[1-4] The underlying pathogenic mechanisms are hypoxaemia (decrease of the quantity of oxygen in the blood) and ischaemia (decrease of blood perfusion). The data as a whole obtained in experimental models suggest a greater relevance of the ischaemia versus cerebral hypoxia in the origin of the harmful effects to the central nervous system (CNS).

The American Academy of Pediatrics, the American College of Obstetrics and Gynecology and the International Cerebral Palsy Task Force have recommended not using the term "asphyxia" at birth, unless there is clear evidence of a causal relationship between the state of the newborn and the intrapartum events.[1] When the hypoxia-ischaemia episode associated with the asphyxia is severe enough to injure the brain of the newborn, then the newborn unavoidably shows neonatal encephalopathy within the first hours of life, which, due to the nature and the moment when it occurs, we call perinatal hypoxic-ischaemic encephalopathy (HIE). The term "encephalopathy" denotes an acute neurological dysfunction of variable severity that is characterised by a difficulty to wake up or stay awake; difficulty to initiate or remain breathing (respiratory depression); an alteration of muscle tone, of motor responses, of responsiveness, of reflexes and of feeding ability; and frequently, convulsions.[3]

Criteria for considering HIE in newborns with a gestational age of greater than or equal to 35 weeks

Perinatal asphyxia is not the only cause of neonatal encephalopathy. An important prerequisite for attributing neonatal encephalopathy to a perinatal hypoxic-ischaemic event is the existence of perinatal metabolic acidosis (pH of less than or equal to 7 or a base deficit of at least 12 mmol/L in the scalp, the umbilical cord or the blood during the first hour of life). Other, additional criteria that, taken as a whole, suggest an origin during birth, but which are not specific of a hypoxic-ischaemic injury, are the presence of low scores in the Apgar test (< 5) during more than 5 minutes, multiple organ dysfunction during the first days of life and acute brain injuries in magnetic resonance imaging (MRI) studies. Moreover, other aetiologies should be included, such as prenatal infections (i.e. listeria), obstetric trauma, coagulation disorders, metabolic diseases and genetic causes.[1, 4]

Impact of perinatal hypoxic-ischaemic encephalopathy

Moderate or severe perinatal HIE in newborns with a gestational age of 35 weeks or more constitutes a major cause of morbidity and mortality in the neonatal period and of permanent disability in a child. Neonates with moderate HIE show a risk of death of 10%, and among survivors, 30-40% will show a permanent disability of varying severity, while newborns with severe HIE have a risk of death of 60%, and practically the vast majority of those that survive will have a permanent disability. It has been calculated that HIE is responsible for 20% of all children with Cerebral Palsy (CP).[5] In Denmark, it has been estimated that every child with complex neurological sequelae, such as those that occur after hypoxic-ischaemic injury, costs the state approximately one million dollars (800,000 euros) in healthcare, social support and loss of productivity throughout

life. The real cost must be far greater, insofar as the cost of the intensive care during the neonatal period and the impact on scholastic assistance, the behavioural and psychiatric disorders of the child and the impact of scholastic failure have not been calculated.

Asphyxia at birth and the consequence thereof, neonatal encephalopathy, has one of the highest DALY indexes (disability-adjusted life years) and QALY indexes (quality-adjusted life years) of all illnesses, given that newborns have their whole life ahead of them.

In brief, the major medical, family, social and legal implications associated with this devastating entity make HIE a relevant social-health problem.

Magnitude of the problem

The incidence of HIE is distributed unequally throughout the world, occurring mainly in countries with poor resources or where income is low. The World Health Organization (WHO) estimates that 25% of neonates and 8% of all deaths under 5 years of age in countries with few resources suffer from birth asphyxia. In 2010, it was estimated that 1.15 million newborns in the world showed perinatal HIE; 96% were born in between 7.7 and 4.4‰ for live newborns, while the rates referring to the end of the 90s and the beginning of the 21st century were always below 1.5 ‰.[6-13]. The incidence noted in the first 10 years of the 21st century in a teaching hospital of Madrid was approximately 1‰ of live newborns.[14] Even though the denominator should not be the total of live newborns, rather the total of term newborns, the majority of live newborns are born at term age, and therefore the real rate shouldn't differ significantly from the indicated rate.

Moderate or severe forms, which are those that involve the risk of brain injury and permanent disability, happen in our territory at 0.5-1.0‰ of live newborns,[14, 15], which is an incidence that is similar to that of other European countries. Considering the data of the National Institute of Statistics, with 471,999 live newborns in 2011, it is calculated that in Spain every year between approximately 235 and 471 newborns will develop moderate or severe HIE.

Clinical severity of HIE

All neonates with a history of perinatal asphyxia should undergo a detailed neurological examination to evaluate the existence of neurological dysfunction and grade the severity. Even though the signs that define the severity of hypoxic-ischaemic encephalopathy show a continuous spectrum of alteration, there are a series of grading schemes, more qualitative than quantitative, which classify the depth of the encephalopathy in different stages of severity. The classification used the most is the Sarnat classification.16 Other semi-quantitative gradings of the severity of HIE are the classifications by the following: Amiel-Tison,[17] García-Alix et al.,[18] Miller et al.,[19] and Thompson et al.[20] In general, the classifications by Sarnat, Amiel-Tison, García-Alix and Thompson assess severity based mainly on the level of consciousness, the alteration of muscle tone and reflexes and the existence of clinical convulsions. Thus, these three classifications are based on the premise that the greater the alteration to the level of consciousness, the greater the clinical symptoms.

The degree of clinical encephalopathy in the neonatal period has been the main approach used to predict the development of children with HIE. Studies in the 70s and 80s of last century consistently showed that the immense majority of children with mild HIE had a very low risk of having serious alterations of neurodevelopment; but children with severe HIE almost invariably died during the neonatal period or after discharge, or they showed significant alterations, such as severe cerebral palsy, cognitive deficit and epilepsy. The prognosis of children with moderate HIE has always been much more variable and difficult to predict.[21]

This approach to the neurodevelopmental prognosis has a few limitations: first of all, grading the clinical severity of HIE is not always easy, especially if a newborn is receiving or has received antiepileptic or sedative and analgesic medication. Moreover, the severity classifications of encephalopathy used in studies are not uniform, which leads to overlaps between the mild-moderate categories and even between the moderate and severe categories. Secondly, it leaves children with moderate HIE with a prognosis that is too uncertain. And third, long-term studies show that newborns with mild HIE, traditionally considered to be "without risk" and therefore often not included in follow-up programmes, have a rate of alteration in development that is higher than what had been considered up to now. These alterations include fine motor problems in the absence of cerebral palsy, neuro-psychological and memory disorders, behavioural problems (especially attention and social integration problems) and special educational needs.[22, 23]

All these data about the predictive value of the severity of HIE basically come from a period prior to treatment with hypothermia, when the severity was established according to its maximum expression in the first days of life. But now, in the era of therapeutic hypothermia, the severity of HIE is established in the first 6 hours of life.

Prognostic testing

In the last 30 years, various complementary evaluations have been incorporated, which allow discarding other conditions and demonstrating the evolution of the injury, but even more importantly, they have prognostic value. Any newborn with HIE should have access, during the neonatal period, to those diagnostic tests with proven capacity to establish the prognosis as accurately as possible. Among the tests regularly used in clinical practice, we would highlight the following:

Amplitude-integrated EEG (aEEG) or EEG

Electrocortical activity should be monitored in all children with HIE. This activity is mainly monitored through the aEEG, whose observed findings must be documented in the patient's medical record and be classified according to the base patterns, wake-sleep cycles and ictal paroxysmal activity.[24] The aEEG, in addition to helping within the first few hours of life to decide whether or not to treat a child with hypothermia, currently seems to be one of the best prognostic evaluations during the first 48 hours of life.[25]

The standard EEG should be run at any time if clinical or electrical convulsions are observed during the hypothermia-rewarming period and before discharge if alterations were noted.

Brain ultrasonography

This evaluation should be done upon being admitted to the NICU. It allows excluding anomalies of brain development or showing prenatal damage or detecting anomalies that indicate an origin other than neonatal encephalopathy: hypoplasia of the corpus callosum suggests nonketotic hyperglycinaemia, or marked germinolytic cysts suggest a mitochondrial disorder, a peroxisomal disorder or congenital infections.

Serial Doppler ultrasonography clearly shows the evolution of the damage, and the Doppler evaluation by determining the pulsatility index (normal values: 0.65-0.85) provides useful prognostic information in the stage prior to treatment with hypothermia. Values below 0.55 are noted in neonates with severe HIE generally between days 2 and 4 after birth,[26] while abnormal values within the first 6 hours of life suggest a hypoxic-ischaemic injury that has occurred 1-2 days before birth.[27] When injuries are detected, Doppler ultrasonography is performed upon discharge and beyond the first week, given that it allows showing the evolution thereof.

Magnetic Resonance Imaging (MRI)

MRI clearly shows the structural injuries that occur from a hypoxic-ischaemic injury. These injuries show a characteristic topography that closely resembles what is noted in immature animal models of hypoxic-ischaemic injury. Moreover, injuries can be graduated, and this graduation is well correlated with the subsequent evolution.[28, 29] MRI is regularly done at the end of the first or during the second week of life, and it includes T1 and T2 weighted sequences, diffusion-weighted sequences and magnetic resonance spectroscopy (MRS). Occasionally, especially when limiting the therapeutic effort is being considered, MRI is done in the first 96 hours.

Biomarkers of brain injury

The clinical evaluation and the aEEG can be affected by medication and therapeutic interventions, such as antiepileptic medication, sedatives and muscle relaxants. Thus, certain biomarkers of injury, generally more or less specific proteins of the nervous system, have been examined and used as an additional strategy for evaluating the severity of the injury and providing information about the prognosis. The main biomarkers of injury used in blood or CSF have been neuron-specific enolase (NSE), the S100B protein (S100B), the glial fibrillary acidic protein (GFAP) and S100B in urine and the lactate/creatinine ratio. The determination of these biomarkers in blood, CSF or urine is used in some groups, but its predictive capacity can differ according to the biological fluid.[18, 30]

Treatment of HIE

During all the 20th century, HIE had been devoid of specific therapeutic interventions targeted at preventing or reducing the brain damage associated with this entity. Fortunately, this panorama has changed in the first decade of the 21st century, given that various clinical trials showed that reducing the brain temperature by 3-4º C, either by complete cooling of the body or selective cooling of the head, decreases mortality and major disability in survivors.[31-38] Various meta-analyses (MA) have clearly shown that the number of neonates with HIE that need to be treated (NNT) to prevent a case of death or disability is in a range of 6 to 9 patients.[39-42] This evidence has led to the fact that therapeutic hypothermia is now considered a standard therapeutic intervention for this illness. This therapeutic intervention has been uniform in all randomised clinical trials (RCTs): cooling initiated before 6 hours of life and, once the target temperature of 33-34º C is reached, this moderate hypothermia is maintained for 72 hours, after which slow rewarming is performed (≤ 0.5º C per hour).

Care challenges related to therapeutic hypothermia

The maximum therapeutic effectiveness of therapeutic hypothermia seems to be obtained the sooner that therapeutic hypothermia is initiated after birth, and always within the first 6 hours of life. This tight time frame of therapeutic opportunity, a few hours of gold, conditions the need to establish quick and well-ordered operational activities in which the actions to be performed in each one of the care stages must be precisely established: from the delivery room to intensive care, and once there, the actions during both the hypothermia phase and the subsequent stage.

Newborns with moderate or severe perinatal HIE must be cared for at hospital centres with level III neonatal or paediatric intensive care units, with the availability of applying controlled hypothermia and the capability to respond to the complex care needs of these children and their families.[43]

In cases of neonates that develop HIE and that are born at hospitals without neonatal intensive care units or without hypothermia programmes or integrated handling of the hypoxic-ischaemic pathology, a patient suspected of having HIE must be urgently moved to tertiary centres of reference. However, it is necessary to evaluate the conditions and how to apply hypothermia at centres without a specific program, how to apply hypothermia during transport (monitoring and cooling equipment that can be used in an ambulance) and what complications can happen during transfer, in order to establish recommendations targeted at offering and assuring the adequate care that these newborns need while being transported.[44, 45]

Consensus guidelines and clinical practice guidelines for HIE

Therapeutic hypothermia in newborns with moderate or severe perinatal HIE has become generalised in recent years, and today it is a daily reality in the majority of tertiary neonatal units of Europe, America and Oceania. Not only in our country,[45] but also in the United Kingdom,[46] the United States,[47] Australia[48] and Canada,[49] consensus guidelines on how to handle newborns with HIE have been developed. These guidelines, with practical recommendations, are basically directed at incorporating hypothermia in tertiary neonatology units. However, they have been established without a systematic review of the scientific evidence, and therefore they have not been drafted while explicitly stating the available evidence, particularly regarding the diagnostic and therapeutic aspects.

To date, there are two CPGs published on perinatal HIE. The first, produced in the United States by physicians and nurses, focuses on hypothermia as a therapeutic intervention.[50] The second, produced in Mexico, covers very general aspects about HIE, and it is therefore of limited practical utility.[51]

Justification of the need in current clinical practice to prepare this CPG

The incorporation of therapeutic hypothermia to the treatment of HIE has given rise to new questions, and concomitantly a large quantity of literature has been generated in recent years, which makes it difficult to critically assimilate the available volume of information in scientific literature regarding the diagnosis, treatment and prognosis of HIE. All this information is critical for comprehensive improvement of the healthcare of these newborns. The non-availability of CPGs or other current documents in literature that are based on evidence and that cover this entity comprehensively make it necessary to conduct a synthesis and critical evaluation designed to establish recommendations based on the evidence, thereby optimising treatment and providing for more uniform handling of newborns with perinatal HIE.

The justification of the following CPG can be summarised by the following points:

- Identification of the factors or comorbidity conditions that can worsen or facilitate brain damage in the first hours of life and during treatment.
- Knowing if the administration of 21% oxygen versus concentrations above 21% during the resuscitation of newborns with asphyxia has an influence on neurological morbidity and mortality.
- Clarifying if the severity of HIE conditions the effectiveness of the treatment with hypothermia

and if the severity before treatment with therapeutic hypothermia predicts subsequent adverse development.

- Systematically reviewing if other pharmacological treatments (EPO, xenon, topiramate, phenobarbital, allopurinol), either alone or in combination with hypothermia, reduce brain damage.
- Knowing if treatment of the electrical seizures of newborns with HIE in treatment with hypothermia have an influence on the severity of subsequent brain damage.
- Clarifying if sedation with opioid derivatives in newborns with HIE (with or without hypothermia) decreases the severity of brain damage.
- Examining if hypothermia has modified the value of the clinical examination to predict neurodevelopmental disorders in newborns with moderate or severe HIE.
- Knowing the prognostic value of the aEEG, of the biomarkers of damage in the different biological fluids and the NMR to predict neurodevelopmental problems in newborns with moderate or severe HIE and if hypothermia has modified the value of these studies.
- Establishing if the current data for predicting neurological damage based on both clinical data and/or the pattern of involvement in the NMR allow establishing differentiated and effective programmes of neurodevelopmental monitoring.
- Preparing informative material for the parents and relatives of these children while considering the feelings, needs and emotions of the parents and outlining specific family support strategies during the healthcare process of these newborns.

2. Scope and objectives

Scope

Population

Newborns with a gestational age of greater than or equal to 35 weeks with perinatal HIE.

- We understand ***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:
  - The presence of an obstetric background of risk (sentinel event, non-reassuring foetal status or labour dystocia) and/or
  - 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.

Healthcare scope

- Hospital centres, both secondary and tertiary of the public network of the National Health System, or private centres in which newborns with HIE are born and/or are cared for.
- Health teams involved in the transport of newborns with a gestational age of greater than or equal to 35 weeks with moderate or severe HIE.
- Children's Development and Early Care Centres (CDIAPs) and rehabilitation centres.
- Management bodies or suppliers of healthcare or services.

This 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.

Main users

The recommendations contained in this CPG are designed for the following groups:

- **Health care professionals**
  - Neonatal paediatricians, neonatal nurses and other professionals, such as intensive care paediatricians, health transport teams, general paediatricians, neuro paediatricians, neuro physiologists, neuro radiologists and midwives who participate in the healthcare process during the acute and convalescent phases of newborns with HIE.
  - Hospital and non-hospital specialists (general paediatrician, neuro paediatricians, rehabilitation specialists, nutritionists, speech therapists and others) who actively participate in the continued healthcare process during the infancy and childhood of these patients after discharge from neonatology.
  - Clinical managers whose interest are primary and secondary diagnostics, procedures and the costs of healthcare processes.
- **Allied professionals, fundamentally in the interdisciplinary management of patients** (social assistants, speech therapists, cultural mediators).
- **The families and caregivers of these children, including parent associations.**
- **Forensic specialists, lawyers and legal personnel** who, for professional reasons, assist the families of these children in legal aspects.

Objectives

General objective

Prepare a CPG that provides healthcare professionals and the families of these children with a tool, based on scientific evidence, that helps them to make therapeutic, diagnostic, prognostic and follow-up decisions that are tackled in the care of neonates with HIE.

Specific objectives

- Establish recommendations for the purpose of supporting, in the entire National Health System, the decisions of healthcare professionals involved with neonates with HIE. These recommendations will affect elements of resuscitation, comorbidity conditions in the first hours, diagnosis, treatment, prognosis and follow-up.
- Evaluation of the cost-effectiveness, ethical, cultural and organisational aspects that must be taken into account in the recommendations.
- Examine the impact on families and provide useful information for parents (or relatives/caregivers) whose children have HIE in order to offer them the help and support they need, as well as establish actions that facilitate their parental role in this difficult circumstance.

3. Methodology

The methodology used to prepare the CPG is included in the Methodological Manual for Drafting CPGs in the National Health System.[52]

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 HIE when formulating the recommendations of the CPG and to prepare information for parents, relatives and caregivers (Appendix 1), a qualitative study was conducted.
- The formulation of clinical questions following the Patient-Intervention-Comparison-Outcome 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.
- Synthesis and evaluation of the quality of the evidence. The two CPGs on perinatal CPG that were found[50, 51] 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 (see Appendix 2 of methodological material).
- 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).[56, 57]
- 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.

- At www.guiasalud.es, there is material available that provides detailed information about the methodological process of the CPG.
- Updating of the guideline is planned for every three or five years, or within a shorter period of time if new evidence arises that could modify some of the recommendations offered in this guideline. Updates will be made to the on-line version of the guideline, available at: http://www.guiasalud.es.

4. Risk / comorbidity factors

Questions to be answered:

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

4.1. 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?

4.1.1. Introduction

100% oxygen (100% O_2) has been the gas traditionally recommended for cardiopulmonary resuscitation. However, there are increasingly more experimental and clinical data that suggest that 21% O_2 (ambient air) can be just as effective as 100% O_2. Moreover, 100% O_2 can cause hyperoxia, can increase the production of free oxygen radicals and can increase the damage due to oxidative stress and can even have adverse effects on the respiratory physiology.

4.1.2. Outcomes

4.1.2.1. Mortality

5 SRs were identified (Davis, 2004; Tan, 2005; Saugstad, 2005; Rabi, 2007; and Saugstad 2008[58-62]), which assess, in newborns that require cardiopulmonary resuscitation at birth, if the use of ambient air versus 100% O_2 determines differences in mortality. The Saugstad, 2008[62] review was selected due to being of good quality and the most current.

Low quality

The Saugstad, 2008[62] SR identified 6 randomised studies and 4 quasi-randomised studies that included 2133 newborns that required ventilation (generally due to apnea and bradycardia) in the first minute of life (1082 treated with ambient air; 1051 with 100% O_2). These studies included newborns of over 1000 g of any gestational age, a large part coming from countries of the third world. The SR found the mortality to be the following: in the ambient air group, 5/1082 (1.1%), and in the 100% O_2 group, 15/1051 (3.9%), RR 0.69 (95% CI, 0.54 to 0.88), NNT 25 (95% CI, 16 to 100).

The authors decided to separately analyse the subgroup of randomised studies conducted in Europe (3 in Spain and 3 in Romania), which included only term newborns and late premature newborns (n = 836), and they found results similar to those found when analysing the total of all studies: mortality in the ambient air group was 5/449 (1.1%) and in the 100% O_2 group was 15/387 (3.9%), RR 0.32 (95% CI, 0.12 to 0.84). The authors of the SR do not explain the reason for the difference between the number of patients randomised to each branch of treatment (449 vs 387), which to a large extent depends on a study conducted in Spain (Vento, 200163). The SR refers to the fact that, in this study, which is the one that provides a greater difference in the mortality between the groups (1 patient deceased with ambient air versus 7 patients with 100% O_2), 300 newborns received ambient air and 237 newborns received 100% O_2. The authors of the SR report that they corrected for the fact that some of the newborns of the Vento[63] study had also been reported in one of the other studies included in the SR (Saugstad, 1998: including 6 patients from Valencia, none of whom died), but they do not explain why the SR only considered 537 of the 830 newborns included in the primary study by Vento, 2001 (304 with ambient air and 526 with 100% O_2), whose authors report not having either randomised or masked all the cases.

Finally, the authors of the SR report in the discussion that they also analysed the subgroup of the 3 studies conducted in Europe that evaluated term newborns and late premature newborns who were randomised and masked (the Vento, 2001 study is included), with similar results (data not shown).

4.1.2.2. Cerebral palsy

3 SRs were identified (Davis, 2004;[58] Tan, 2005;[59] and Saugstad, 2012[65]), which evaluate, in children who required ventilation at birth due to apnea and bradycardia, if the use of ambient air versus 100% O_2 determines differences in long-term neurological morbidity. The Saugstad, 2012[65] SR was selected due to being of good quality and the most current.

Low quality

This SR does not specifically pose the question of cerebral palsy, but one of the included studies (Saugstad, 2003), which conducted follow-up on 66% of the eligible 213 newborns up to 18-24 months, explains that CP was diagnosed when the examiner found the child to be spastic and hyperreflexic, which occurred in 9 of the 91 children followed-up on in the ambient air group (9.9%) and in 9/122 in the 100% O_2 group (7.4%), OR 1.38 (95% CI, 0.52 to 3.62).

4.1.2.3. Moderate/severe cerebral palsy (3-5)

No study that specifically evaluates this outcome was identified.

4.1.2.4. Death or moderate/severe disability

The Saugstad, 2012[65] SR identified 1 randomised study and 2 quasi-randomised studies that included 417 newborns that required ventilation at birth due to apnea and bradycardia in the first minute of life (195 treated with ambient air; 219 with 100% O_2). These studies included newborns of over 1000 g of any gestational age, 51.4% coming from countries of the third world. Follow-up was conducted at 1-2 years of age (chronological in the study, corrected in another and correction not necessary in the third). The neurological assessment was conducted informally, without structure, in the broadest study (51.4% of the patients). In this SR, the combined outcome of mortality and altered neurodevelopment was not evaluated, rather just the "altered neurodevelopment" outcome on its own. No significant differences regarding altered neurodevelopment were found between the group resuscitated with ambient air versus the group resuscitated with 100% O_2, average RR of 1.24 (95% CI, 0.73 to 2.10). Due to the high losses in follow-up (24.3%), the authors calculated the extreme scenarios, therefore subsequently attributing the best and the worst of the possible outcomes to the lost patients. Thus:

Low quality

- The extremes favour treatment with air (all children not followed-up on who received air were coded as normal, and those who received 100% O2 were coded as altered neurodevelopment). The potential for greater benefit would be: RR of 0.33 (95% CI, 0.22 to 0.50).
- The extremes favour 100% O_2 (the opposite coding of the children not followed-up on). The potential for greater damage would be: RR of 4.09 (95% CI, 2.63 to 6.38).

For the preparation of this guideline, as a secondary analysis, we performed our own MA. For the preparation thereof, the combined outcomes of mortality and altered neurodevelopment were obtained, which hadn't been done in either the primary studies or in the MAs conducted to date. Therefore, the data coming from the studies that analysed mortality (Saugstad, 2008[62]) and that subsequently offered data on neurological follow-up (Saugstad, 2012[65]) were used. To do so, standard software was used (Revman®). The result of this MA does not show heterogeneity ($I^2 = 0\%$), and following a model of fixed effects, it shows that the use of ambient air versus 100% O_2 would mean a relative risk of 0.88 for this compound variable (95% CI, 0.68 to 1.16). This means that no significant differences were found between using ambient air compared to 100% O_2 for this outcome (see Appendix 3 of the methodological material for more details).

Low quality

4.1.3. From the evidence to a recommendation

4.1.3.1. Quality of the evidence

Low quality	**Mortality.**[62] The quality of the evidence decreased in the assessed outcome variables due to limitations in the design of the studies (many were not adequately randomised or masked, and they included patients mainly from the third world of any gestational age and with a weight of over 1000 grams and with other pathologies that required resuscitation).
Low quality	**Death or disability**.[62, 65] The quality of the evidence decreased when limitations in the design of the study were detected (see the preceding section, mortality variable), and also due to considerable losses in follow-up, a non-structured evaluation of neurodevelopment in many of the patients and inaccuracy of the results (few events and small sample size).

4.1.3.2. Balance between benefits and risks

	No risk could be expected due to the use of ambient air. However, there are patients who would not be offered the possible benefit of treatment with intermediate concentrations of O_2 not yet assessed.

4.1.3.3. Costs and use of resources

	Resuscitation with ambient air represents a lower cost and use of resources. However, no economic evaluation studies that specifically analyse this aspect were found.

4.1.3.4. Values and preferences of the patients

	The values and preferences of the parents of the patients have not been considered to be a determining factor for assessing the strength of the recommendation regarding the use of 100% O_2.

4.1.4. Final decision about the strength (strong or weak) and the direction (in favour or against) of the recommendation

Aspects that have determined the direction and strength of the recommendation:

The studies suggest that in newborns that require ventilation at birth due to apnea and bradycardia, the use of ambient air is safe and could decrease mortality compared to the use of 100% O_2, although it has not been demonstrated that the combined variable of "death or altered neurodevelopment" decreases. In a high proportion of newborns assigned randomly to ambient air, the use of 100% O_2 for resuscitation was resorted to.[62, 65]

Intermediate concentrations of oxygen have not been evaluated in term asphyxial children, nor have sub-groups been analysed according to the aetiology.

Secondary effects due to the use of ambient air are not expected, except that these patients would not be offered the possible benefit of treatment with intermediate concentrations of O^2 that have yet to be evaluated.

There could be a favourable cost/benefit ratio, but there are no studies in this regard.

4.1.5. Summary of the evidence[62, 605]

Low quality	In newborns that require ventilation due to apnea and bradycardia in the first minute of age, the use of ambient air with respect to 100% O_2 determines a reduction of mortality.
Low quality	In newborns that require ventilation due to apnea and bradycardia in the first minute of age, no significant differences were detected between the use of ambient air versus 100% O_2 with respect to the variable, cerebral palsy, at 1-2 years of age.
Low quality	In newborns that require ventilation due to apnea and bradycardia in the first minute of age, no significant differences were detected between the use of ambient air versus 100% O_2 with respect to the combined variable, "death or alteration of neurodevelopment" at 1-2 years of age.

4.1.6. Recommendations

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, we suggest not beginning the administration of 100% O_2.
√	In newborns with a gestational age of greater than or equal to 35 weeks that require ventilation due to apnea and bradycardia at birth, we suggest beginning resuscitation with ambient air or intermediate concentrations of oxygen and suggest that the concentration of O_2 be adjusted according to the patient's clinical response and saturation.

4.1.7. Implications for research

There is a need for randomised and masked CTs that evaluate more adequate concentrations of oxygen and blood saturation to achieve a better response to the resuscitation measures of asphyxial newborns and to achieve lower mortality and greater neurological development in the long term.

4.2. 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 HIE always related to neurological mortality or morbidity?

4.2.1. Introduction

The current international consensus for neonatal cardiopulmonary resuscitation, ILCOR 2010[66], considers that newborns with an Apgar score of 0 to 1 at 5 and 10 minutes of life that develop HIE will very likely die or will have severe neurological sequelae. It therefore recommends considering the suspension of resuscitation measures at 10 minutes postpartum when the Apgar score continues to be 0 at 10 minutes, but it states that there is insufficient data for establishing recommendations in patients with an Apgar of 1 at 10 minutes.

However, the majority of patients based on which this consensus has been established did not receive treatment with hypothermia, which could improve the prognosis of this group of newborns. Moreover, diagnostic tools have been progressively made easily available (NMR, aEEG, biochemical markers in CSF), which allow a more precise assessment of the severity and extent of the brain damage in the neonatal period compared to the Apgar score at 10 minutes. Finally, the severity of the clinical state of these newborns, which makes them dependent upon respiratory support in the first days of life, could allow delaying the decision to limit the therapeutic effort as from 10 minutes of life (Apgar at 10 minutes) to making the decision within the first 72 hours of life, with the objectives of increasing predictive capacity and providing time to learn the opinion of the parents (very rarely available during initial resuscitation in the delivery room), in the event that there is the possibility of survival that is free from severe sequelae in this subgroup of newborns.

4.2.2. Outcomes

4.2.1. Mortality

Two studies that assess mortality in newborns with HIE that received an Apgar score of 0 at 10 minutes were identified: a systematic review (SR) (Harrington, 2007[67]) and a secondary analysis of a randomised clinical trial (RCT) (Laptook, 2009[68]).

Low quality

The SR by Harrington[67] identified 7 observational cohort studies (Haddad, 2000; Jain, 1991; Patel, 2004; Casalaz, 1998; Thornberg, 1995; Koppe, 1984; and Socol, 1994), and it provided data from their own hospital-based cohort. In some of these studies, there is no record of the presence of congenital malformations or any record of gestational age; the data on follow-up are scarce regarding the duration and mode of assessment; the majority were published more than a decade ago; and treatment with hypothermia was not available in any of them. This SR found a mortality of 83% in the set of patients with an Apgar score of 0 at 10 minutes (n = 94).

Subsequently, Laptook68 conducted a secondary observation study on newborns that were included in an RCT (Shankaran, 2005[32]) to assess treatment with hypothermia in HIE, from which the newborns that showed clinical signs of imminent death or that died before being included were excluded. Moderate quality

In the Laptook study, 12 (48%) of the 25 newborns with an Apgar score of 0 at 10 minutes included in the RCT died. The risk of mortality in newborns with an Apgar score of 1 and 2 at 10 minutes was similar to that of newborns with an Apgar score of 0 at 10 minutes. Thus, 64% of the children with an Apgar of 1 at 10 minutes died (7 of 11); and 47% of the patients (7 of 15) with a score of 2 at 10 minutes died. Treatment with hypothermia decreased the risk of death associated with the set of possible Apgar scores at 10 minutes (OR 0.5; 95% CI, 0.25 to 0.97).

4.2.2.2. Cerebral palsy

No study that specifically evaluates this outcome was identified.

4.2.2.3. Moderate/severe cerebral palsy (GMFCS 3-5)

No study that specifically evaluates this outcome was identified.

4.2.2.4. Death or moderate disability

One SR (Harrington, 2007[67]) and one secondary analysis of an RCT (Laptook, 2009[68]) that assess death or moderate/severe neurological disability in newborns that received an Apgar score of 0 at 10 minutes were identified. Both studies have been previously described in this guideline. The Harrington SR showed the aforementioned limitations. Regarding the Laptook study, neurological follow-up was conducted at 18-22 months of age. Low quality

The SR by Harrington,[67] upon assessing the studies together with Harrington's own data (n = 94), found that 90 patients (95.7%) died or showed signs of moderate/severe disability (95% CI, 75.4 to 100). Survival that is free from moderate or severe sequelae was 1.06% of the total (6.25% of the survivors).

In the Laptook RCT,[68] 19 (76%) of the 25 newborns with an Apgar score of 0 at 10 minutes died or showed signs of moderate or severe disability (95% CI, 54.8 to 90.6%). Survival that is free from moderate or severe sequelae was 6 out of 13 (24% of the total, 46.2% of the survivors). Upon analysing this study together with the 8 studies included in the Harrington SR, an RR of death or disability of 90.6% was obtained for children with Apgar 0 at 10 minutes (95% CI, 73.4 to 100). In the Laptook RCT, the risk of death or disability for scores of 1 at 10 minutes was 81.8% (95% CI, 48.2 to 97.7), and the risk with an Apgar score of 2 at 10 minutes was 80% (95% CI, 51.9 to 95.6). This reflects that in this study, which was the only one in which hypothermia treatment was used (randomised), no differences were observed between the prognosis of children with a score of 0 at 10 minutes versus those with a score of 1 or 2. However, in newborns with an Apgar score of 3 at 10 minutes, the risk of death or disability was 6.15% (95% CI, 44.9 to 78), notably lower than the aforementioned. Moderate quality

Treatment with hypothermia decreased the risk of death or moderate/severe disability associated with the 10-minute Apgar score (OR 0.44; 95% CI, 0.23 to 0.83).

The CART analysis (classification and regression tree) for predicting death or moderate/severe disability in asphyxial newborns showed, as a first cut-off point, an Apgar score of < 5 at 10 minutes (65% of newborns with an Apgar < 5 at 10 minutes showed "adverse development", versus 30% of newborns with an Apgar ≥ 5), and as a second cut-off point, treatment with hypothermia (75% showed adverse development in the normothermia group, versus 54% in the group treated with hypothermia). An Apgar score of 0 at 10 minutes did not contribute additional discrimination in this model.

4.2.3. From the evidence to a recommendation

4.2.3.1. Quality of the evidence

Low quality	**Mortality.**[67, 68] The quality of the evidence decreased in the SR due to limitations in the design of the studies (in some of them, there is no record of the presence of congenital malformations or any record of gestational age, the data on follow-up are scarce regarding the duration, and the assessment of neurodevelopment is not structured) and due to the inaccuracy of the results (few events and small sample size). Moreover, the majority were published over a decade ago (different clinical practice), and treatment with hypothermia was not available in any of them, which is currently common practice. The quality of the evidence in the outcome variable assessed in the observational study increased, given that it consisted in the secondary analysis of an RCT in which treatment, in accordance with current practice, was offered to half of the assessed patients (branch of treatment with hypothermia).
Low quality	**Death or disability**.[67, 68] The quality of the evidence in this outcome variable assessed in the SR has decreased (see the mortality outcome). The quality of the evidence in the outcome variable assessed in the observational study has increased, in which the patients were randomised to receive treatment with hypothermia or the usual care and in which a structured assessment of neurodevelopment with scarce losses was conducted.

4.2.3.2. Balance between benefits and risks

The risk associated with continuing resuscitation beyond 10 minutes of life in patients with an Apgar score of 0 at 10 minutes would consist in increasing the survival of patients with moderate/severe neurological sequelae.

Based on the consideration of a very high risk of mortality or survival with severe sequelae, the current international consensus for neonatal cardiopulmonary resuscitation, ILCOR 2010[66], recommends suspending resuscitation measures at 10 minutes postpartum when the Apgar score at 10 minutes continues to be 0, but it states that there is insufficient data for establishing recommendations in patients with an Apgar of 1 at 10 minutes.

Given the results of the Laptook[68] RCT regarding the development, at 18-24 months of age, of children with an Apgar of 0 at 10 minutes, it is necessary to be cautious about establishing the limit for the duration of resuscitation to 10 minutes.

The current availability of diagnostic tools for more precisely assessing brain damage in the neonatal period, together with the severity of the clinical state of these newborns, could allow delaying the decision to limit the therapeutic effort from 10 minutes of life (Apgar at 10 minutes) to making the decision within the first hours of life, when they are still dependent on respiratory support. This objective of this delay would be to make the decision based on more specific data about the severity of the brain damage, with greater prognostic capacity, and not exclusively based on a generic estimate of risk.

The benefit of continuing with resuscitation beyond 10 minutes of life in patients with an Apgar score of 0 at 10 minutes, thereby considering the rest of the patient's clinical data, would represent the possibility of survival that is free from moderate/severe sequelae in a subgroup of these patients.

4.2.3.3. Costs and use of resources

The cost and use of resources due to prolonged cardiopulmonary resuscitation beyond 10 minutes is small (scarce time of personnel and low-cost medication), but greater survival by patients that would have died in the delivery room increases the costs in the neonatal acute phase and, in the case of survival with moderate/severe disability, in the sequelae phase.

No studies of economic analysis that specifically evaluate this point within the context of the clinical question were found.

4.2.3.4. Values and preferences of the patients

The assessed studies do not contribute information about this aspect.

The opinion of the parents (guardians of the patient) is very rarely available during initial resuscitation in the delivery room. However, delaying the limitation of the therapeutic effort from 10 minutes of life (Apgar at 10 minutes) to the first hours of life could provide time to learn the values and preferences of the parents.

4.2.4. Final decision about the strength (strong or weak) and the direction (in favour or against) of the recommendation

Studies suggest that an Apgar score of 0 at 10 minutes in newborns that are admitted to neonatology units is associated with a high risk of death or moderate/severe neurological disability, although an approximate percentage of greater than 20% could survive free from moderate/severe neurological sequelae. The evolution of these children seems to be similar to newborns with an Apgar score of 1 or 2 at 10 minutes. Treatment with hypothermia could decrease the risk of death or moderate/severe neurological disability associated with a low Apgar score at 10 minutes.[67, 68]

The risk of continuing with resuscitation beyond 10 minutes of life in patients with an Apgar score of 0 at 10 minutes would consist in increasing the survival of patients with moderate/severe sequelae. However, the diagnostic tools currently available for assessing brain damage in the neonatal period, together with the severity of the clinical state of these newborns (which makes them dependent upon respiratory support during the first days of life), could allow delaying the decision to limit the therapeutic effort from 10 minutes of life (Apgar at 10 minutes) to the first hours or days of life, with the objectives of increasing the predictive capacity of the Apgar at 10

minutes due to having diagnostic tests with greater prognostic value, providing time to learn the opinion of the parents (very rarely available during initial resuscitation in the delivery room) and offering the possibility of survival that is free from moderate/severe sequelae for the subgroup of newborns with less brain damage.

The treatment of these children in the neonatal period, as well as the treatment of possible sequelae, could represent an increase in the costs.

4.2.5. Summary of the evidence

Moderate quality	An Apgar score of 0 at 10 minutes in newborns is not always related to the death of the patient, but it is associated with a high risk of mortality, similar to that of newborns with an Apgar score of 1 or 2 at 10 minutes.[67, 68]
Low quality	Treatment with hypothermia decreases the risk of death associated with the Apgar score at 10 minutes.[67, 68]
Moderate quality	An Apgar score of 0 at 10 minutes is not always related to death or to moderate/severe neurological involvement, but it is associated with a high risk (R of 90.6%; 95% CI, 73 to 100).[67, 68]
Low quality	Treatment with hypothermia decreases the risk of death or moderate/severe disability associated with a low 10-minute Apgar score (OR 0.44; 95% CI, 0.23 to 0.83).[67, 68]
Low quality	Newborns with an Agpar score of 0 treated with hypothermia seem to have a risk of death or moderate/severe disability that is similar to that of newborns with an Agpar score of 1 or 2 at 10 minutes.[67, 68]

4.2.6. Recommendations

Weak	Given that an Apgar score of 0 at 10 minutes is not always related to death or moderate/severe neurological disability, we suggest 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, we suggest 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.

4.2.7. Implications for research

More studies are needed regarding the risk of death and neurological morbidity associated with Apgar scores of 0, 1 and 2 in neonates that receive therapeutic hypothermia. Studies must differentiate between moderate and severe disability with greater precision, and they must separately

show the outcomes associated with an Apgar score of 0, 1 or 2. Studies should not exclude from the analysis either the newborns that die in the resuscitation room, or those that show clinical signs of apparent death or those that are admitted dying to intensive care units. The cause of death should be shown, and when it is due to having limited the therapeutic effort, the objective data (clinical, neuroimaging, electroencephalography, biochemical markers) based on which the decision is made should be shown.

4.3. 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?

4.3.1. Introduction

Variations of temperature, blood sugar and CO2 levels have been related to the modulation of neonatal brain damage.

The brain temperature during and after a hypoxic-ischaemic event occurring in animal experimentation can modify the severity of the resulting damage, such that small reductions attenuate the injurious processes involved in the brain damage (energy depletion, excitotoxicity, production of nitric oxide and apoptosis), while small increases in brain temperature can increase the severity of the damage.

Cerebral blood flow is extremely sensitive to changes in CO_2 levels, such that hypocapnia results in vasoconstriction. Animal experimentation studies have shown that hypocapnia alters neuronal energy metabolism and increases the proteins that induce apoptosis in the cortex. Moreover, both decreased and increased levels have been associated with a greater incidence of cerebral pathology in other pathologies, such as intraventricular haemorrhage in premature newborns.

Glucose is the primary energy substrate for the developing brain, and studies on experimental models have demonstrated the critical role of hypoglycaemia in the pathogenesis of brain damage. Perinatal asphyxia is an important cause of hypoglycaemia due to the anaerobic metabolism of glucose. Moreover, the concomitant presence of hypoxaemia and ischaemia could increase the vulnerability of the neonatal brain to hypoglycaemia. On the other hand, hyperglycaemia has also been associated with adverse development in some groups of patients, including premature newborns and children with cerebral ischaemic attacks. This effect has been related to a possible increase in neuronal apoptosis after reperfusion with high levels of substrate (glucose) in ATP-depleted cells.

Consequently, hyperthermia, blood sugar or CO_2 levels could increase the risk of mortality or brain damage in newborns with HIE.

4.3.2. Outcomes

4.3.2.1. Mortality

a- Hyperthermia

One cohort study that evaluates the relationship between an increase in temperature and mortality in newborns with HIE has been identified (Laptook, 2008[69]). This study was prepared based on a re-analysis of the cases of a clinical trial that compares treatment with hypothermia during 72 hours of life versus standard care without hypothermia (Shankaran, 2005[32]). The analysis included 208 newborns ≥ 36 weeks of gestation with HIE, 196 of which were studied (99 controls). For each newborn, the mean temperature of the upper, intermediate and lower quartiles was obtained between 2 and 72 hours of life. The relationship thereof with mortality up to 18-22 months of age was assessed.

Moderate quality

The authors observed that in newborns not subject to hypothermia (controls), the OR for death increased 3.2-6.2 times for every 1º C increase in the upper temperature quartile on the skin and in the oesophagus. No association between temperature and development in newborns treated with hypothermia was observed.

b-Hypocapnia

No study that specifically evaluates this outcome was identified.

c-Hypercapnia

No study that specifically evaluates this outcome was identified.

d-Hypoglycaemia

Tam, 2012,[70] conducts a prospective cohort study that includes 94 patients to assess the impact of the existence of hypoglycaemia in the first 24 hours of life in term newborns with the risk of encephalopathy. It included 15 children with hypoglycaemia and 79 normoglycaemic children recruited between 1994 and 2010. Follow-up was conducted up to one year of life, and the neurological assessment included MRI at a median of 4 days (range between 2 and 5), a motor function exam at one year and a Bayley II or III test to evaluate cognitive function. Hypoglycaemia was defined as a blood glucose value of less than 40 mg/dl. Of the children in the cohort, one died in the perinatal period, corresponding to a patient with hypoglycaemia. The scarce sample size prevents drawing conclusions for this outcome.

Low quality

e-Hyperglycaemia

No study that specifically evaluates this outcome was identified.

4.3.2.2. Cerebral palsy

a-Hyperthermia

No study that specifically evaluates this outcome was identified.

b-Hypocapnia

No study that specifically evaluates this outcome was identified.

c-Hypocapnia

No study that specifically evaluates this outcome was identified.

d-Hypoglycaemia

The aforementioned study by Tam, 2012,[70] assesses motor function at one year. Of the 94 newborns with a risk of encephalopathy that were included, there was follow-up on 73 patients (losses of 22.34%). For the motor assessment, a score was used, ranging from 0 (normal examination) to 5 (spastic tetraplegia). A multivariate analysis adjusted for perinatal hypoxia-ischaemia factors showed that, in the presence of hypoglycaemia (glucose < 46 mg/dL), the likelihood of obtaining 1 more point in the motor assessment (equivalent to worse motor function) was 4.82 times greater (95% CI, 1.09 to 21.35), and the likelihood of injury to the corticospinal tract was 3.72 times greater (95% CI, 1.02 - 13.57). The limitations include the fact that follow-up was only conducted up to one year of life, the losses were relevant, and the blood sugar level was not systematically determined (it was analysed according to the judgement of the attending physician). Moderate quality

e-Hyperglycaemia

No study that specifically evaluates this outcome was identified.

4.3.2.3. Moderate/severe cerebral palsy (GMFCS 3-5)

a-Hyperthermia

No study that specifically evaluates this outcome was identified.

b-Hypocapnia

No study that specifically evaluates this outcome was identified.

c-Hypercapnia

No study that specifically evaluates this outcome was identified.

d-Hypoglycaemia

No study that specifically evaluates this outcome has been identified. Overall, motor alteration is only assessed by a score at one year of life in the study by Tam, 2012,[70] as described in the preceding section.

e-Hyperglycaemia

No study that specifically evaluates this outcome was identified.

4.3.2.4. Death or moderate/severe disability

a-Hyperthermia

The previously cited study by Laptook, 2008,[69] assesses the relationship between the temperature mean of the upper, intermediate and lower quartiles between 2 and 72 hours of life and death or severe/moderate disability at 18-22 months of age in children with HIE. It was observed that in children not treated with hypothermia, the OR for death or severe/moderate neurological disability increased 3.6-4 times for each temperature increase of 1° C in the upper quartile of temperature on skin and in the oesophagus. No association between temperature and development in children treated with hypothermia was observed.

Moderate quality

b-Hypocapnia

One retrospective cohort study was identified (Klinger, 2005[71]), plus one retrospective analysis of a prospective cohort (Nadeem, 2010[72]) and one secondary analysis of a multicentre randomised controlled trial (Pappas, 2011[73]) that directly discuss this question.

Low quality

Klinger[71] analysed 173 newborns of the cohort of 244 eligible children with gas analysis as from 20 minutes up to 120 minutes of life and with standardised neurological follow-up at 12-24 months of age. In the multivariate analysis, severe hypocapnia (pCO_2 < 20 mm Hg) increased the OR for death or severe/moderate neurological disability by 2.34 times (95% CI, 1.02 to 5.37); when it was associated with severe hypoxia (PaO_2 > 200 mm Hg), the OR increased 4.56 times (95% CI, 1.4 to 14.9). A greater risk of death or of severe disability associated with moderate hypocapnia was not found.

Nadeem72 conducted a retrospective analysis of a cohort study, thereby assessing the value of the EEG in children with HIE. 55 newborns were included, on which 551 pCO_2 determinations were made according to the clinical indication in the first 72 hours of life, and the neurological development was assessed at 24 months of age. As outcomes, no significant association was found between either moderate hypocapnia (pCO_2 20-25 mm Hg) or severe hypocapnia (pCO_2 < 20 mm Hg) and death or severe/moderate neurological disability, although a trend towards an increase of the OR in the presence of hypocapnia was observed (OR 1.07; 95% CI, 0.24 to 5.45).

Very low quality

Finally, the cohort study by Pappas[73] included 208 newborns ≥ 36 weeks of gestation with HIE, of which 204 with gas analysis data repeated over the first 12 hours of life were analysed. This is a secondary analysis of a randomised controlled trial that compares hypothermia with standard treatment in children with HIE. The relationship with death or severe/moderate disability at 18-22 months of age was assessed. Notable among the outcome is that both the minimum pCO_2 and the cumulative exposure to hypocapnia under 35 mm Hg in the first 12 hours increased the OR for death or severe/moderate neurological disability (minimum pCO_2 OR of 2.0; 95% CI, 1.1 to 3.4). The relationship between CO_2 and death/disability ceased to be significant in children treated with hypothermia: OR of 1.64 (95% CI, 0.71 to 3.78).

Low quality

c-Hypercapnia

One retrospective analysis of a prospective cohort (Nadeem[72]) and one secondary analysis of a multicentre randomised controlledtrial (Pappas[73]) that cover this question were identified.

Very low quality

In the study by Nadeem,[72] cited in the preceding paragraph, no significant association between hypercapnia (pCO_2 > 50 mm Hg) and death orsevere/moderate neurological disability was found.

Pappas,[73] in the cohort study described in the preceding section, did not find an increase in the risk associated with the maximum level of pCO_2 or with the cumulative exposure to hypercapnia in the first 12 hours of life. Low quality

The outcomes of these studies must be interpreted with caution due to the scarce number of patients with hypercapnia.

d-Hypoglycaemia

One retrospective cohort study has been identified (Nadeem[74]), which assesses the relationship between hypoglycaemia and mortality or moderate/severe neurological disability in newborns with HIE. This study included 55 term newborns with HIE, in which 465 blood sugar determinations were conducted in the first 72 hours of life (according to clinical criterion). The relationship with death or severe/moderate disability at 24-22 months of age was assessed. Consequently, the detection of early hypoglycaemia (< 46.8 mg/dL) (0-6 hours of life) was associated with a high risk of death or severe/moderate neurological disability (OR 5.8; 95% CI, between 1.04 and 32). No significant relationship between late hypoglycaemia (6-72 hours of life) and a greater risk of this outcome was found. In the multivariate analysis, only moderate and severe HIE continued to be significantly associated with adverse development. d-Hypoglycaemia Low quality

In the Tam study,[70] the authors studied, at one year, the motor and cognitive alteration of their cohort of 94 term newborns with a risk of encephalopathy. The motor assessment made by the authors is described in the preceding section. To assess the cognitive alteration, a Bayley II or III test was conducted. In the multivariate analysis, the authors found that the presence of hypoglycaemia was associated with 15 points less in the MDI *score* of the Bayley II test (95% CI; -26 to -3). Similar outcomes were found for the Bayley III (decrease of the MDI in children with hypoglycaemia after a 12-point multivariate analysis, from -23 to -2). Low quality

In addition, two cohort studies that assessed this outcome indirectly were identified (Basu, 2009,[75] and Salhab, 2009[76]). They analysed the relationship between hypoglycaemia and mortality or neurological development in the neonatal period (HIE), but without conducting long-term follow-up, wherefore they do not provide direct data regarding disability in order to respond to this question. Very low quality

e-Hyperglycaemia

One retrospective cohort study was identified, (Nadeem[74]) which assesses the relationship between hyperglycaemia in the first 72 hours of life and mortality or moderate/severe neurological disability in newborns with HIE, described in the preceding section. No significant association was found between hyperglycaemia (> 150 mg/dL) and a greater risk of this outcome, but these results must be interpreted with caution due to the scarce number of patients. Very low quality

4.3.3. From the evidence to a recommendation

4.3.3.1. Quality of the evidence

Moderate quality	**Mortality** *Hyperthermia*.[69] The quality of the evidence in the outcome variables assessed in the observational study increased, given that it consisted in a secondary analysis of a randomised study with the adjustment of confounding factors, in which a dose-response relationship and a time relationship were observed between the duration of the exposure and the effect. The OR for death increased 3.2-6.2 times for each 1º C increase in the upper temperature quartile on the skin and in the oesophagus.
Moderate quality	**Death or disability** *Hyperthermia*.[69] The quality of the evidence in the outcome variables assessed in the observational study increased, given that the study consisted in a secondary analysis of a randomised study with the adjustment of confounding factors, in which a dose-response relationship and a time relationship were observed between the duration of the exposure and the effect. The OR for death or severe/moderate neurological disability increased 3.6-4 times for each temperature increase of 1º C in the upper temperature quartile on the skin and in the oesophagus.
Moderate quality	*Hypocapnia*.[71-73] The quality of the evidence in the assessed outcome variables increased, given that the study consisted in a secondary analysis of a randomised study with the adjustment of confounding factors, and a dose-response relationship and a time relationship were observed between the duration of the exposure and the effect.
Very low quality	*Hypercapnia72*,[73] In newborns with HIE but not treated with hypothermia, the scarce number of patients studied does not allow drawing conclusions about the association between hypercapnia and the risk of death or severe/moderate neurological disability.
Moderate quality	*Hypoglycaemia*[70, 74] The quality of the evidence in the outcome variables assessed in the observational study increased, given that it consisted in a secondary analysis of a prospective study. The cohorts study is high quality, although it is limited by the scarce sample size and by follow-up of only one year. Moreover, two observational studies that indirectly assess this outcome provide data in the same sense, one of which with a dose-response relationship.
Very low quality	*Hyperglycaemia*[74] In newborns with HIE but not treated with hypothermia, the scarce number of patients studied does not allow drawing conclusions about the association between hyperglycaemia and the risk of death or severe/moderate neurological disability.

4.3.3.2. Balance between benefits and risks

No risk due to the use of normothermia could be expected, and the beneficial effect of treatment with hypothermia has been demonstrated. No risk could also be expected due to controlling pCO_2 and blood sugar within the normal range.

4.3.3.3. Costs and use of resources

There are neither costs nor a greater need for resources related to either normothermia or normal blood sugar levels. To maintain good control of pCO_2, it could be necessary to implement, in these patients, new techniques for the non-invasive monitoring of the exchange of carbon dioxide (CO_2) in the respiratory tract.

4.3.3.4. Values and preferences of the patients

It was not deemed that the values and preferences of the patients regarding the control of temperature, pCO_2 and blood sugar in the normal range were determining factors for assessing the strength of the recommendation.

4.3.4. Final decision about the strength (strong or weak) and the direction (in favour or against) of the recommendation

Aspects that have determined the direction and strength of the recommendation:

a-Hyperthermia

One study[69] suggests that, in patients with HIE not treated with hypothermia, it would be advisable to avoid high temperatures, given that such high temperatures could be associated with the risk of death or moderate/severe neurological disability.

No adverse effects due to normothermia are expected.

There seems to be a favourable cost-benefit ratio.

b-Hypocapnia

Two studies[71, 73] suggest that, in patients with HIE not treated with hypothermia, it would be advisable to avoid severe hypocapnia and sustained moderate hypocapnia, given that they could be associated with the risk of death or moderate/severe neurological disability.

No adverse effects due to normocapnia are expected.

There seems to be a favourable cost-benefit ratio.

c-Hypercapnia

The available studies[72, 73] have not found an association between hypercapnia and a greater risk of death or moderate/severe neurological disability in patients with HIE, but they also don't have the sufficient power to establish that such an association doesn't exist. On the other hand, there are data coming from basic and animal experimentation, as well as clinical studies on other pathologies of the central nervous system, which indicate a greater risk of brain damage associated with hypercapnia.

No adverse effects due to normocapnia are expected.

There seems to be a favourable cost-benefit ratio.

d-Hypoglycaemia

One study[74] suggests that in patients with HIE not treated with hypothermia, it would be advisable to avoid hypoglycaemia (blood sugar < 46.8 mg/dL) in the first 6 hours of life, given that it could be associated with a greater risk of death or moderate/severe neurological disability. Another study[70] shows that the existence of hypoglycaemia < 40 mg/dl in the first 24 hours of life is associated with a greater risk of motor and cognitive alteration assessed at one year of life.

No adverse effects due to normal blood sugar levels are expected.

There seems to be a favourable cost-benefit ratio.

e-Hyperglycaemia

The available studies[74] have not found an association between hyperglycaemia and a greater risk of death or moderate/severe neurological disability in patients with HIE, but they also don't have the sufficient power to establish that such an association doesn't exist. On the other hand, there are data coming from basic and animal experimentation, as well as clinical studies on other pathologies of the central nervous system, which indicate a greater risk of brain damage associated with hyperglycaemia.

No adverse effects due to normal blood sugar levels are expected.

There seems to be a favourable cost-benefit ratio.

4.3.5. Summary of the evidence

Moderate quality	In newborns with HIE not treated with hypothermia, an increase in temperature (*hyperthermia*) is associated with a greater risk of neonatal death or of moderate/severe neurological disability, or of death or of moderate/severe disability analysed individually.[69]
Low quality	In newborns with HIE not treated with hypothermia, *severe hypocapnia* (pCO_2 < 20 mm Hg) and the cumulative exposure to *moderate hypocapnia* (pCO_2 < 35 mm Hg) in the first 12 hours of life are associated with a greater risk of severe/moderate neurological disability.[71-73]
Very low quality	In newborns with HIE not treated with hypothermia, the scarce number of patients studied does not allow drawing conclusions about the association between *hypercapnia* and the risk of death or severe/moderate neurological disability.[72-73]
Low quality	In newborns with HIE not treated with hypothermia, *hypoglycaemia* (blood sugar < 46.8 mg/dL) in the first 6 hours of life is associated with a greater risk of death or severe/moderate neurological disability.[70, 74]
Very low quality	In newborns with HIE not treated with hypothermia, the scarce number of patients studied does not allow drawing conclusions about the association between *hyperglycaemia* and the risk of death or severe/moderate neurological disability.[74]

4.3.6. Recommendations

Strong	In newborns with a gestational age of greater than or equal to 35 weeks with HIE, we recommend 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, we recommend avoiding severe hypocapnia (pCO_2 < 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, we suggest 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, we recommend 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, we suggest avoiding hyperglycaemia in the first 72 hours of life.

4.3.7. Implications for research

More randomised and controlled studies or prospective cohorts with a multivariate analysis of the diversity of potentially adverse factors on the nervous system in the first hours of life are required, while considering the exposure time to the potential adverse factor. It is also necessary for said factors to be correlated with graduated and precise classifications of neurodevelopment.

5. Treatment

Questions to be answered:

- In newborns with a gestational age of greater than or equal to 35 weeks with perinatal hypoxic-ischaemic encephalopathy, does therapeutic hypothermia, in comparison with normothermia, reduce the the risk of death or neurological morbidity in the long term?
- In newborns with a gestational age of greater than or equal to 35 weeks with perinatal HIE, does the clinical severity of the encephalopathy condition the effectiveness of treatment with hypothermia?
- 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?
- 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?
- Are there pharmacological treatments that, initiated in the first hours of life of a newborn with a gestational age of greater than or equal to 35 weeks with severe or moderate perinatal HIE, decrease neurological morbidity and mortality?
- Does the combination of hypothermia with pharmacological treatments, such as topiramate, EPO, allopurinol or xenon, reduce the risk of death or disability at 18-24 months in newborns with moderate or severe HIE versus treatment for these patients with hypothermia alone?
- Does treatment of the electrical seizures in newborns with a gestational age of greater than or equal to 35 weeks with perinatal HIE, treated or not with therapeutic hypothermia, have an influence on the risk of death or disability at 18-24 months?
- Does sedation with opioid derivatives in newborns with HIE (with or without hypothermia) decrease the risk of death or disability at 18-24 months?

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

5.1.1. Introduction

Perinatal hypoxic-ischaemic encephalopathy has an incidence of approximately 1/1000 live newborns in developed countries. In its moderate form, it is associated with a mortality of ap-

proximately 10%, and 30-45% of surviving patients have long-term neurological sequelae. The mortality of severe HIE is approximately 50%, and over 90% of the cases that survive do so with neurological disabilities. Thus, the major medical, social, economic and legal implications of this entity make it a relevant health problem. Up until relatively recently, the only available treatments for newborns with HIE were supportive care and treatment of the convulsions. In recent years there has been intensive research on neuroprotective strategies for newborns with HIE, which are designed specifically to block the molecular mechanisms of brain damage and thereby reduce long-term neurological morbidity. To date, therapeutic hypothermia has been the neuroprotective intervention with the greatest clinical application.

Through the bibliographic search conducted to respond to the posed question, a total of six meta-analyses (MAs) on therapeutic hypothermia in term or near-term newborns with HIE were identified: Shah, 2007[40]; Shulzke, 2007[39]; Jacobs, 2008[41]; Edwards, 201107; Shah, 2010[78]; and Tagin, 2012.[42] In the two most recent ones (Shah, 2010[78] and Tagin, 2012[42]), the totality of randomised clinical trials (RCTs) published to date were assessed (Gunn, 1998[79]; Shankaran, 2002[80]; Zhou, 2002[81]; Akisu, 20038[2]; Inder, 2004[83]; Eicher, 2005[84]; Gluckman, 2005[31]; Shankaran, 2005[32]; Bhat, 2006[85]; Lin, 2006[86]; Robertson, 2008[87]; Li, 2009[88]; Azzopardi, 2009[34]; Zhou, 2010[38]; Simbruner, 2010[37]; and Jacobs, 2011[36]). The MA by Tagin[42] was used to respond to the "death or severe disability", "death", "severe disability", "cerebral palsy" and "intact survival" outcomes, for which the follow-up age was 18-24 months. The more longer-term outcomes of the patients included in the two most relevant RCTs on hypothermia for perinatal HIE (Gluckman, 2005[31] and Shankaran, 2005[32]) have been published recently in the corresponding articles (Guillet, 2012[89] and Shankaran, 2012[90]). Both studies, which cannot be integrated in a MA because they have different characteristics, were the source of the response to the most long-term outcomes (6-8 years). The safety or adverse effects outcomes in the short term were answered based on the MA by Shah, 2010.[78]

5.1.2. Outcomes

5.1.2.1. Outcomes at 18-24 months

The MA by Tagin[42] included seven RCTs selected between 1966 and May 2011 (Gunn, 1998; Gluckman, 2005; Shankaran, 2005; Azzopardi, 2009; Zhou, 2010; Simbruner, 2010; and Jacobs, 2011), which meant a total of 1214 patients. The inclusion criteria of the RCTs were: neonates with a gestational age of equal to or greater than 35 weeks, data on perinatal hypoxia-ischaemia and moderate or severe encephalopathy. Three RCTs included the presence of an abnormal amplitude-integrated electroencephalography tracing as entry criteria (Gluckman, 2005; Azzopardi, 2009; and Simbruner, 2010). The exclusion criteria were the following: the presence of major congenital anomalies or an age of over 6 hours at the time of randomisation. In four RCTs (Shankaran, 2005; Azzopardi, 2009; Simbruner, 2010; and Jacobs, 2011), total body hypothermia was applied (target core temperature: 33-34º C), and in three (Gunn, 1998; Gluckman, 2005; and Zhou, 2010), selective cooling of the head was applied (average core temperature: 34-35º C). Hypothermia began in the first 6 hours of life, it was maintained for 72 hours, and it was followed by slow rewarming at the rate of no more than 0.5º C per hour. The patients of the control groups were cared for in a radiant warmer in order to maintain an average core temperature of 37 ± 2º C. In none of the RCTs were aggressive control measures of the hypothermia applied in the group of control patients.

The main measurement of outcome of the MA was the combination of death or major disability in long-term neurodevelopment (age of 18-24 months). Major disability was defined as: cerebral palsy, development delay [score <-2 standard deviations (SDs) in the Mental Development Index (MDI) of the Bayley II Scale of Infant Development, the cognitive or language scales of

the Bayley III scales or of the Griffiths, BrunetLézine or Gessell tests] intellectual deficit [intelligence quotient (IQ) <-2 SD], blindness (vision < 6/60 in both eyes) and neurosensory deafness requiring amplification. The secondary measurements of outcome were: each one of the primary components of the primary outcome and survival with normal neurological function (absence of cerebral palsy, normal development or intelligence (score ≥ 1 SD in the aforementioned standardised tests), normal vision and hearing].

The percentage of losses for follow-up on the set of patients included in the MA was 6.3%. The study with the least number of losses had 0% (Gunn, 1998), and the RCT with the most had 17.4% of patients without an assessment of the available primary outcome (Zhou, 2010).

This MA complied with quality criteria (according to the PRISMA declaration), insofar as it encompassed a comprehensive search, it detailed the included and excluded studies, it assessed the quality of each one of the selected RCTs, it conducted control of heterogeneity, and it assessed publication bias. The main limitations of the MA were the non-blind nature regarding the intervention (which did exist regarding the assessment of the outcomes) and the limited follow-up age. Another limitation of the included RCTs was the absence of aggressive treatment of hyperthermia in the control groups, which meant a high frequency of fever in this group, a complication that could have a detrimental effect on long-term neurological development.

5.1.2.1.1. Death or severe disability

According to the MA by Tagin, 2012,[42] hypothermia had the following protective effect for said outcome: ARR of 15.3% (95% CI 9.8-20.8%), RRR of 24.2% (15.5-32.9%), NNT of 7 (5-10), RR of 0.76 (0.69-0.84), OR of 0.54 (0.36-0.69), $I^2 = 0\%$. High quality

Broken down by the type of cooling used, the outcomes were the following:

- Whole body cooling: ARR of 15.7% (8.9-22.4%), RRR of 24.6% (14.0-35.1%), NNT of 6 (4-11), RR of 0.75 (0.67-0.85), OR of 0.53 (0.40-0.70), I2 = 9%.
- Selective head cooling: ARR of 14.5% (4.9-24.1%), RRR of 23.4% (7.9-39.0%), NNT of 7 (4-20), RR of 0.77 (0.64-0.92), OR of 0.55 (0.37-0.82), I2 = 15%.

5.1.2.1.2. Death

The results for this outcome were: ARR of 8.9% (3.9-13.9%), RRR of 25.3% (11.1-39.5%), NNT of 11 (7-26), RR of 0.75 (0.63-0.88), OR of 0.66 (0.52-0.83), $I^2 = 0\%$. High quality

Regarding the RCTs (Shankaran, 2005; Azzopardi, 2009; Simbruner, 2010; and Jacobs, 2011), they indicated the figures of patients that died in relation to the withdrawal of life support: 82 of the 110 cooled children died (74.5%) and 108 of the 152 children not cooled died (71%). It is important to keep in mind that the criteria for limiting the therapeutic effort were not specified in the original articles. Likewise, said decisions were not made blindly to the treatment with or without hypothermia.

5.1.2.1.3 Major disability

The results for this outcome were: ARR of 31.9% (16.0-47.7%), RRR of 12.3% (6.2- 18.5%), NNT of 8 (5-16), RR of 0.68 (0.56-0.83), OR of 0.57 (0.43-0.75), I2 = 12%. High quality

5.1.2.1.4. Cerebral palsy

The MA by Tagin, 2012, showed that treatment with hypothermia generated an ARR of 11.9% (6.2-17.7%) for cerebral palsy assessed at 18-24 months. Other data of the MA were the following: RRR of 38.1% (19.7-56.4%), NNT of 8 (6-16), RR of 0.62 (0.49-0.78), OR of 0.53 (0.39-0.72), $I^2 = 33\%$. High quality

5.1.2.1.5. Death or cerebral palsy

According to the MA by Tagin, 2012, for this outcome the effect was the following: ARR of 15.4% (9.9-20.8%), RRR of 27.4% (17.7-37.0%), NNT of 7 (5-10), RR of 0.73 (0.65-0.82), OR of 0.54 (0.43-0.67). High quality

5.1.2.1.6. Intact survival

In the MA by Tagin, 2012, we find that in the group treated with hypothermia the ARR was -15.7% (-21.1/-10.3%) for this outcome assessed at 18-24 months. Other data were: RRR of -65.3% (-87.8/-43.0%), NNT of -7 (-5/-11), RR of 1.63 (1.36-1.95), OR of 2.08 (1.61-2.7), $I^2 = 0\%$. High quality

5.1.2.2. Longer-term outcomes

As stated, the longer-term outcomes (6-8 years) of the patients included in two of the more relevant RCTs of hypothermia (Gluckman, 2005, and Shankaran, 2005) have been published recently (Guillet, 2012, and Shankaran, 2012). The outcomes of these studies cannot be integrated in an MA, given that they used a different methodology. Each one of these works are summarised below.

Guillet, 2012.[89] The objective of this work was to determine if the neurodevelopmental outcomes at 18-22 months predict the functional outcomes at 7-8 years in surviving children of the CoolCap study (Gluckman, 2005). The sample size was 135 children [234 patients participating in the CoolCap, less 83 deceased (78 before 18 months and five between 18 months and 7 years) and 16 not assessed at 18 months]. The predictive strategy to be assessed was the assessment of neurodevelopment at 18-22 months, whose outcomes were classified as favourable or unfavourable (Bayley MDI < 70, a score of 3-5 in the Gross Motor Function Classification or bilateral cortical visual impairment). The long-term functional assessment was done by telephone through the parents using the WeeFIM instrument, which quantitatively assesses the self-care, mobility and cognitive function of the child. A score of less than -1 SD for the age was defined as unfavourable. Of the 135 eligible patients, 73 were lost for the long-term assessment, which represents a loss percentage of 54%. The demographic characteristics and the outcomes at 18 months were compared between assessed patients and non-assessed patients in the longer term, without finding significant differences. Low quality

The main limitations of this work were the high loss rate for follow-up and the use of a telephone tool for assessing the long-term patients. Moreover, the relationship of the results with our outcomes is indirect, and the study does not provide an answer to our question. Therefore, the quality of the evidence contributed by this study was categorised as low

The outcomes of this study are summarised below.

- The outcome at 18 months was strongly related to an overall score in the WeeFIM at 7-8 years of age ($P < 0.001$).
- A favourable outcome at 18 months predicted an overall score in the range of normalcy in the WeeFIM at 7-8 years: Sensitivity of 0.87 (0.77-0.93); Specificity of 0.56 (0.42-0.66); PPV of 0.74 (0.66-0.8); NPV of 0.74 (0.55-0.87).
- A favourable outcome at 18 months predicted normal mobility according to the WeeFIM: Sensitivity of 0.87 (0.80-0.91); Specificity of 0.81 (0.62-0.93); PPV of 0.93 (0.86-0.97); NPV of 0.68 (0.52-0.78).
- No significant effect by hypothermia on the scores of the WeeFIM was found ($P = 0.83$).

Shankaran, 2012.[90] This study presents the outcomes of mortality, cognitive deficit and other neurodevelopmental and behavioural outcomes associated with whole body hypothermia at 6-7 years of age in participants in the RCT of the NICHD NRN (Shankaran, 2005). Of the 208 patients included in the original clinical trial, 18 (8.6%) were lost for the follow-up at 6-7 years, such that the sample of this second study was 190 patients (97 cooled and 93 not cooled). The patients lost for follow-up were not exactly equal to those followed-up on with respect to some of the basic variables (maternal race and civil status, as well as pH of the umbilical cord. The primary outcome was death or an IQ < 70. Cerebral palsy was classified according to the *Surveillance of Cerebral Palsy in Europe*. Motor function was assessed using the *Gross Motor Function Classification System* (GMFCS). Cognitive function was measured using the Weschler scales for pre-school (version III) and school-age children (version IV). The degree of disability was classified as: severe (IQ < 55, GMFCS IV-V or bilateral blindness), moderate (IQ of 55-69, GMFCS III, bilateral deafness or refractory epilepsy) or mild (IQ of 70-84, GMFCS I-II).

The main limitation of the study, as its own authors acknowledge, was the lack of power to assess some outcomes due to the fact that the sample size of the original trial was not calculated according to the long-term outcomes analysed in this follow-up study. Moreover, even though the follow-up percentage was relatively high, the losses could have had an influence on the outcomes, given that some of the basic characteristics differed between follow-up patients and non-follow-up patients. Therefore, even though this study met some quality criteria, such as the adjustment of covariables (i.e. the participating centre), the overall quality was considered moderate.

For the main outcome of death or IQ < 70, the results at 6-7 years were: ARR of 14.9% (1.0-28.9%), RRR of 24.0% (1.5-46.4%), NNT of 7 (3-105), RR of 0.76 (0.58-0.99), OR of 0.54 (0.31-0.57). The difference between groups lost its statistical significance after the regression analysis to adjust for the centre: RR of 0.78 (0.61-1.01).

The results of the effect of the hypothermia are presented below regarding each of the outcomes selected by the authors of this guideline, after the regression analysis to adjust for the participating centre.

5.1.2.2.1. Death or severe disability: RR of 0.72 (0.54-0.97)	
For the outcome of death or moderate-severe disability, the RR was 0.84 (0.66-1.06).	Moderate quality
5.1.2.2.2. Death: RR of 0.66 (0.45-0.97)	Moderate quality
5.1.2.2.3. Major disability (moderate or severe): RR of 0.92 (0.57-1.48.	Moderate quality
5.1.2.2.4. Cerebral palsy: RR of 0.60 (0.31-1.18)	Moderate quality
5.1.2.2.5. Death or cerebral palsy: RR of 0.71 (0.54-0.95)	Moderate quality
5.1.2.2.6. Survival with normal neurological function (absence of moderate or severe sequelae): RR of 1.05 (0.80-1.39).	Moderate quality

One interesting aspect of this work is that it analysed the capacity of the assessments made at 18-22 months to predict the outcomes at 6-7 years, with the following results:

- PPV of moderate-severe disability at 18-22 months for moderate-severe disability at 6-7 years: 88% in patients treated with hypothermia and 95% in control patients.
- PPV of moderate or severe cerebral palsy at 18-22 months for the same outcome at 6-7 years: 100% for both groups.

5.1.3. From the evidence to a recommendation

5.1.3.1. Quality of the evidence

High quality	The evidence of the effects of treatment with hypothermia at 18-24 months comes from well-designed studies with high quality.[42]
Moderate quality	There are fewer data about the long-term effects of treatment (6-7 years), and the quality of the evidence is somewhat inferior.[89, 90]

5.1.3.2. Balance between benefits and risks

The adverse effects of treatment with hypothermia were analysed in the MA by Shah 2010,[78] which included the safety outcomes available in 13 RCTs (Gunn, 1998; Shankaran, 2002; Zhou, 2002; Akisu, 2003; Eicher, 2005; Gluckman, 2005; Shankaran, 2005; Bhat, 2006; Lin, 2006; Robertson, 2008; Azzopardi, 2009; Zhou, 2010; and Jacobs, 2011), selected between 1966 and November 2009 (N = 1440). This MA, of high quality, only found differences between the patients treated with hypothermia and the control patients with respect to two adverse effects, which were the following:

- Arrhythmias (5 studies / 806 patients): ARR of 4% (1-6%), RR of 4.08 (1.55-10.74), NNT of 25 (16-100).
- Thrombocytopenia (4 studies / 638 patients): ARR of 10% (3-18%), RR of 1.28 (1.07-1.52), NNT of 10 (5-33).

Most of the Arrhythmias consisted in sinus bradycardia, and in the original RCTs no significant clinical impact by any of these secondary effects was recorded. The importance of this sinus bradycardia in clinical practice is very low.

The MA did not observe differences between both groups with respect to other adverse effects, such as coagulopathy [7 studies / 1114 patients, RR of 0.96 (0.80 to 1.15)] or pulmonary hypertension [5 studies / 636 patients, RR of 1.36 (0.95 to 1.96)].

5.1.3.3. Costs and use of resources

Of the 4 articles detected in the search of neonatal hypothermia: the articles that were found were from 2008,[91] 2009,[92] 20109[3] and 2012,[94] but only the one conducted by Regier et al. at the University of Oxford (United Kingdom)[93] is valid for the proposed economic evaluation study. The study by Regier, 2010, is an economic evaluation study with a high degree of quality, given that it meets all the considered criteria for an economic evaluation study. The data were obtained from 3 of the large RCTs on hypothermia: TOBY Trial,[34] NICHD Trial[32] and CoolCap Trial.[31] In this study, it is objectively estimated that hypothermia represents a cost increase of €5155 (95% CI, 3398 to 16,694), and it achieves an AVGLD of 0.19 (95% CI, 0.l07 to 0.31) in the first 18 months. According to this, the incremental cost-effectiveness index by the AVGLD is €26,290.

In the cost-effectiveness acceptability curves, it shows that there is a 69% probability that hypothermia is cost-effective when the price threshold willing to pay is approximately €40,000. This probability is 99% when the annual number of children cooled per centre is 15 or when the time horizon is extended to 18 years. As conclusions, neonatal hypothermia is cost-effective for treating moderate-severe HIE with the threshold accepted by the British National Health System in outcomes with a time horizon of the first 18 months of life. The cost-effectiveness improves substantially when an increase in both the treated cases (15 or more) and in the time horizon (to 18 years) is considered.

The other three articles were excluded, but we can draw some partial conclusions:

- The studies conducted by Harvard University (United States)[91, 94] use a computerised simulation model of perinatal regionalisation for neonatal asphyxia and HIE, and in the first study,[91] they assess the impact by selective neonatal head cooling with aEEG, and in the second study,[94] they assess the number of hypothermia systems that are viable for covering the care needs of newborns with moderate-severe HIE. Both models obtain favourable results from an economic viewpoint (cost-effectiveness) for the combined use of selective neonatal hypothermia and aEEG, as well as the viability of having two neonatal hypothermia

devices at a hospital that treats at least 20 annual cases of moderate-severe HIE (if more annual cases are treated, the benefit-risk-cost balance of having a third neonatal hypothermia device is still pending assessment).

– The study conducted at the hospital of Cape Town (South Africa)[92] explores the use of hypothermia in developing countries through a pilot study that uses a prototype of an inexpensive hypothermia system. It is not an economic evaluation study, but it tangentially poses the subject of costs in the applicability in these types of countries.

5.1.3.4. Values and preferences of the patients

There are no studies published that specifically assess the values and preferences of the parents regarding treatment with hypothermia. Based on our own qualitative study conducted during the period when this guideline was being prepared, some conclusions can be drawn. Thus, according to this study, for parents, HIE is a synonym of trauma and brain damage, and they do not name any other vital organs in their responses. The talk about many doubts about the illness (HIE), and they verbalise their need to have more information about the causes. *"Personally, I need to know the causes of things and the 'why'"*. *"What I was never clear about is what this illness is"*. *"You feel like you need to know more"*. Some parents relate the favourable evolution of the brain injury with the possibility of "treating it on time" (emergency action). *"I never imagined this about the brain injury. It was something like, if you catch it on time, that's it, right?"*. And they recognise that their child was in a life or death situation, and they identify the first 24 hours as a critical period in which the uncertainty related to death is more intense. *"I thought that it would turn out OK, even though he was between life and death"*. *"Probably the first 24 hours, I think in our case and everyone else's, are the most critical"*. They describe having been very afraid and anxious regarding the development of their child after treatment with hypothermia and related to the disability in the future. And that fear remains until their children grow up and they can see that everything is normal.

"We've always lived with the fear that he's small and you still don't know how he'll develop, right?

When they talk about hypothermia, they refer to it as a special and novel treatment that allows improving the survivability of children. *"It seems that hypothermia is so that they can survive or something like that"*. However, their comments don't show any clear association between hypothermia and the reduction of sequelae. They relate a positive outcome to the science of medicine and to the professionalism of the team. *Thanks to the doctors, to medicine, to research and to the team that was working that day"*. For them, authorising and setting up hypothermia treatment is an act of responsibility, which allows them to feel useful by perceiving that they are fighting for their children. *"At least this is being done for a reason, right? To prevent them from dying"*. *"It's more responsible to let them try it all the way to the end"*. And they express ambivalent feelings related to the balance between positive outcomes (survival) and suffering due to the treatment and pain.

It can be noted through their statements that they know that hypothermia consists in cooling the newborn, but they don't know how it is achieved or how long it lasts (some talk about hours and others talk about days). *"They tell you that the child is in hypothermia, but you really don't know what it is"*. They describe needing to have more comprehensible information about this treatment. They relate the fact that seeing their child "frozen" is a very unpleasant image, one that is not easily forgotten. *"Seeing your daughter there, frozen, it's not a pretty picture; it's not how you expect to see her"*. As well as seeing your child completely nude, with their legs open and completely unprotected. *"I felt completely unprotected..., she's completely naked, and with her legs open like that..."*

5.1.4. Final decision about the strength and direction of the recommendation

Aspects that have determined the direction and strength of the recommendation:

Studies show that, in newborns with a gestational age of greater than or equal to 35 weeks with severe or moderate perinatal HIE, therapeutic hypothermia reduces both mortality and the rates of major disability and cerebral palsy at 18-24 months, and survival increases according to normal neurological function at this age. The quality of the evidence available in this regard is high.[42] The benefits of the treatment are greater than the risks (adverse effects).[78] In the longer term, the beneficial effects are maintained over mortality and the combined outcomes of death / severe disability and death / cerebral palsy, although there are fewer studies and the quality is weak.[89, 90]

The cost/benefit ratio is favourable.[93]

The preferences of the parents in this regard based on published studies are unknown, although our own qualitative study when preparing this guideline allows us to learn some of the concerns of parents of newborns treated with hypothermia.

5.1.5. Summary of the evidence

Death or severe disability, death, severe disability, cerebral palsy, death or cerebral palsy, intact survival

High quality	In newborns with a gestational age of greater than or equal to 35 weeks with severe or moderate perinatal HIE, sustained moderate hypothermia (initiated in the first 6 hours of life, maintained for 72 hours and followed by slow re-warming at the rate of ≥ 0.5º C per hour), in comparison with normothermia, reduces both mortality and the rates of major disability and cerebral palsy at 18-24 months, therefore increasing survival according to normal neurological function at this age.[42] The protective effect takes place with the two ways of applying hypothermia: whole-body and selective head cooling.[42]
Moderate quality	The reduction of mortality associated with therapeutic hypothermia is maintained in the longer-term follow-up on patients (6-7 years of age), without observing an increase in the risk of deficit in neurodevelopment between surviving children treated with hypothermia in comparison with those managed in normothermia.[89, 90]

5.1.6. Recommendations

Strong	We recommend 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 18-24 months of age.
Weak	We recommend 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 6-8 years.
√	We recommend 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.

5.1.7. Implications for research

Even though therapeutic hypothermia initiated in the first 6 hours of life has a proven neuroprotective effect in newborns with a gestational age of greater than or equal to 35 weeks with moderate or severe perinatal HIE and it constitutes the only neuroprotective intervention that is used in clinical practice as of today, said beneficial effect is relatively modest, such that, among treated patients, mortality is around 25%, and approximately 20% survive with sequelae. Therefore, more research that leads to optimising this treatment is needed (for example, to answer the question of whether or not cooling should be deeper or longer). It is also very desirable to develop new interventions to be applied in combination with hypothermia in order to improve the neuroprotective effect. Moreover, as of today, there are no neuroprotective treatments that can be safely used on premature newborns with HIE.

With respect to corroborating the benefit of hypothermia over the longer term (6-8 years), it is highly important to publish follow-up data at said age from all the RCTs that are conducted. Research is being conducted in one RCT about whether or not cooling past the "window period" of 6 hours is beneficial in comparison with maintaining normothermia. It is of interest in this study that the newborns of the control population receive strict monitoring of temperature and that hyperthermia be aggressively prevented or treated.

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

5.2.1. Introduction

As it was developed in question 4, therapeutic hypothermia has shown that it decreases the risk of death or major disability in newborns with a gestational age of greater than or equal to 35 weeks with significant perinatal HIE. To answer the question of whether or not the level of encephalopathy (moderate or severe) conditions the neuroprotective effect of hypothermia, a *post-hoc* analysis (Wyatt, 2007[95]) of the CoolCap trial (Gluckman, 2005[31]) was used, in which the influence of the severity of the encephalopathy on the effectiveness of the hypothermia was specifically examined. The most recent MA on therapeutic hypothermia in term or near-term newborns with HIE with a follow-up age of 18-24 months (Tagin, 2012[42]) was also used. Finally, articles (Guillet, 2012[89], and Shankaran, 2012[90]) on the longer term outcomes (6-8 years) of patients included in the two most relevant hypothermia RCTs for perinatal HIE (Gluckman, 2005, and Shankaran, 2005) were reviewed.

5.2.2. Outcomes

5.2.2.1. Outcomes at 18-24 months

5.2.2.1.1. Death or severe disability

The *post-hoc* analysis (Wyatt[95]) of the CoolCap trial (Gluckman, 2005) explored the determining factors of the effectiveness of hypothermia for the treatment of perinatal HIE, including the initial severity of the encephalopathy according to the Sarnat classification.16 The primary outcome was the combined incidence of death or severe disability at 18 months (defined as GMFCS 3-5, Bayley MDI of <70 or bilateral cortical visual impairment). Follow-up data were available for this secondary analysis in 218 patients (108 cooled and 110 controls) of the 234 patients (116 cooled and 118 controls) included in the original RCT (93%). The analysis was conducted by intention to treat. 8 newborns with minor encephalopathy randomised by error (5 cooled and 3 controls) were included, and in 4 patients there was no recorded information about the initial degree of encephalopathy (thus the percentage of assessed patients for this predictor was 85.4%).

Moderate quality

The limitations of this work were basically due to its design after the fact, which meant a reduced sample size of the subgroups, and this conditioned the consideration of its quality as moderate. Moreover, the follow-up was limited to 18 months of age.

In this study, a reduction of the incidence of an unfavourable outcome with hypothermia was observed both in children with moderate or stage 2 HIE [28 of 62 cooled neonates (45%) and 39 of 69 controls (57%)] and in those with severe or stage 3 encephalopathy [28 of 40 cooled newborns (70%) and 32 of 35 control patients (91%)].

The most recently published MA on therapeutic hypothermia in newborns with HIE (Tagin[42]) considered seven RCTs as eligible (Gunn, 1998; Gluckman, 2005; Shankaran, 2005; Azzopardi, 2009; Zhou, 2010; Simbruner, 2010; and Jacobs, 2011), thereby including a total of 1214 patients. Information about the revision period, about the inclusion and exclusion criteria and about the interventions is detailed in Question 4 of this guideline. The aforementioned MA included an assessment of the effect of the hypothermia on the outcome composed of death or major disability at 18-24 months (see the operational definition in Question 4) in two subgroups according to the initial degree of the encephalopathy (in the first 6 hours of life): moderate or severe. The severity of the encephalopathy was defined based on the clinical examination (Sarnat, 1976) or the amplitude-integrated electroencephalography (aEEG). This latter criterion was used in three of the studies (Gluckman, 2005; Azzopardi, 2009; and Simbruner, 2010). The background tracing of the aEEG was classified as moderately abnormal, (upper margin > 10 μV and the lower margin < 5 μV) or severely altered (upper margin < 10 μV).

High quality

This MA complied with quality criteria, insofar as it encompassed a comprehensive search, it detailed the included and excluded studies, it assessed the quality each one of the selected RCTs, it conducted control of heterogeneity, and it assessed publication bias. The main limitations of the MA or of the RCTs included in it were the non-blind nature regarding the intervention (which did exist regarding the assessment of the outcomes), the high percentage of patients with hyperthermia in the control group and the relatively limited age of follow-up.

The results of the main outcome according to the degree of encephalopathy at the time of inclusion (during the first 6 hours of life) were the following:

- Moderate HIE: ARR of 16.9% (95% CI, 9.3-24.5%), RRR of 32.5% (17.9-47.1%), NNT of 6 (4-11), RR of 0.67 (0.56-0.81), OR of 0.50 (0.36-0.69), $I^2 = 0\%$.
- Severe HIE: ARR of 13.7% (6.2-21.2%), RRR of 17.7% (8.0-27.4%), NNT of 7 (5-16), RR of 0.83 (0.74-0.92), OR of 0.51 (0.35-0.74), $I^2 = 0\%$.

5.2.2.1.2. Death

No studies were found that specifically studied the differences in the effect of hypothermia, with respect to this outcome, between patients with moderate HIE and patients with severe HIE.

5.2.2.1.3. Major disability

Not analysed independently in any of the works found.

5.2.2.1.4. Cerebral palsy

Not analysed independently in any of the works found.

5.2.2.1.5. Death or cerebral palsy

Not analysed independently in any of the works found.

5.2.2.1.6. Intact survival

Not analysed independently in any of the works found.

5.2.2.2. Longer-term outcomes

As it was detailed in Question 4, the longer-term outcomes (6-8 years) of the patients included in two of the more relevant RCTs of hypothermia (Gluckman, 2005, and Shankaran, 2005) have been published recently (Guillet, 2012, and Shankaran, 2012).

In the first of these works (Guillet[89]), whose objective was to learn the correlation between the neurodevelopment assessments at 18-22 months and the functional outcomes at 7-8 years in surviving children, no significant effect by hypothermia on the long-term outcomes was found. The outcomes of the subgroups according to the initial degree of encephalopathy were not presented.

In the second (Shankaran[90]), the outcomes at 6-7 years of 190 patients included in the RCT of Shankaran et al. were assessed, and the the main outcome was death or IQ < 70. As it was previously stated, no differences were found with respect to the primary outcome between the treated and not-treated groups in the adjusted analysis for the study centre. There also were no significant differences regarding the primary outcome when it was stratified in an analysis according to the initial degree of encephalopathy:

- Moderate HIE: RR of 0.78 (0.61-1.01).
- Severe HIE: RR of 0.97 (0.77-1.22).

This work did not reflect the results for the "death or severe disability" outcome or for any of the other voted outcomes.

5.2.3. From the evidence to a recommendation

5.2.3.1. Quality of the evidence

High quality	The evidence of the beneficial effects of treatment with hypothermia at 18-24 months, both in newborns with moderate HIE and those with severe HIE, comes from well-designed studies of high quality.[42]

5.2.3.2. Balance between benefits and risks

No studies were found that analysed the differences with respect to the incidence of adverse effects related to hypothermia between patients with moderate HIE versus severe HIE. In any event, as it is explained in Question 4, no clinically significant harmful effects associated with hypothermia were observed overall in patients with significant HIE (moderate or severe).

5.2.3.3. Costs and use of resources

No cost-effectiveness studies that specifically assess this question were identified.

5.5.3.4. Values and preferences of the patients

There are no specific studies that have assessed the impact by treatment with hypothermia on the parents. The values and preferences of the parents of the patients have not been considered to be a determining factor for assessing the strength of the recommendation.

5.2.4. Final decision about the strength and direction of the recommendation

Aspects that have determined the direction and strength of the recommendation:

Studies show that therapeutic hypothermia reduces the risk of death or major disability at 18-24 months, in both newborns with moderate HIE and those with severe HIE. The quality of the available evidence in this regard is high.[42, 95] The benefits of the treatment are greater than the risks (adverse effects).

There seems to be a favourable cost-benefit ratio.

The preferences of the parents in this regard are unknown.

5.2.5. Summary of the evidence

Death or severe disability

High quality	– Therapeutic hypothermia reduces the risk of death or major disability at 18-24 months, in both newborns with moderate HIE and those with severe HIE.[42, 95] – The overall estimators of the protective effect of hypothermia are slightly superior in the group of patients with moderate HIE than in those with severe HIE.[42, 95] – In the longer-term follow-up studies (6-8 years), there has been no analysis as to whether the protective effect of hypothermia regarding the combined outcome of death / severe disability differs between patients with moderate HIE and those with severe HIE.[89, 90]

Death, severe disability, cerebral palsy, death or cerebral palsy

There are no studies that have specifically analysed the difference in the effect of hypothermia with respect to these outcomes between patients with moderate HIE and patients with severe HIE.

5.2.6. Recommendations

Strong	We recommend 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 18-24 months of age.

5.2.7. Implications for research

Future research could help to clarify whether or not deeper or longer cooling could be accompanied by a more powerful neuroprotective effect. Likewise, it is very desirable to develop new

interventions to be applied in combination with hypothermia, especially in newborns with severe HIE.

Finally, an important limitation of hypothermia RCTs is the difficulty in preventing the hyperthermia described in the control groups, which could accentuate the protective effect associated with hypothermia.

Given that therapeutic hypothermia initiated within the first 6 hours of life constitutes the standard treatment for newborns with moderate or severe HIE in our environment, it is highly unlikely that new trials might more accurately resolve if the severity of the encephalopathy conditions the effectiveness of treatment with hypothermia.

5.3. 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?

5.3.1. Introduction

This question is aimed mainly at elucidating if the clinical grading of neonatal HIE allows identifying the newborns that are at an increased risk of an unfavourable outcome and are therefore are candidates for neuroprotection using hypothermia.

The population to which the question refers is the population of patients in the stage prior to introducing therapeutic hypothermia or the control groups of hypothermia RCTs in which the absence of neuroprotective treatment allows knowing the evolution of the illness according to natural history thereof.

Our review focused on those works in which the classification by Sarnat16 was used, or systems based on that classification. This scale constitutes a barometer that is sensitive to the severity of the involvement of the CNS; it probably represents the grading system used the most in general; and in the majority of hypothermia RCTs for perinatal HIE, modifications of the scale have been used to include patients with moderate or severe HIE. However, in our opinion, the Sarnat classification has major limitations. The original study on which it is based included a highly reduced number of patients, there was no control population, and neither the assessment ages nor the operational definitions are clear. On the other hand, the classification system includes manifestations of the autonomic nervous system, whose assessment in clinical practice is scarcely feasible, as well as conventional electroencephalography, a test with reduced immediate availability. Finally, our group does not share the observation of the "hyperalert" state in newborns with mild HIE. An additional problem is that the majority of observational studies or RCTs that state using the Sarnat classification in reality used simplified modifications of this classification (in which the assessment of autonomic function was eliminated, in addition to the vestibulo-ocular reflexes and/or the EEG), and those versions lack suitable validation.

Given that in newborns with HIE there is a narrow window of therapeutic opportunity and hypothermia must begin during the first 6 hours of life, it was attempted to specifically assess the clinical severity of the HIE within said time frame. Question 7 talks about the prognostic value for the clinical severity of neonatal HIE at birth and throughout the entire course of acute encephalopathy, until discharge, both in patients managed with normothermia and those treated with hypothermia.

We base our answer to the posed question on an updated SR and MA of the studies of the pre-hypothermia area regarding the correlation between the clinical severity of HIE in term and near-term newborns (categorised according to Sarnat's classification or derived systems) and long-term neurological mortality / morbidity. Likewise, a re-analysis of the data corresponding to the control groups of the RCTs on hypothermia included in the MA by Tagin, 2012, was conducted.[42] The reasons for not jointly analysing both groups of studies (pre-hypothermia and hypothermia RCT) were the following. (1) Unlike hypothermia RCTs, in the pre-hypothermia studies the clinical grading of the encephalopathy was not done during the first 6 hours of life. (2) The hypothermia RCTs did not include newborns with mild encephalopathy, while the observational studies of the pre-hypothermia era theoretically cover the entire spectrum of severity of neonatal HIE (meaning the mild, moderate and severe degrees). (3) As it is detailed further below, there are limitations in the pre-hypothermia studies that make the generalisable nature of the outcomes questionable. However, in the hypothermia RCTs, both the inclusion of the patients and follow-up on the same were more systematic.

5.3.2. Outcomes

5.3.2.1. Analysis of the studies from the stage prior to the introduction of treatment with hypothermia

We identified one MA (Pin, 2009[96]) that investigated the relationship between the severity of neonatal HIE and the long-term outcomes of neurodevelopment. Said work included those studies of term newborn (gestational age of greater than 36 weeks) that met the first two essential criteria of the recommendations of the International Cerebral Palsy Task Force (MacLennan, 199[94]), meaning moderate or severe neonatal encephalopathy and severe metabolic acidosis. In order to clarify the neurodevelopment outcomes of the complete spectrum of patients with perinatal HIE, the studies of neonates with mild encephalopathy were also included. The search covered from the earliest possible date up to March 2008. In order to identify all the relevant studies published to date, our group reproduced the search strategy of the MA by Pin, 2009, from March 2008 up to the current date. 7 studies were selected (McShane, 1987;[97] Gray, 1993;[98] Yudkin, 1994;[99] Handley-Derry, 1997;[100] Hallioglu, 2001;[101] Carli, 2004;[102] and van Schie, 2010[103]), in which the severity of the encephalopathy was graded using Sarnat's classification or simplified modifications, and it was correlated with the long-term neurological prognosis. All the works were pre-hypothermia, and they included a total of 242 subjects (52 with mild encephalopathy, 118 with moderate encephalopathy and 72 with severe encephalopathy). The moment when the degree of neonatal encephalopathy was assessed was not restricted to the first 6 hours after birth in any of the studies.

The long-term outcomes were classified into two categories:

- Adverse outcome: death, cerebral palsy or cognitive/motor deficit of greater than -2 SD.
- Favourable outcome: normal neurodevelopmental results or mild impairment without repercussions to daily functions.

The age of the neurodevelopment assessments of the studies was relatively limited, with follow-up at 1 or 2 years in the majority of the works, and only two of them (including 11 patients overall) had results of ages ranging between 4 and 8 years (Yudkin, 1994, and HandleyDerry, 1997). On the other hand, the percentage of losses for follow-up was high, and not all the studies described the characteristics of the patients without an available assessment of outcomes, which makes the representativeness of the outcomes questionable.

Other limitations of the studies included in the MA were the presence of selection and assessment bias, given that in many of the studies the follow-up was not blind. On the other hand, the influence by the severity of the neonatal encephalopathy on the decisions to remove life support could have constituted a confusion factor in the analysis of mortality. As it was already stated, this MA did not allow knowing the prognostic value of the clinical assessment of the perinatal HIE within the time frame of interest of 6 hours of life.

5.3.2.1.1. Death or severe disability

Table 12 of Appendix 7.2 presents the meta-estimate of the proportion of patients with said outcome according to the degree of perinatal HIE without treatment with hypothermia. Moderate quality

The analysis of the risk of death or of severe disability for serious HIE versus moderate HIE showed an OR of 26.59 (9.49, [74.52]).

5.3.2.1.2. Death, severe disability, cerebral palsy, cerebral palsy or death

Given the scarce representativity of the identified studies, estimating the risks of these outcomes separately was not considered.

5.3.2.2. Analysis of the control groups of the RCTs regarding the efficacy of treatment with hypothermia

One source of information about the prognostic significance of the severity of perinatal HIE in the first 6 hours of life consists in the control groups of RCTs on hypothermia, in which the patients were selected and randomised within said framework of therapeutic opportunity. The most recent MA (Tagin, 2012[42]) included 7 RCTs (Gunn, 1998; Gluckman, 2005; Shankaran, 2005; Azzopardi, 2009; Zhou, 2010; Simbruner, 2010; and Jacobs, 2011), and its characteristics are described in Questions 4 and 5. It should be taken into account that the analysis exclusively included patients that were eligible for hypothermia (neonates with moderate or severe HIE), and it did not include neonates with mild encephalopathy, which would complete the entire spectrum of severity of perinatal HIE. As stated, for studies of the stage prior to the introduction of hypothermia as treatment for HIE, it is important to consider the influence that the degree of encephalopathy could have had in the decision-making about whether or not to continue or limit therapeutic efforts.

5.3.2.2.1. Death or severe disability

Table 13 of Appendix 7.2 presents the meta-estimate of the proportion of patients with said outcome as per the degree of neonatal HIE according to our re-analysis of hypothermia RCTs. High quality

The analysis of the risk of death or severe disability for serious HIE versus moderate HIE showed an OR of 4.14 (2.40, 7.13).

The moderate discrepancy observed between the outcomes of the patients from the pre-hypothermia era and the control groups of the hypothermia RCTs could be due to selection bias. It is unknown if the differences at the time of the assessment of the clinical severity of the encephalopathy could have had an influence on said discrepancy of outcomes.

5.3.2.3. Death, severe disability, cerebral palsy, cerebral palsy or death

Neither the MA by Tagin, 2012, nor any of the hypothermia RCTs included in it described the proportions of patients with said outcomes, separated according to the initial degree of encephalopathy.

5.3.3. From the evidence to a recommendation

5.3.3.1. Quality of the evidence

Moderate quality	The evidence of the correlation between the initial clinical severity of perinatal HIE and the risk of death or long-term neurological morbidity originates, on the one hand, from observational studies, and on the other, from the control groups of hypothermia RCTs.[42, 96] The observational studies have limitations, including high losses for follow-up, selection bias and assessment bias, which lowered the quality of the evidence. However, the magnitude of the association between the degree of encephalopathy and the risk of an unfavourable outcome increased the quality of the evidence. The quality of the RCTs was considered high, insofar as the inclusion of and the follow-up on the patients were adequate. On the other hand, these studies do not include the outcomes of patients with milder HIE. It is unknown how many of the patients from all the studies died as a consequence of having limited the therapeutic effort based on the presence of severe encephalopathy in the clinical examination, which could alter the prognostic value of the clinical grading of the encephalopathy whenever the "death" outcome is assessed (the "self-fulfilling prophecy" theory).

5.3.3.2. Balance between benefits and risks

No adverse effect directly related to the application of the clinical grading schemes of HIE for the selection of patients as candidates of neuroprotection/hypothermia could be expected. Even though there are no specific data published about the risks of an erroneous categorisation, an

over-estimation of the severity of HIE could lead to the cooling of patients without an indication for hypothermia. On the other hand, the under-assessment of the degree of encephalopathy could mean the loss of an opportunity to improve the evolution of a neonate that could have benefited from neuroprotective intervention.

5.3.3.3. Costs and use of resources

Conducting a neurological examination does not involve any additional financial cost, given that it is performed by the clinician or group of clinicians taking care of the patient with HIE. The cost-effectiveness aspects that were relevant for determining the strength of the recommendation for this question were not considered.

5.3.3.4. Values and preferences of the patients

There are no specific studies that have assessed the impact on the parents from applying clinical grading schemes of HIE for selecting candidate patients of neuroprotection / hypothermia. The values and preferences of the parents of the patients regarding this point have not been considered to be a determining factor for assessing the strength of the recommendation.

5.3.4. Final decision about the strength and direction of the recommendation

Aspects that have determined the direction and strength of the recommendation:

For a term or near-term newborn with HIE, the clinical grading of encephalopathy is correlated to the risk of death or neurological disability in the long term. The clinical categorisation of encephalopathy as moderate or severe during the first 6 hours of life adequately identifies the candidate patients for neuroprotection.[42, 96] The available evidence in this regard is moderate-high quality. The benefits of this selection tool are greater than the risks.

The cost/benefit ratio is favourable.

The preferences of the parents in this regard are unknown.

5.3.5. Summary of the evidence

Death or severe disability

Moderate quality	– For term or near-term newborns with HIE, the degree of encephalopathy during the first 6 hours of life, assessed using schemes based on Sarnat's system, is correlated to the risk of death or severe disability. An unfavourable outcome in neonates with mild encephalopathy is not expected. In patients with severe encephalopathy, the risk of adverse development is very high. Finally, children with moderate encephalopathy show more variable outcomes.[42, 96] – The clinical categorisation of encephalopathy as moderate or severe within said time frame adequately identifies those patients with a risk of an unfavourable outcome and therefore identifies candidates for neuroprotection.[42, 96]

Death, severe disability, cerebral palsy, cerebral palsy or death

There are no relevant studies in which the correlation between the clinical severity of the encephalopathy and the risk of each one of these outcomes were analysed.

5.3.6. Recommendations

Strong	In newborns with a gestational age of greater than or equal to 35 weeks with HIE, we recommend, 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).

5.3.7. Implications for research

Given that therapeutic hypothermia initiated within the first 6 hours of life constitutes the standard treatment for newborns with moderate or severe HIE in our environment, it is highly unlikely that new studies might help to more precisely clarify the prognostic value of the clinical categorisation of perinatal HIE in the absence of neuroprotective interventions and its role in the selection of patients that could benefit from treatment with hypothermia.

5.4. 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?

5.4.1. Introduction

In term or near-term newborns with HIE, the clinical severity of encephalopathy is correlated to the risk of death or neurological disability in the long term. Hypothermia has proved to be effective in these patients, and it currently constitutes the standard treatment for perinatal HIE in our environment. The objectives of this question were to compare the prognostic value of the clinical grading of perinatal HIE in the first 6 hours of life between the patients managed with normothermia and those treated with hypothermia, as well as investigate the predictive value of the clinical course of encephalopathy during neonatal hospitalisation, both in patients managed with normothermia and those who were cooled.

The RCTs included in the most recently published MA on hypothermia for neonatal HIE (Tagin, 2012[42]) were identified as relevant, and they were subjected to one *ad-hoc* re-analysis and to two secondary analyses of hypothermia RCTs (Gunn, 2008[104] and Shankaran, 2012[105]).

5.4.2. Outcomes

5.4.2.1. Association between the clinical severity of HIE in the first 6 hours of life and the outcomes

Therapeutic hypothermia has involved a reduction of the risks associated with the presence of moderate or severe HIE in the first 6 hours of life. The numerical expression of this fact is formed by the estimators of the reduction of the risk in relation to treatment with hypothermia for each one of the relevant outcomes presented in Questions 4 and 5 of this guideline. As it was stated, to answer the question of correlation between the clinical severity of HIE in the first 6 hours of life and the outcomes, therefore comparing patients managed with normothermia and those treated with hypothermia, we conducted a re-analysis of the relevant hypothermia RCTs (Gunn, 1998; Gluckman, 2005; Shankaran, 2005; Azzopardi, 2009; Zhou, 2010; Simbruner, 2010; and Jacobs, 2011), whose results are presented below.

5.4.2.1.1. Death or major disability

Table 14 of Appendix 7.2 offers the meta-estimates of the proportions of patients with said outcome according to the initial degree of HIE, both for the cases treated with hypothermia and for the controls. Moderate quality

Table 15 of the same Appendix 7.2 presents the estimate of the risks of death or major disability for severe versus moderate HIE in patients treated with hypothermia and patients managed with normothermia.

5.4.2.1.2. Death, severe disability, cerebral palsy, cerebral palsy or death

None of the hypothermia RCTs describe the results of these outcomes according to the degree of HIE (severe versus moderate).

5.4.2.2. Clinical course of the encephalopathy after the first 6 hours and the association thereof with the outcomes

5.4.2.2.1. Death or major disability

The study by Gunn, 2008,[104] a secondary analysis of the data of the CoolCap RCT (Gluckman, 2005), was the first one to analyse the effect of hypothermia on the prognostic value of the course of encephalopathy, clinically evaluated according to Sarnat's criteria (Sarnat, 1976) between the hours prior to randomisation and day 4. Of the 234 patients in the original trial, the information about the primary outcome (which was the combined incidence of death or severe disability at 18 months) was available for 218 (93%). On the other hand, 31 patients died before day 4, and data were missing for 10 patients. Thus, for the analysis of the changes in the severity of the encephalopathy between onset and day 4, and for its predictive value, 177 patients were evaluated (corresponding to 75% of the trial population), including 7 patients with mild encephalopathy. Moderate quality

The main factors that limited the quality of this study were its *a posteriori* design, the erroneous randomisation of a small number of neonates with mild encephalopathy, the relatively high number of non-evaluated patients due to death, the lack of neonatal or follow-up data and the short evaluation age of neurodevelopment. Moreover, it must be kept in mind that the presence of persistent severe encephalopathy could be a limiting criterion of the therapeutic effort and could therefore be a cause more than a predictor of death.

According to this study, treatment with hypothermia did not significantly affect the degree of HIE on day 4. In the analysis adjusted by treatment groups, the degree of encephalopathy on day 4 showed that it was predictive of the long-term neurodevelopmental outcome [OR for severe or moderate encephalopathy versus mild or absent = 5.7 (3.3-9.9)].

Of the 53 patients of both groups (hypothermia and control) with severe HIE on day 4, all except for 3 of the hypothermia group showed unfavourable development. The majority (> 75%) of the 46 children of both groups with mild encephalopathy or a normal neurological state at day 4 survived without a disability. Among the children with moderate HIE on day 4, significantly more cooled children showed a favourable outcome (31/45 versus 12/33; P = 0.006).

There is also a secondary analysis (Shankaran, 2012[105]) of the NICHD NRN RCT (Shankaran, 2005) in which the evolution of the encephalopathy during the first 3 days and upon discharge was examined, as well as the relationship thereof with the long-term neurodevelopmental outcomes. The original RCT included 208 newborns (102 in hypothermia and 106 controls), 3 of which (controls) were lost for follow-up. One (hypothermia) was included due to convulsions, but there was no complete neurological examination upon hospitalisation. In brief, the sample size for this post-hoc analysis was 204 (101 in hypothermia and 103 controls). Sarnat's modified neurological examination was used, which was applied in the first 6 hours and at 24, 48 and 72 hours, as well as upon discharge. The main outcome was death or moderate or severe disability at 18-22 months. The analyses were adjusted by participating centre, and treatment with drugs that could have an influence on the neurological examination (anticonvulsants, analgesics/ sedatives, neuromuscular blocking agents) was compared among patients receiving hypothermia and control patients, without finding differences. In addition to the aforementioned losses, for each moment of evaluation there were few patients without a neurological examination, but a growing number of deceased infants for each moment of evaluation.

Moderate quality

The limitations to the quality of the study include its *post-hoc* nature and the fact that there was no distinction between mild encephalopathy and a completely normal neurological state. On the other hand, as in other, similar studies, persistent severe encephalopathy could have been a limiting factor of the therapeutic effort, therefore acting as a confusion factor for the "death" outcome.

The neonates that received hypothermia showed less severe encephalopathy at 24 hours [OR = 0.44 (0.25-0.77)] and at 48 hours [OR = 0.49 (0.28-0.87)]. However, the groups were comparable with respect to the severity of the encephalopathy at 72 hours [OR = 0.65 (0.38-1.14)] and at discharge [OR = 0.58 (0.22-1.54)].

In the logistic regression models, thereby controlling for the treatment group and the degree of encephalopathy at the time of randomisation, the degree of encephalopathy at 72 hours proved to be the most significant predictor of death or disability [OR of moderate encephalopathy versus mild or absent = 9.15 (2.85- 29.39), OR of severe encephalopathy versus mild or absent = 59.95 (14.61-245.96)]. The persistence of significant encephalopathy (moderate or severe) at discharge was infrequent, occurring in 19 of 143 cases (13.2%). This condition was associated with an increased risk of unfavourable evolution [OR = 8.47 (1.76-40.88)]. In children with significant encephalopathy at discharge, the presence of altered neurological signs (hypertonia, closed fists, abnormal movements, absence of the gag reflex and asymmetrical tonic reflex of the neck) increased the risk of death or disability [OR = 2.69 (1.09-6.67)]. Likewise, the need for tube feeding or a gastrostomy was associated with a greater risk of unfavourable evolution [OR = 8.55 (2.73-26.82)]. However, the sensitivity of said alterations at discharge for predicting an unfavourable evolution was low.

5.4.2.2.2. Death, major disability, cerebral palsy, cerebral palsy or death

There are no studies that have evaluated the correlation between the clinical course of neonatal HIE, with and without hypothermia, and each one of these outcomes in the long term.

5.4.3. From the evidence to a recommendation

5.4.3.1. Quality of the evidence

Moderate quality	The evidence of the predictive capacity of the degree of HIE in neonates treated with hypothermia comes from an analysis conducted by the development group of this guideline from the RCTs included in the SR by Tagin, 2012, as well as from post-hoc studies of two hypothermia RCTs.[42, 104, 105] The initial quality of the evidence was low, and it was increased to moderate due to the magnitude of the association of the degree of HIE with the risk of an unfavourable outcome. It is unknown how many of the patients from all the studies died as a consequence of having limited the therapeutic effort based on the presence of severe encephalopathy in the clinical examination, which could alter the prognostic value of this test whenever the "death" outcome is assessed (the "self-fulfilling prophecy" theory).

5.4.3.2. Balance between benefits and risks

No adverse effect related directly to the clinical grading of HIE could be expected. Even though there are no specific data published about the risks of erroneous categorisation, both the overestimation and the underestimation of the severity of HIE could involve errors in the decision-making about the suitability of removing or continuing with life support.

5.4.3.3. Costs and use of resources

Similarly to the preceding question, the cost-effective aspects have not been deemed to be important for answering this question (the cost of the clinical evaluation is very low).

5.4.3.4. Values and preferences of the patients

There are no specific studies that have assessed the impact on the parents from applying clinical grading schemes of HIE for the purpose of establishing a prognosis. The values and preferences of the parents of the patients regarding this point have not been considered to be a determining factor for assessing the strength of the recommendation.

5.4.4. Final decision about the strength and direction of the recommendation

Aspects that have determined the direction and strength of the recommendation:

As with term or near-term newborns with HIE managed with normothermia, in newborns treated with hypothermia, the decree of encephalopathy, especially approaching 72 hours of life, shows an adequate predictive capacity of an unfavourable outcome. The available evidence in this regard is of moderate quality.[42, 105, 106] The benefits of this predictive tool are greater than its risks.

The cost/benefit ratio is favourable.

The preferences of the parents in this regard are unknown.

5.4.5. Summary of the evidence

Death or severe disability

Moderate quality	– In term or near-term newborns with HIE, the degree of encephalopathy continues to be predictive in the era of therapeutic hypothermia.[42, 104, 105] – The recovery of the neurological state seems to be accelerated in cooled patients, although hypothermia does not modify the degree of encephalopathy at 72 hours of life. – The degree of encephalopathy at 72 hours shows a high predictive – capacity of death or disability in the long term, in both patients – managed with normothermia and patients treated with hypothermia. – The presence of severe encephalopathy at 72 hours of life is generally associated with an unfavourable prognosis. – In patients subjected to hypothermia, the presence of moderate HIE upon hospitalisation that persists at 72 hours is associated with a more favourable prognosis than in patients managed in normothermia.[42, 105, 106]

Death, severe disability, cerebral palsy, cerebral palsy or death

There are no studies that have evaluated the correlation between the clinical course of neonatal HIE, with and without hypothermia, and each of these outcomes in the long term.

5.4.6. Recommendations

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, we recommend that the clinical grading of the encephalopathy at 72 hours be used as a tool for predicting the risk of death or severe disability.

5.4.7. Implications for research

Given that therapeutic hypothermia constitutes the standard treatment for newborns with moderate or severe HIE in our environment, it is highly unlikely that new studies might help to more accurately answer this question, except for additional analyses of published RCTs or more longer term follow-up studies.

5.5. 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?

5.5.1. Introduction

Perinatal HIE is associated with high rates of death and disability throughout the world. Even though treatment with hypothermia has reduced these rates, as we have seen, this reduction is far from being optimal. Certain drugs administered to newborns with HIE in the "window period" of damage could increase the neuroprotection, either by extending this "window" or by acting in synergy with hypothermia (the next question of this guideline). A large part of the current research on neuroprotection in HIE is focused on pre-clinical studies and clinical trials with some drugs, with the hope that the combination of different therapies could improve the neuroprotective results of hypothermia. It is also important to conduct pharmacokinetic and safety studies with these drugs, given that any substance administered in the neonatal period can be toxic in the immature brain.

5.5.2. Pharmacological treatments

5 articles were found for three pharmacological treatments: 2 for allopurinol (one of them is a Cochrane review that includes 3 RCTs) and the other an extension of follow-up on two of the RCTs included in the MA; 2 for EPO and 1 for phenobarbital.

5.5.2.1. Treatment with allopurinol (ALO)

Chaudhari, 2008,[106] is a Cochrane SR that includes 114 patients coming from 3 RCTs (Gunes, 2007[107]; Van Bel, 1998[108]; and Benders, 2006[109]). The included studies have slight differences in the administration guideline of ALO (Van Bel, 1998, and Benders, 2006: 20 mg/ kg ALO in the first 4 hours and a 2nd dose of 20 mg/kg 12 hours later; Gunes, 2007: 20 mg/ kg in the first 2 hours, the second 12 hours later and subsequently every 12 hours for 3 days).

The characteristics of the group of patients included also differ in some aspects, notably:

- The number (11/11, 17/15 and 30/30 for the number of cases/controls of the studies by Van Bel, 1998; Benders, 2006; and Gunes, 2007, respectively).
- The comparator, which in the case of Benders, 2006, and Gunes, 2007, is a placebo, isn't one in the case of Van Bel, 1998 (there isn't any).

– There is a blind in the administration of ALO in the case of Benders, 2006, and Gunes, 2007, but not in the case of Van Bel, 1998.

– The degree of the HIE of the patients and how it is classified: Benders, 2006, establishes the criteria of severe HIE according to aEEG (burst suppression, continuous low voltage or flat). All other studies include patients with mild-moderate-severe HIE (Gunes, 2007, Van Bel, 1998), in which 30-40% correspond to the moderate-severe HIE group.

– The studies by Van Bel, 1998, and Benders, 2006, do not have follow-up beyond the neonatal period, and the one by Gunes, 2007, at least reaches one year of life.

Kaandorp, 2012.110 It is an expansion of the follow-up on the studies by Van Bel, 1998, and Benders, 2006, and it includes 54 patients with moderate-severe HIE who were followed up on over an average of 5 years and 5 months (SD of 1 year and 2 months).

5.5.2.1.1. Neonatal death

The ALO SR (Chadhari, 2008106) includes, in the joint outcome, the combined variable of "death during the neonatal period and infancy", wherefore for this outcome we preferred to separately analyse the data from the 3 RCTs that were included (Van Bel, 1998; Benders, 2006; and Gunes, 2007). After accessing the data of the original article, in the study by Benders, 2006, it can be assured that 22 of the 23 deaths occurred during the neonatal period, as it can be likewise assured in the Van Bel study in 3 of the 5 cases that received ALO and in all the cases (5/5) from the study by Gunes, 2007. In all other cases, death could have occurred in the neonatal period or somewhat later.

Low quality

Summary of the deaths in the neonatal period (treated vs not): Benders, 2006 (13/17 versus 10/15); Van Bel, 1998 (2/11 versus 5/11); Gunes, 2007 (3/30 versus 3/30).

There are no differences in the death outcome in the neonatal period.

5.5.2.1.2. Death in the first two years of life

No differences were found in the meta-analysis of the 3 RCTs (RR of 0.92; 95% CI, 0.59 to 1.5), although the studies by Van Bel, 1998, and Benders, 2006, only recorded the neonatal period, and Gunes, 2007, reaches a minimum of 12 months. In the expansion of the follow-up from the studies by Van Bel, 1998, and Benders, 2006, up to the age of 4-8 years, the article by Kaandorp, 2012, finds a trend of lower mortality in the group treated with ALO for the subgroup of mild-moderate HIE (25% vs 59%, p = 0.053).

Low quality

5.5.2.1.3. Death or severe disability

Two studies include this outcome (Gunes, 2007, and Kaandorp, 2012). Gunes, 2007, does so at the age of 18-21 months and finds no differences (RR of 0.73; 95% CI, 0.41 to 1.30). Kaandorp, 2012, finds no differences at the age of 4-8 years, although those with mild-moderate HIE (including the most severe cases according to the aEEG) treated with ALO do seem to have lower death or severe disability (RR of 0.40; 95% CI, 0.17 to 0.94).

Low quality

5.5.2.1.4. Severe cerebral palsy / severe disability outcome

Gunes, 2007, finds no differences (8/28 ALO versus 12/28 control), nor does Kaandorp, 2012 (0/16 in the ALO group versus 1/17 in the control group, p = 0.36). Low quality

5.5.2.1.5. Severe cerebral palsy outcome

Gunes, 2007, finds no differences (6/58 ALO versus 11/58 control group), nor does Kaandorp, 2012 (1/28 ALO versus 1/26). Low quality

5.5.2.1.6. Neonatal morbidity

a) Neonatal convulsions: the MA (Chadhari, 2008) finds no differences (RR of 0.93; 95% CI, 0.75 to 1.16). Low quality

b) Alterations in the neuroimaging: one study (Benders, 2006) indicates this outcome without finding differences in the findings with ultrasound in the early neonatal period (RR of 1.12; 95% CI, 0.81 to 1.55) or in the findings of the MRI taken of survivors (RR of 1.88; 95% CI, 0.56 to 6.31). Low quality

5.5.2.1.7. Intact survival outcome

Gunes, 2007, and Kaandorp, 2012, contribute this data without finding differences. Low quality

5.5.2.1.8. Cost-effectiveness outcome

No study with ALO that specifically assesses this result has been identified.

5.5.2.1.9. Adverse effects outcome

Not assessed jointly in the MA.

5.5.2.2. Treatment with recombinant human erythropoietin (EPO)

Two articles were considered, although the administration of EPO in one of them occurs within the interval of the first 48 hours of life:

Zhu C., 2009.[11] This is a randomised, controlled and blind study (for the evaluation of the outcomes of the variables, but not for the treatment). The doses used were 300 U/kg/dose/day in a group of 47 newborns and 500 U/kg/dose/day in another group of 29 newborns for 2 weeks. The control group consisted of 82 newborns and received no placebo. The first dose of EPO was administered at any time within the first 48 hours of life, with a median of 20 hours for the 300 U/kg dose and 24 hours for the 500 U/kg dose of EPO. It includes patients with moderate-severe HIE. Follow-up was up to 18 months of life. Moderate quality

Elmadhdy H., 2010.[112] This was a randomised, controlled, non-blind study for administering the treatment, and it was for the evaluation of the results. It included patients with mild-moderate HIE. The EPO doses used were 2500 U/kg/dose subcutaneously, 5 doses, one each day, with the first one beginning within the first 6 hours of life. Three groups are established: 15 HIE-EPO, 15 HIE-no EPO, 15 healthy. Follow-up was conducted up to 6 months of life. | Low quality

5.5.2.2.1. Neonatal death

No study refers to this outcome on its own, although the study by Zhu, 2009, indicates 2/76 vs 3/82 deaths in the group treated with EPO versus the control, wherefore there are no differences in the death outcome in the neonatal period. | Moderate quality

5.5.2.2.2. Death in the first two years of life

Both Zhu, 2009, with follow-up lasting up to 18 months, and Elmahdy, 2010, lasting up to 6 months, found no differences in this outcome. In the study by Zhu, 2009, there also are no differences for this outcome between the two doses of EPO used. | Moderate quality

5.5.2.2.3. Death or severe disability

Only the study by Zhu, 2009, gives this outcome in combination, and it is lower in the EPO group (RR of 0.62; 95% CI, 0.41 to 0.94). Breaking down the outcome between those with moderate or severe HIE, differences existed for those with moderate HIE (RR of 0.26; 95% CI, 0.09 to 0.76), but not for severe HIE (RR of 0.67; 95% CI, 0.30 to 1.52). In this same study, upon comparing the two EPO parameters, there were no differences. | Moderate quality

5.5.2.2.4. Severe cerebral palsy / severe disability outcome

Zhu, 2009, indicates less moderate-severe disability in the group treated with EPO (RR of 0.59; 95% CI, 0.38 to 0.93), without differences for the two parameters used. Considering the group with an MDI < 70, the MDI is lower in those treated with EPO (RR of 0.56; 95% CI, 0.3 to 1.08) (p = 0.048). | Moderate quality

Elmahdy, 2010, in the evaluations conducted at 6 months of life, finds fewer screening tests (Denver II) and pathological neurological screening exams: 27% versus 71% with respect to the controls (p = 0.03). | Low quality

5.5.2.2.5. Severe cerebral palsy outcome

Zhu, 2009, indicates a less cerebral palsy trend in the group treated with EPO (RR of 0.51; 95% CI, 0.23 to 1.11), reaching statistically significant differences for the subgroup with moderate HIE (RR of 0.23; 95% CI, 0.04 to 1.47) (p = 0.039). There are no differences between the two EPO parameters. | Moderate quality

5.5.2.2.6. Neonatal morbidity

a) Neonatal convulsions: Elmahdy, 2010, finds a lower incidence of crisis at 72 hours and 5 days in the EEG of children treated with EPO. Low quality

b) Alterations in the neuroimaging: Elmahdy, 2010, finds no differences.

c) Alterations in the clinical examination: Zhu, 2009, finds better neurological examinations in the Thompson scales assessed at 7 days of life (very low scores) and in the NBAS tests at 14 and 28 days of life (very high scores) in the group treated with EPO, according to both one parameter and the other.

5.5.2.2.7. Intact survival

No study with EPO that specifically assesses this result has been identified.

5.5.2.2.8. Cost-effectiveness

No study with EPO that specifically assesses this result has been identified.

5.5.2.2.9. Adverse effects

Both Elmahdy, 2010, and Zhu, 2009, indicate the absence of adverse effects in the group treated with EPO. In the study by Zhu, 2009, the control group had lower haemoglobin and reticulocyte levels at 2 weeks of life.

5.5.2.3. Treatment with phenobarbital (PB)

One article was found

Singh D., 2005.[113] It was a randomised, controlled and blind study to assessment of the outcomes, but it was not blind to administration of the treatment. There was no placebo. It included 25 newborns in the treatment group versus 20 in the control group. 20 mg/kg of phenobarbital was administered in the first 6 hours of life. The patients of the control group received treatment with PB if they had seizures (although the discussion highlights that always after 6 hours of life). It includes patients with mild, moderate and severe HIE, although they conduct a posthoc analysis for the moderate-severe HIE group. Follow-up is limited to 3 months.

5.5.2.3.1. Neonatal death outcome

Even though the Singh study does not establish the age of death of the patients, it can be inferred that they occur in the neonatal period, without differences between the group treated with PB and the control group. The post-hoc analysis, which restricts the analysis to cases of moderate-severe HIE, finds fewer neonatal deaths, with an RR of 0.21 (0.05-0.87). p = 0.01. Low quality

5.5.2.3.2. Death outcome in the first two years of life

The only data on death given by Singh, 2005, is that of death at discharge, which is the data incorporated in the preceding outcome. Low quality

5.5.2.3.3. Death or severe disability outcome

The combined outcome is only indicated for the time of discharge by Singh, 2005, and no differences are found (RR of 0.73; 95% CI, 0.42 to 1.30). Low quality

5.5.2.3.4. Severe cerebral palsy / severe disability outcome Singh,

2005, finds no differences either at discharge or at 3 months. Low quality

5.5.2.3.5. Severe cerebral palsy outcome

Singh, 2005, finds no differences. Low quality

5.5.2.3.6. Neonatal morbidity

a) Neonatal convulsions: the article by Singh, 2005, indicates a lower incidence of convulsions (without EEG) in the group treated with PB (RR of 0.20; 95% CI, 0.05 to 0.84). Low quality

b) Alterations in the neuroimaging: no study with PB that specifically assesses this result was found.

c) Alterations in the clinical examination: assuming that the discharge of patients occurs during the neonatal period (it is not possible to assure this data from the article), no differences are found in the article by Singh, 2005.

5.5.2.3.7. Intact survival outcome

Singh, 2005, finds no differences between both groups at the age of 3 months (14/20 vs 8/17, p = 0.15). Low quality

5.5.2.3.8. Cost-effectiveness outcome

No study with PB that specifically assesses this result has been identified.

5.5.2.3.9. Adverse effects outcome

In the study by Singh, 2005, there are no adverse effects associated with PB (only the need for ventilation and the multiple organ dysfunction syndrome were studied). Low quality

5.5.2.4. Other pharmacological treatments

No articles that respond to the posed question were found for other pharmacological treatments, including topiramate and xenon.

5.5.3. From the evidence to a recommendation

5.5.3.1. Quality of the evidence

The administration of ALO in the first 6 hours of life in newborns with moderate-severe HIE could decrease the combined outcome of death or severe disability in the group of newborns with moderate HIE.	Low quality
The quality of this evidence was scored as low due to the inclusion of patients with mild HIE in some studies or with exclusively severe HIE in another, and due to the differences in the follow-up time. The number of patients is not high, and the statistical power is 18%. Moreover, the trend indicated for the moderate HIE group includes mild cases, and it is a post-hoc study, with the limitations this involves.[106-110]	
The administration of high doses of EPO (2500 U/kg) in the first 6 hours of life seems to reduce the incidence of neonatal convulsions and improve neurodevelopment in the short term, without adverse effects of note in the group of newborns with mild-moderate HIE.[110]	Low quality
The quality was qualified as "low" due to the short follow-up and the evaluation used, which is not well defined (with a screening test at 6 months) and due to the number of patients included in each bracket, which is scarce. Moreover, patients with mild HIE are included.	
The administration of EPO in the first 48 hours of life does not reduce isolated mortality, although it does reduce the combination of death or severe disability in the long term, regardless of the dose used (300 U/kg versus 500 U/kg), without adverse effects of note in the group of newborns with moderate-severe HIE, above all in the latter.[111]	Moderate quality
The quality was qualified as moderate, given that it is a well-designed clinical trial, with an acceptable number of patients, although regarding the recommendation about EPO, it is important that administration take place within the first 48 hours. The moderate quality is maintained, but the value of the RR is close to 1 (0.94). The analysis, thereby separating the group with severe HIE from the group with moderate HIE, was a post-hoc analysis, and it was therefore not taken into account.	
The administration of PB in the first 6 hours of life in newborns with moderate-severe HIE does not seem to reduce death or short-term disability, although it could reduce the number of neonatal convulsions.[114]	Low quality
The quality was kept low, because the RR is 0.2 for the neonatal morbidity outcome (neonatal convulsions), because the diagnosis of convulsions is done according to the clinical symptoms, and moreover, because the control group also receives the study treatment (PB) during evolution. Moreover, follow-up only reaches 3 months. There could be doubts about neonatal death in moderate-severe HIE, because even though it is post-hoc, the RR is very strong, at 0.21 (0.05-0.8%), p = 0.01.	

5.5.3.2. Benefit-risk balance

The studies that were conducted are insufficient for establishing a balance in favour of the administration of ALO due to a lack of more evidence showing an absence of adverse effects and clearer benefits.

The studies conducted with EPO show the absence of adverse effects with reasonable security, and although more RCTs are required, there seems to be certain evidence of a benefit from using it, even though it comes quite a few hours after the therapeutic window.

The insufficient evidence of a benefit from PB does not justify the administration thereof, despite the fact that the risks are not apparently considerable.

Perhaps the benefit-risk balance should be assessed differently for the group with moderate HIE than for the group with severe HIE. In newborns with severe HIE, the benefits of pharmacological treatment could exceed the risks of very pathological neurodevelopment; however, while there is already little evidence in general, there is even less evidence for this subgroup (severe HIE). The group of newborns with moderate HIE is the one in which there is somewhat more evidence of a benefit, but in turn it is the group where the evolution is more uncertain and whose risk-benefit balance is currently the most difficult, given the lack of more evidence.

Therefore, for the treatment with EPO, even though it is not possible to establish a recommendation, and considering the risk-benefit balance after adequately informing the parents, administering treatment with EPO during the first 48 hours of life could be considered if it was not possible to initiate hypothermia within the therapeutic window, given the high risk of sequelae, above all in the case of severe HIE. The study by Elmahdy uses the highest doses, which could reach neuroprotective doses that are more therapeutic, according to the preclinical studies, although this study does not include newborns with severe HIE. Moreover, only the study by Zhu has shown a benefit in death/disability at 18 months. This risk-benefit balance is more difficult to establish in the case of moderate HIE.

5.5.3.3. Costs and use of resources

The costs of the presented pharmacological treatments are clearly less than the costs represented by death or the long-term disability of these patients, although these aspects have not been evaluated in any study.

No financial assessment studies that specifically evaluate these pharmacological treatments were found.

5.5.3.4. Values and preferences of the patients

The values and preferences of the patients have not been considered for directing the strength of the recommendations.

5.5.4. Final decision about the strength (strong or weak) and the direction (in favour or against) of the recommendation

Aspects that have determined the direction and strength of the recommendation:

The current scientific evidence does not show benefits from the administration of ALO or PB within the first 6 hours of life in children with HIE.[106, 110, 113] The administration of EPO has shown benefits in some short-term studies,[111, 112] but more long-term data are needed. Moreover, the periods of administration and the doses are not uniform among the studies. Up to now, no cost-effectiveness assessments have been conducted with the drugs described in this question. The opinion of the parents in this regard are unknown.

5.5.5. Summary of the evidence

Low quality	The administration of ALO in the first 6 hours of life in newborns with moderate-severe HIE does not decrease the isolated death rate or the combined rate of death or severe disability, although there could be a reduction of both outcomes in the group of newborns with moderate HIE.[107-111]
Low quality	The administration of high doses of EPO (2500 U/kg) in newborns with mild-moderate HIE in the first 6 hours of life reduces the incidence of neonatal convulsions and improves neurodevelopment in the short term.[113]
Moderate quality	The administration of EPO in the first 48 hours of life does not reduce isolated mortality in newborns with moderate-severe HIE, although it does in the combination of death or severe disability in the long term, regardless of the dose used (300 U/kg versus 500 U/kg).[112]
Low quality	The administration of PB in the first 6 hours of life in newborns with moderate-severe HIE does not reduce death or short-term disability, although it could reduce the number of neonatal convulsions.[114]

5.5.6. Recommendations

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

5.5.7. Implications for research

Multicentre, randomised, controlled and blind trials are necessary, which allow determining the effect of the different drugs on mortality and on long-term neurodevelopment in newborns with moderate and severe HIE. In any event, these trials must be conducted in conjunction with treatment with hypothermia.

In the treatments analysed in this guideline, it would be justified to conduct RCTs with more patients, given that the biological efficacy of these treatments has been demonstrated in preclinical and experimental studies on animals, and there is certain evidence of a benefit in other groups of neonatal patients.

Given the high number of treatments that could be used as therapy together with hypothermia, it is necessary to establish an ordered sequence based on experimental trials that would allow the most efficient selection of those with the greatest likelihood of success in the final phases of the RCTs. In this regard, it would be desirable to have a multinational network for coordinating potential therapeutic trials and publishing those treatments that were not successful in the more initial phases of application in order to gain in efficiency.

The use of simple inclusion criteria, with uniform parameters for administering treatments and assessing disability using similar tests would facilitate a comparison of the results in future MAs. Newborns with moderate or severe HIE would be the candidates for participating in these RCTs, given the existing evidence that therapeutic hypothermia is beneficial in this group of patients. Given the existing limitations due to the narrow "therapeutic window" in this group of children, within 6 hours after birth, it would be recommendable to establish strategies that would allow informing parents before birth about the possibility of applying these therapies if they were necessary.

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

5.6.1. Introduction

As we already indicated regarding the preceding question, the combination of different therapies with hypothermia treatment can improve the results obtained in children with perinatal HIE. When assessing the possible toxicity of these drugs, we must consider that hypothermia can modify the excretion of numerous drugs and their metabolites.

5.6.2. Outcomes

Only two studies that answer the "adverse effects" outcome assessed in the neonatal period were found. One was for topiramate114 and the other for EPO.[115]

Filippi, 2010.[114] This study includes 27 cases (between 2007 and 2009) that receive treatment with topiramate (TP) and hypothermia (HT), and 27 with hypothermia only (historical group between 2004 and 2007). Both groups receive HT, and two subgroups are established: one for cooling at 32-34º C and another at 30-33º C. The cases receiving TP do so at 3-5 mg/k/dose/day according to two different parameters (5-3-3 mg/k or 5-5-5 mg/k). The first dose is administered in the first 6 hours of life. The patients are distributed as follows: 15 (HT 30-33º C), 12 (HT 32-34º C), 10 (HT 30-33º C + TP 5-5-5), 1 (HT 30-33º C + TP 5-3-3), 6 (HT 32-34º C + TP 5-5-5),

10 (HT 32-34º C + TP 5-3-3).

Wu YV, 2012.[115] This is a phase I, open-label clinical trial on EPO with escalating doses that includes 24 patients. The first dose is received in the first 24 hours of life. The next doses are received every 48 hours up to a maximum of 6 doses. Only 38% receive the 6 doses. The patients are distributed as follows: 3 cases (250 U/kg/dose), 6 cases (500 U/kg/dose), 7 cases (1000 U/kg/dose), 8 cases (2500 U/kg/dose).

In both groups, patients with mild HIE could have been included.

5.6.2.1. Neonatal death outcome

No study that specifically evaluates this outcome was identified. In the safety study for TP,[114] there were no more deaths in the group that received TP, and in the EPO[115] study, there were no deaths associated with the treatment.

5.6.2.2. Death outcome in the first two years of life

No study that specifically evaluates this outcome was identified.

5.6.2.3. Death or severe disability outcome

No study that specifically evaluates this outcome was identified.

5.6.2.4. Severe cerebral palsy / severe disability outcome

No study that specifically evaluates this outcome was identified.

5.6.2.5. Severe cerebral palsy outcome

No study that specifically evaluates this outcome was identified.

5.6.2.6. Neonatal morbidity

a) Neonatal convulsions: no study that specifically evaluates this outcome was identified.	Very low quality
b) Alterations in the neuroimaging: the TP study[115] finds no differences in the injuries in the MRI between the group treated with TP and the group not treated.	

5.6.2.7. Intact survival outcome

No study that specifically evaluates this outcome was identified.

5.6.2.8. Cost-effectiveness outcome

No study that specifically evaluates this outcome was identified.

5.6.2.9. Adverse effects outcome

No greater incidence of adverse effects was found in the two safety studies for TP and EPO.[114]	Very low quality
No greater incidence of adverse effects was found in the two safety studies for TP and EPO.[115]	Low quality

5.6.3. From the evidence to a recommendation

5.6.3.1. Quality of the evidence

No studies that evaluate the outcomes established for this question were found, except for adverse effects in the neonatal period.

There is no increase in the incidence of adverse effects with the administration of the drug topiramate together with hypothermia versus the use of hypothermia on its own.	Very low quality
The qualify of the evidence of the outcome of the adverse effects for the drug topiramate has been qualified as "very low", given that there is only one study (Filippi, 2010[114]), which is a cohort study with a control group that is historical, in which numerous subgroups are established for the doses used, with a scarce number of patients in each group. The temperature ranges used in the control group and in the treatment group with TP overlap each other (30-33º C versus 32-34º C), and they can hardly be extrapolated to current clinical practices, given that the target range is 33-34º C. Moreover, patients with less severe HIE could have been included, such as mild HIE.	
The quality of the evidence of the outcome for the drug EPO has been qualified as low, because there is only one article (Wu, 2012[115]). Moreover, even though it is a well-designed article, the number of patients is not extensive: only 9 out of the 24 receive the 6 established doses, and the first dose is administered within a broad period of time (24 hours of life), together with hypothermia, which is initiated between one hour and 18 hours of life. It also excludes some children with a severely altered aEEG or children with an EEG at normal voltage who could show symptoms of moderate HIE.	Low quality

5.6.3.2. Benefit-risk balance

The conducted studies do not allow establishing a balance in favour of administering any treatment in conjunction with therapeutic hypothermia for decreasing death or disability in newborns with moderate-severe HIE. The number and quality of those studies are also very limited for establishing that they are safe in this population of children, although the two studies shown [114, 115] indicate that they are.

5.6.3.3. Costs and use of resources

The costs of the presented pharmacological treatments are clearly less than the costs represented by death or the long-term disability of these patients, although these aspects have not been specifically evaluated in any study.

5.6.3.4. Values and preferences of the patients

The values and preferences of the patients have not been considered for directing the strength of the recommendations.

5.6.4. Final decision about the strength (strong or weak) and the direction (in favour or against) of the recommendation

Aspects that have determined the direction and strength of the recommendation:

No studies that evaluate the outcomes established for this question were found, except for adverse effects in the neonatal period. There are various clinical trials in progress using different drugs. Up to now, no cost-effectiveness studies have been conducted with the drugs described in this question. The opinion of the parents in this regard are unknown.

5.6.5. Summary of the evidence

Very low quality	There are no differences between the adverse effects of children with HIE treated with hypothermia and TP or EPO versus those not treated with these drugs.[114, 115]
Low quality	There are no differences in the findings in the control images taken of children treated with hypothermia and TP versus those treated with hypothermia alone.[114, 115]

5.6.6. Recommendations

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

5.6.7. Implications for research

It is necessary to conduct multicentre, randomised, controlled and blind trials with sufficient power to clarify the effect of different drugs in conjunction with treatment with hypothermia on mortality and long-term neurodevelopment in newborns with moderate and severe HIE.

There are some treatments whose biological efficacy has been proved in preclinical and experimental studies on animals, and there is certain evidence of benefit in other groups of neonatal

patients, wherefore it would be desirable to include them in pharmacokinetic and safety studies. Likewise, treatments such as EPO or topiramate, which point to evidence of safety, are potential candidates for being included in multicentre trials that determine death and long-term disability outcomes.

Given the high number of treatments that could be used as therapy together with hypothermia, it is necessary to establish an ordered sequence based on experimental trials in the laboratory and on animals that would allow selecting, in the most efficient way possible, those with the most likelihood of success in the final phases of clinical trials. In this regard, it would be desirable to have a network that coordinated potential therapeutic trials and that publicised those treatments that were not successful in the more initial phases of application in order to gain in efficiency.

The use of simple inclusion criteria, with uniform parameters for administering the treatments and assessing disability using similar tests would facilitate a comparison of the results in future meta-analyses. Newborns with moderate or severe HIE would be the candidates for participating in these trials, given the existing evidence that therapeutic hypothermia is beneficial in this group of patients. Given the existing limitations due to the narrow "therapeutic window" in this group of children (within 6 hours after birth), it would be recommendable to establish strategies that would allow informing parents before birth about the possibility of applying these therapies if they were necessary.

5.7. 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 18-24 months?

5.7.1. Introduction

Electrographic seizures are frequent in neonates with HIE, and the treatment thereof is controversial. There is the potential impact that these subclinical seizures could mean a worse outcome in terms of death or moderate-severe disability or epilepsy during development.

To answer this question, 4 articles were selected. Three did not consider hypothermia as neuroprotective therapy in newborns with HIE, wherefore the question would not be answered directly (Evans, 2007;[116] Van Rooij, 2010;[117] and Singh, 2005[113]). The fourth study did answer the question directly (Wusthoff, 2010[118]).

5.7.2. Outcomes

5.7.2.1. Death or severe disability

Evans DJ[116] conducted an SR, thereby evaluating the effect of treatment with anticonvulsants in children with perinatal asphyxia on the variables of death or severe neurodevelopmental disability at 12 months or more (combination of cerebral palsy, development delay (IQ < 70), blindness). This SR included 7 randomised and controlled studies. No significant differences in the rates of severe neurodevelopmental disability were recorded between the experimental and control groups (Goldberg, 1986; Ruth, 1991; Hall, 1998) (typical RR of 0.61; 95% CI, 0.30 to 1.22). Only one study included in the review (Hall, 1998) found a significant reduction of the relative risk of the combined result of severe neurodevelopmental disability or death in the group treated with phenobarbital (RR of 0.30; CI of 95%: 0.10 to 0.93). The meta-analysis, which combined the results of these three studies, also didn't reveal significant differences in the risk of the combined result of death or severe neurodevelopmental disability (RR of 0.78; CI of 95%: 0.49 to 1.23). Low quality

However, all the included studies had insufficient methodologies, such as: scarce sample size, significant losses after the random assignment (23% in Hall, 13% in Kuzemko, 3% in Goldberg), possible bias of concomitant intervention and the evaluation of results without blinding, wherefore the validity of these results is limited.

5.7.2.2. Mortality

Only one prospective study indirectly examined this question, given that its objective was to clarify the incidence and the moment of the convulsions that occurred in term neonates with HIE while receiving total body hypothermia (Wusthoff, 2011[118]). This study included only 26 patients, 18 of which (69.2%) received antiepileptic drugs. The small sample size did not allow knowing if the presence of convulsions aggravated the risk of death. Very low quality

The SR (Evans DJ,[116]), which included 7 RCTs in newborns over 37 weeks of gestational age with perinatal asphyxia, did not find significant differences in the rates of mortality between the experimental and control groups in the five studies that compared barbiturates with the standard treatment: RR of 1.13; 95% CI, 0.59 to 2.17 (Goldberg, 1986; Hall, 1998; Ruth, 1991; Singh, 2004; Vargas-Origel, 2004). Low quality

The RCT by Singh D.[113] reports that the administration of phenobarbital during the first 6 hours of life in patients with asphyxia does not reduce mortality upward (5/20 versus 3/15, RR = 1.33 (0.36 to 4.92, 95% CI). Low quality

The RCT by Singh D.[113] reports that the administration of phenobarbital during the first 6 hours of life in patients with asphyxia does not reduce mortality upward (5/20 versus 3/15, RR = 1.33 (0.36 to 4.92, 95% CI). Low quality

5.7.2.3. Cerebral palsy

No study that specifically assesses this result was identified

5.7.2.4. Severe-moderate disability

The SR by Evans DJ[116] also didn't record significant differences in the rates of severe neurodevelopmental disability between the experimental and control groups: typical RR of 0.61; 95% CI: 0.30 to 1.22 (Goldberg, 1986; Ruth, 1991; Hall, 1998). As we previously pointed out, only the study by Hall, 1998, showed a decrease in the combined outcome of death or disability. Low quality

The second RCT, of low quality, is a randomised, controlled study by Singh[113] with the objective of determining if the administration of phenobarbital in the first 6 hours of life in newborns ≥ 34 weeks with HIE decreases the adverse outcomes. Therefore, phenobarbital at 20 mg/kg IV was administered to 25 newborns with clinical convulsions. Control group of 20 patients. It defines "disability" as: upward neurological alteration (abnormal tone, altered cortical function and persistent neonatal anomalies in reflexes). The results show a 6/20 (30%) reduction of the disability outcome in the treatment group versus 9/17 (53%) in the control group: RR of 0.57 (95% CI, 0.25-1.27). Low quality

5.7.2.5. Clinical or electrical convulsions

The only study that includes hypothermia as treatment in patients with moderate-severe HIE is the non-randomised prospective study by Wusthoff CJ.[118] This study determines the incidence and moment of appearance of the electrical seizures detected by conventional EEG (start 9.1 ± 5.75 hours). It includes a small representative sample (n = 26). 18 patients (69.2%) were treated with antiepileptics during hypothermia, and phenobarbital was administered to 10 (38.5%) due to the suspicion of clinical convulsions before monitoring the patients with EEG. Out of these 10, seven had electrical seizures. Electrical seizures were detected in 17 (65.4%) patients, and electrical-clinical seizures were detected in 9 (34.6%). In 4 (15.4%), an epileptic state was noted. They found that 65% of term newborns had electrical seizures during or immediately after treatment. They conclude that hypothermia does not affect the incidence of the appearance of convulsions, given that the incidence thereof on this cohort coincides with the 22-64% described in literature in children not treated with hypothermia (Murray DM, 2006; Shankaran, 2005; Gluckman PD, 2005). Given the scarce sample size, it couldn't be appreciated if there was a correlation between the presence of seizures and brain injury in the NMRI. Low quality

The SR by Evans DJ[116] assesses the control of convulsive seizures as a secondary outcome. Two studies compared phenobarbital vs a control, and they reported the convulsive seizure rates during the neonatal period (Hall, 1998; Vargas-Origel, 2004). Neither of them found significant differences in the rates. Goldberg, 1986, compared thiopental vs a control and reported the following: A) the proportion of newborns that suffered convulsive crises during the first three days of life and B) at three days of life. No significant differences were noted (RR = 1.03; CI of 95%, 0.74 to 1.44 and RR = 1.06; CI of 95%, 0.40 to 2.77, respectively). Vela, 1987, when comparing phenobarbital with phenytoin related similar rates of convulsive crises during the first week. Kuzemko, 1972, did not find significant differences in the proportion of children who suffered convulsive seizures after three days of life in neonates treated with chloral hydrate or with diazepam after birth. All these studies have a very small sample size (fewer than 40 patients). Low quality

Of the studies included in the SR, only Hall, 1998, provided adequate concealment of assignment, and none of the studies used a placebo. Only the studies by Vela, 1987, and Kuzemko, 1972, were blind. In the five studies that did not blind the caregiver, there is the potential bias associated with concomitant interventions (Goldberg, 1986; Hall, 1998; Ruth, 1991; Singh, 2004, and VargasOrigel, 2004).

Van Rooij[117] analysed the effect of the treatment (reduction of the duration of seizures and a decrease of brain damage in NMRI at 4-10 days) on the subclinical seizures detected by aEEG in newborns of over 37 weeks with HIE diagnosed according to Sarnat and Sarnat criteria. The patients were not treated with hypothermia and were randomised into two groups: A (19 newborns with clinical and subclinical seizures) and B (14 newborns with clinical seizures). Treatment was initiated according to the protocol: 1) phenobarbital, 2) midazolam, 3) lidocaine, 4) clonazepam, 5) pyridoxine, 6) others, although between 2003 and 2005, lidocaine was the second-line treatment of choice. Of the 33 newborns that were included, 26 (78%) received treatment with midazolam as the second line. In group A, 11 (58%) had moderate HIE and 8 (42%) had severe HIE. In group B, 7 (50%) had moderate HIE and 7 (50%) had severe HIE. There were losses of 7%. Even though the duration (mean ± SD) of the seizures was shorter in group A (196 ± 340 min) with respect to group B (503 ± 1084 min), it was not statistically significant. The duration of the seizures was longer in patients with severe HIE versus moderate HIE, but without statistical significance. An epileptic state was present in 12/19 (63%) patients of group A and in 10/14 (71%) of group B. The total number of patients with fewer than 3 antiepileptic drugs in group A was 5/19 (26%) and in group B was 7/14 (50%). The number of patients with ≥ 3 drugs in group A was 14/19 (74%) and in group B was 7/14 (50%). There was no statistical significance. Even though the patients with a greater severity of HIE had seizures of longer duration, the differences were not significant. An NMRI was taken of 26 patients (79%), 15 in group A and 11 in group B, at 4-10 days of life. The severity of the damage in the NMRI was established by a score that considered the damage in BG, PLIC, WM (minimum score of 0; maximum of 11). In both groups, the mean was 4; RR of 1.36 (0.79 to 2.35). Low quality

They conclude that there is a trend towards reducing the duration of seizures (clinical and subclinical detected with aEEG) when they are treated. Despite their data, they suggest that the early detection of electrical and clinical seizures and the early treatment thereof would decrease brain damage.

The second RCT (Singh [113]) is a randomised, controlled study in which the diagnosis of convulsion was clinical. As a second outcome, they assessed the presence of convulsions 2 (8%) versus 8 (40%); RR = 0.20; 95% CI, 0.05 to 0.84; OR = 0.13; 95% CI, 0.01 to 0.83. They were also assessed in the subgroup of moderate-severe HIE: 2 (10%) versus 8 (47%); RR = 0.21 [0.05 to 0.87]. In this study, the administration of phenobarbital in the first 6 hours of life in asphyxia patients decreases the incidence of convulsions.	Low quality

5.7.3. From the evidence to a recommendation

5.7.3.1. Quality of the evidence[113, 116-118]

Low quality	Mortality, disability or death/disability The quality of the evidence was decreased due to inconsistency, due to indirect evidence, due to inaccuracy and due to the risk of bias.
Low quality	Convulsions. The quality of the evidence was decreased due to inconsistency, due to indirect evidence, due to inaccuracy and due to the risk of bias.

5.7.3.2. Balance between benefits and risks

	The study by Ruth, 1991 (in the SR by Evans DJ, 2007), reflected that there were no significant differences in the intelligence quotient of survivors at six years of age among those that had been treated with phenobarbital or a control during the neonatal period. Singh, 2004, stated that no secondary effects by phenobarbital were observed during the study (hypotension, respiratory depression or excessive somnolence). Goldberg, 1986, reported an increase of the relative risk of neonatal hypotension, which required the support of inotropic drugs, associated with the treatment with thiopental, although this increase was not significant (RR = 1.76; 95% CI: 0.98 to 3.16). The described benefits regarding the duration of seizures, in the short term, are greater than the possible risks of certain anticonvulsant drugs (arterial hypotension not significantly greater in treated patients versus those not treated, non-decrease of the intelligence quotient in the follow-up on patients treated with phenobarbital).

5.7.3.3. Costs and use of resources

	The anticonvulsant drugs used in regular clinical practice (phenobarbital, midazolam, lidocaine) have a low cost. The electrical monitoring of convulsions requires a relatively inexpensive device (aEEG), which nevertheless is usually available at neonatal ICUs. The cost was not considered to be a determining factor in the decision-making for this question. No studies of economic analysis that specifically evaluate this therapeutic intervention in the context of the clinical question were found.

5.7.3.4. Values and preferences of the patients

	No specific information about the values of the parents in this regard were found.

5.7.4. Final decision about the strength (strong or weak) and the direction (in favour or against) of the recommendation

Aspects that have determined the direction and strength of the recommendation:

Current scientific evidence shows that the systematic use of anticonvulsant drugs in children with HIE with electrical seizures does not affect mortality or the risk of subsequent moderate/severe disability. The use of these drugs seems to shorten the duration of seizures. There is a scarce number of evaluated patients, and the quality of the studies is low. There is no evidence of the effect of these drugs on children treated with hypothermia.

5.7.5. Summary of the evidence

Low quality	In newborns with HIE not treated with hypothermia, the administration of anticonvulsants does not affect mortality or moderate to severe disability.[113, 116, 117]
Low quality	In newborns with HIE not treated with hypothermia, the treatment of electrical seizures decreases the duration thereof, and it is unknown if this could be related to less damage in the long term.[118]

5.7.6. Recommendations

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, we suggest 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, we suggest that anticonvulsant drugs be administered if there are maintained electrical seizures

5.7.7. Implications for research

Adequately masked, controlled and randomised studies with adequate power (sample size) are needed to examine whether or not the treatment of electrical seizures has a beneficial impact on neurological morbidity in neonates with HIE in treatment with hypothermia.

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

5.8.1. Introduction

The induction and maintenance of hypothermia in a neonate with HIE could cause stress or discomfort, which means an ethical imperative to relieve it. Thus, the majority of international guidelines recommend sedoanalgesia in these newborns (Azzopardi, 2009;[34] Hoehn, 2008[119]). Evidence has been shown in animal models that stress and/or pain can counteract the neuroprotective benefits of hypothermia and that these drugs seem to have neuroprotective properties, but this has not been evidenced in newborns.

To answer this question, two articles were selected: the first is an RCT (Simbruner, 2010[37]) that indirectly answers the selected question, and the second article (Ángeles, 2005[120]) is a low-quality, retrospective, non-randomised study in which hypothermia is not applied as therapeutic treatment.

5.8.2. Outcomes

5.8.2.1. Death or severe disability

The European RCT by Simbruner, 2010,[37] evaluated hypothermia versus normothermia. As an initial result, they considered death or severe disability at 18-21 months (impairment of 3 out of 5 as per Palisano or a development coefficient < 2 SD or severe cortical visual impairment). The ARR was 31.8% (95% CI, 15.2% to 48.4%); the RRR was 38.4% (95% CI, 18.4% to 18.5%) and the ORa (adjusted for the severity of the HIE): 0.21 (95% CI, 0.09 to 0.54); and an NNT of 4 (95% CI, 3 to 9). Regarding death or severe disability at 18-21 months in children with severe HIE, the ORa (adjusted for the severity of the HIE) was 0.17 (95% CI, 0.05 to 0.57). The basal risk or the risk of death or of severe disability in the control group was 83% (in children with severe HIE, 90.7%).

Very low quality

In this RCT, both groups of patients, treated or not with hypothermia, received morphine in continuous infusion (0.1 mg/kg/4 hours) or fentanyl at an equivalent dose. The authors argued that, indirectly, the administration of these sedoanalgesics could have decreased the NNT in comparison with other hypothermia RCTs (see questions 3 and 4 of this guideline, where the NNT of the various RCTs that evaluate treatment with hypothermia in children with HIE is analysed). The authors make no reference to the administered dose of fentanyl at the same time as administration of opioids or if they were administered with other drugs. There were losses of 10%. It should also be highlighted that the cohort included the presence of a high percentage of patients born outside of the participating centres. This involves a high basal risk and could condition an overestimation of the effect (hypothermia) with respect to other studies, which thus wouldn't be related to sedation. Finally, there is no masking in the intervention, although there is in the assessment of the outcome.

There is another non-randomised study by Ángeles, 2005,[120] which evaluates this aspect. It is a retrospective study that compares the clinical symptoms, the neuroimaging (NMRI) and the long-term outcomes between 3 and 12 months in asphyxial newborns treated with opioids versus those not treated. It is a study with a small sample, and it does not use hypothermia as the neuroprotective treatment. The study includes 17 newborns that received opioids and 35 that did not. Among the newborns that did receive opioids, both fentanyl and morphine are included at different doses and intervals (they are specified by the authors; see the summary table). None of the newborns received boluses and a continuous drip of opioids at the same time. The results showed that the newborns that received opioids in the first week of life had cerebral NMRI scores that were lower (less evidence of damage) in all the regions of the brain, compared to those that did not receive this treatment. This finding showed statistical significance in all the assessed zones. Regarding the follow-up, those treated had better results in the PCPCS (Pediatric Cerebral Performance Category Scale) and in the neuromotor assessments than those not treated. These measures could be an indirect measure of the outcome of severe disability included in this question. As limitations the short follow-up time and the scarce sample size should be pointed out. Moreover, none of the patients were treated with hypothermia.

Low quality

5.8.2.2. Mortality

In the RCT by Simbruner, 2010,[37] the ORa (adjusted for the severity of the HIE) of death in those treated with hypothermia was 0.48 (95% CI, 0.21 to 1.13). The risk of death in the control group was 57%. Once again, these results are inferior to those of other hypothermia RCTs in which sedation was not used systematically in all the patients.

Very low quality

5.8.2.3. Cerebral palsy

In the RCT by Simbruner, 2010,[37] the OR (adjusted for the severity of the HIE) for debilitating cerebral palsy was 0.21 (95% CI, 0.06 to 0.67), with a rate of debilitating cerebral palsy of 47.6% in the control group. These results are inferior to those of other hypothermia RCTs in which sedation was not used systematically in all the patients. On the other hand, the previously indicated results of Ángeles, 2005, indirectly support the possible beneficial effect of sedation on this outcome.

Very low quality

5.8.2.4. Convulsions

In the RCT by Simbruner, 2010,[37] 27.4% of the patients in hypothermia (17/62) had fewer clinical convulsions compared to those in normothermia 31/63 (49.2%), a statistically significant difference. Conversely, there were no differences in the number of electrical seizures recorded by conventional EEG or in amplitude-integrated EEG or in the number of anticonvulsants administered. The difference in clinical convulsions and therefore in the use of anticonvulsants could have had an influence on the results (although it is not very likely). These results are inferior to those of other hypothermia RCTs in which sedation was not used systematically in all the patients.

Very low quality

5.8.3. From the evidence to a recommendation

5.8.3.1. Quality of the evidence

Very low quality	Sedation with opioid derivatives in newborns with moderate or severe HIE treated with hypothermia decreases the risk of death or severe disability. It is possible that sedation increases the neuroprotective effect exercised by hypothermia.[37]
Low quality	Sedation with opioids in newborns with HIE decreases the risk of brain damage in these patients.[120]

5.8.3.2. Balance between benefits and risks

Systematic sedation in children with moderate or severe HIE could interfere with the clinical assessment of the degree of encephalopathy, given that these drugs can decrease the level of consciousness. They can also cause respiratory depression, which could mean a problem in non-intubated patients, who could require the start of mechanical ventilation.

On the other hand, the dose of these drugs also is not well defined. Many of them have hepatorenal elimination that could be altered in patients with multiple organ failure after hypoxic-ischaemic stress and also due to the fact that the hypothermia could have an influence on the pharmacokinetics and pharmacodynamics of these sedative drugs.

Cooling a patient to 33-34º C without adequate sedation could be considered unethical due to the discomfort that this intervention could cause.

5.8.3.3. Costs and use of resources

The cost of using the most common opioid derivatives in regular clinical practice, such as fentanyl or morphine, is low. This isn't expected to have an influence on the clinical decision when using this therapy on newborns with HIE.

No studies of economic analysis that specifically evaluate this therapeutic intervention in the context of the clinical question were found.

5.8.3.4. Values and preferences of the patients

No specific information about the values of the parents in this regard were found. It is expected that the sedation of their child would be experienced by the parents as something positive due to giving them greater comfort. On the other hand, excess sedation could be perceived by the parents as an indicator of greater severity.

5.8.4. Final decision about the strength and direction of the recommendation

Aspects that have determined the direction and strength of the recommendation:

There is scarce scientific evidence about the efficacy of routinely using opioids on newborns with HIE.[120] Moreover, such evidence is indirect.[37] The use of opioids could condition secondary

effects, such as respiratory depression in a non-intubated patient. Even though it hasn't been demonstrated that the cooling of a baby with HIE involves stress and discomfort, it is noted in healthy neonates, children and adults, wherefore it could be expected that the same thing would occur in neonates with HIE. Alleviating the stress and discomfort associated with cooling is an ethical imperative, and this is the aspect that has given weight to our recommendation.

The cost/benefit ratio is favourable. The opinion of the parents in this regard is unknown.

5.8.5. Summary of the evidence

Low quality	Sedation using opioids in newborns with asphyxia that are *not treated with hypothermia* decreases the risk of death or severe disability.[120]
Very low quality	Sedation using opioids in newborns with asphyxia that are *treated with hypothermia* decreases the risk of death, severe disability or a combination of them both, as well as the severity of the damage noted in a brain MRI.[37]

5.8.6. Recommendations

√	We suggest 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.

5.8.7. Implications for research

More studies that evaluate the stress and discomfort associated with therapeutic hypothermia are needed, as well as the impact that they both have on physiological stability and on neurological morbidity and mortality. It is also necessary to learn if the systematic use of opioid derivatives in children with HIE has a neuroprotective effect. We recommend that the studies that evaluate the neuroprotective efficacy of hypothermia indicate this variable and adjust the results according to the same.

6. Prognostic studies

Questions to be answered:

- In patients with HIE, treated or not with hypothermia, what is the prognostic value of amplitude-integrated electroencephalography (aEEG)?
- In patients with HIE, treated or not with hypothermia, what is the prognostic value of brain magnetic resonance imaging?
- What is the prognostic value of the biomarkers in blood, urine or CSF to predict death or neurodevelopmental problems in newborns with moderate or severe HIE, whether or not they are treated with hypothermia?

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

6.1.1. Introduction

Very low quality

One of the main diagnostic tools in children with HIE is amplitude-integrated electroencephalography or aEEG. Its ease of application and interpretation at the patient's crib by personnel of neonatal units has made it indispensable monitoring in intensive care units. However, the gold standard of monitoring of brain activity, today, stills continues to be conventional electroencephalography. Walsh, 2011,[121] recently reviewed the evidence that supports the use of conventional electroencephalography in children with HIE, thereby pointing out some of its problems, such as the difficulty of having a neuro physiologist available 24 hours a day to interpret the records at the patient's crib. The authors conclude that newborns with HIE with normal or slightly altered EEG tracings have normal development in 78% to 100% of the cases, while patients with anomalous tracings have adverse development in nearly all cases.

To answer the posed question, we decided, as the authors of this guideline, to focus on analysing the prognostic value of the aEEG in patients with HIE, treated or not with hypothermia, given that we think it is the initial prognostic tool currently used at the majority of neonatal units in our European environment.

The initial bibliographic search identified a total of 51 articles, of which 28 were excluded due to not being relevant to the posed question (see methodological materials for details on selecting the literature and preparing this question 11). Among the included articles, there was one MA (Spitzmiller, 2007[25]) that analysed the prognostic value of the aEEG in patients not treated with hypothermia. It included 8 studies published between 1996 and 2005 (Eken, 1995;[27] Toet, 1999;[122] Ter Horst, 2004;[123] Hellstrom Westas, 1995;[124] al Naqeeb, 1999;[125] Thornberg, 1994;[126] van Rooij, 2005;[127] Shalak, 2003;[128]), having evaluated a total of 529 patients with HIE. The aEEG was recorded on the first day of life, although at different times of life between the studies. Evaluation of the patients took place up to 24 months of age, and it included the Griffiths scale (abnormal if less than or equal to 85) and the cerebral palsy classification according to Hagberg. The results of the MA regarding the predictive capacity of neonatal death or moderate or severe disability by an anomalous aEEG in newborns with HIE are Se 91% (95% CI, 87 to 95), Sp 88% (95% CI, 84 to 92), PLR 10.1 (95% CI, 5.5 to 18), NLR 0.09 (95% CI, 0.06 to 15), PPV 86.9%, NPV 92.2% and accuracy 91.7%. However, there are limitations in this MA. Its quality is very low, given that a comprehensive bibliographic search was not conducted, the excluded articles are not detailed and there is no individual assessment of the quality of the included articles that is easily identifiable for the reader (moreover, some methodological criteria are mixed in with the quality assessment criteria, such as other clinical criteria when attaching the aEEG). In addition, the inclusion criteria are not clear, nor is the classification of a normal or anomalous aEEG, or the definition of adverse follow-up. There is distinct heterogeneity between the moment when the aEEG is recorded and the follow-up, which ranges from 5 days post discharge up to 18 months. Regarding the direct relationship with the posed question, the key outcomes voted by the group do not appear: epilepsy, death in the first two years, cerebral palsy, severe cerebral palsy and the combined variable of death or cerebral palsy. Finally, there is no differentiation between the prognostic value of the aEEG at different times in the life of the newborn. This is important in the clinical assessment of the patient.

Given the great heterogeneity existing in this MA, the methodological limitations and the non-differentiation in different hours of life, the development group of this guideline decided to analyse, separately, each one of the studies included in it, and also incorporate works after the publication of the MA. With this, a new MA was conducted, which was used to respond to the 4 outcomes voted on by the group, thereby differentiating between patients that were treated and not treated with hypothermia. To conduct the original meta-analysis of this question, all the works on the prognostic value of the aEEG published up to December 2012 were considered. The target population was newborns with HIE, treated or not with hypothermia, monitored by amplitude-integrated electroencephalography and with long-term follow-up of at least 12 months. In each of the evaluated articles, an anomalous aEEG was considered when the patient showed any of the following records: burst suppression or very low voltage tracings as the continuous low-voltage tracing or the flat (isoelectric) tracing. 14 articles were considered for the final MA: Eken, 1995;[27] Ter Horst, 2004;[123] Hellstrom Westas, 1995;[124] al Naqeeb, 1999;[125] Thornberg, 1994;[126] van Rooij, 2005;[127] Shalak, 2003;[128] Shany, 2006;[129] Ancora, 2009;[130] Ancora, 2011;[131] Hallberg, 2009;[132] Thoresen, 2010;133 Shankaran, 2011;[134] Gucuyener, 2012.[135] All other pre-selected works[138-163] were discarded after reading them completely due to not meeting the inclusion criteria (see Appendix 4 of the methodological material for specific details about conducting this MA).

6.1.2. Outcomes

All were answered using the original MA prepared by the author group of this guideline. The lists of the works included in each time bracket, as well as the figures of true/false positives and negatives are included in the methodological material of this question. High quality

For calculating the pretest probabilities for each one of the indicated outcomes, data taken from the recent MA on hypothermia published in 2012 by Tagin were used.42 According to this MA, we have the following prevalences in children with moderate or severe HIE not treated with hypothermia: of death, 35.12%; of severe disability, 38.69%; of developmental delay, 34.71%; of cerebral palsy, 31.28%; and of death or disability, 63.17%. In children treated with hypothermia, these prevalences were the following: 26.23% for death, 26.26% for severe disability, 22.76% for developmental delay, 19.37% for cerebral palsy and 47.88% for death or disability.

6.1.2.1. Death or moderate/severe disability

After conducting the broken-broken down MA, we observed how the predictive capacity of the aEEG varied according to the hours of life of the patient. For the death or moderate/severe disability outcome, we observed how this capacity is maximum at 24 hours of life in patients not treated with hypothermia, reaching posttest probabilities of close to 98% at this time (97.5%, 95% CI, 80 to 95.2%). In the following hours of life, the predictive capacity of the aEEG remains stable, with posttest values of around 95% (Table 1 of Appendix 7.2). It is important to point out how this prognostic value is present as from 6 hours of life in this group of patients.

On the other hand, in patients treated with hypothermia, the maximum predictive capacity for the death-moderate/severe disability outcome is reached at 48 hours of life (posttest probability of 96.9%, 95% CI, 81.7 to 99.6%), remaining stable as from this moment. In comparison with newborns not treated with hypothermia, it is observed how the predictive capacity of the aEEG is low at 6 hours of life (Table 1 of Appendix 7.2.).

6.1.2.2. Death in the first 2 years of life

For the prediction of death, we observe how, in patients not treated with hypothermia, the maximum positive posttest probability is reached at 24 hours (79.8%, 95% CI, 53.9% to 93%, Table 2). In patients treated with hypothermia, this probability is maximum at 36 hours of life (65.1%, 95% CI, 47.2 to 79.5). The data are imprecise and are therefore of moderate quality (see the GRADE tables). As with the death/disability outcome, the predictive capacity is high at 6 hours in patients not treated with hypothermia but low in treated patients (see Table 2 of Appendix 7.2.).

6.1.2.3. Cerebral palsy

For analysing the outcome of cerebral palsy, we found that far fewer patients are included than in the preceding outcomes (Table 3). This prevents drawing conclusions about the prognostic value of the aEEG in children not treated with hypothermia, where we observe that the value seems maximum at 6 hours of life, but we have no data at 36, 48 and 72 hours to confirm this aspect. In children treated with hypothermia, once again the maximum prognostic value of the aEEG is 48 hours (posttest probability of 61.9%, CI from 28.1 to 87.) (see Table 3 of Appendix 7.2.).

6.1.2.4. Moderate/severe disability

For moderate/severe disability, once again the interpretation of the results is more complicated due to the scarce number of patients for each hour of life. We observe that, for this outcome, the maximum predictive capacity of the aEEG is obtained at 36 hours of life in patients that are both treated and not treated with hypothermia (Table 4). Contrary to what happens in all other outcomes, at 6 hours the aEEG has a greater predictive capacity in children treated with hypothermia than in children without this treatment (see Table 4 of Appendix 7.2).

6.1.2.4. Epilepsy

It was not analysed independently in any of the articles found.

6.1.3. From the evidence to a recommendation

6.1.3.1. Quality of the evidence

High quality	**Death or severe disability** – Few patients (fewer as the hours of life increase). – Difficulty of knowing in how many patients death occurs after limiting the therapeutic effort in view of the prognostic value of the aEEG itself.

Low quality	**Death** – Few patients (fewer than for the combined outcome). A single study on hypothermia that allows calculating this outcome separately. – Difficulty of knowing in how many patients death occurs after limiting the therapeutic effort in view of the prognostic value of the aEEG itself. This is a limitation for evaluating the predictive capacity of all the outcomes that include death.
Very low quality	**Cerebral palsy** – Due to the scarce number of patients, it is not possible to differentiate between different degrees of cerebral palsy. – Scarce sample size (a single study without hypothermia and one study with hypothermia with data beyond 24 hours). – The pretest probability of the MA by Tagin, 2012, is different from what was contributed in the study by Azcora, 2010 (the only one without hypothermia). This study indicates a pretest probability of cerebral palsy of 3.1% at 6 hours and 11% as from 12 hours.
Very low quality	**Moderate/severe disability** – Due to the scarce number of patients, it is not possible to differentiate between moderate and severe disability, or between the different types of disability. The pretest probability is of severe disability, while the actual MA analyses the outcome of moderate/severe disability. This means that the pretest probability would be greater than the one used. However, this shouldn't affect the conclusions of this MA. – The pretest probability of Tagin, 2012, for disability is higher than that of the only study that measures disability in hypothermia (Thoresen, 2010): 32% in children without hypothermia and 16% in children with hypothermia in the Thoresen study, versus 38% without hypothermia and 26% with hypothermia in the study by Tagin.

6.1.3.2. Balance between benefits and risks

The benefit of the aEEG is different according to the hours of life and the evaluated outcome. Its maximum benefit is for predicting death/severe disability. No risk due to use of the aEEG could be expected, except for bleeding due to the use of subcutaneous needles in children with asphyxia and coagulopathy (in this case, the subcutaneous needles could be replaced by stickers, although this could interfere with the quality of the signal obtained).

6.1.3.3. Costs and use of resources

Use of the aEEG conditions a monitoring cost and a specific consumable, in addition to the necessary training for interpreting the tracings.

No economic evaluation studies that specifically analyse this subject were found. However, given the relatively low cost of the equipment and the predictive capacity shown in our MA, the cost-benefit balance must be clearly in favour of aEEG monitoring in children with HIE.

6.1.3.4. Values and preferences of the patients

There are no specific studies. It has not been considered that the values and preferences of the parents of the patients regarding use of the aEEG as a prognostic tool would be a determining factor for assessing the strength of the recommendation. The technological support used in neonatal intensive care units is a major source of stress for families: it causes fear and insecurity and hinders interaction with their children. The potential impact that aEEG monitoring could cause to parents has not been explored in any study up to now. It would be appropriate to cover this aspect in future studies. In the particular qualitative study conducted for this CPG, the parents make a direct equivalence between severity and the quantity of devices. Some of their responses reflect the impact caused by the technological support used in hypothermia treatment (devices that are sometimes bigger than the baby). The electrodes on the head, the catheters, the venous lines and the cables leave an impression, generate fear and hinder affectionate contact with their children. *"I saw him with the electrodes on his head, with catheters all over his little body... and I got a bit dizzy"*. They make a direct equivalence between severity and the quantity of devices, to the point that they celebrate the removal of each device, catheter or line. *"You're hoping to see fewer devices connected... every time they removed one it was a bit of joy"*. They insist on how painful it is not to be able to hold their child in their arms during treatment, above all considering their uncertainty about the possible final outcome. *"You're upset about the fact that you're going to lose her, and you haven't even touched her"*. They especially value the moment when they are able to do so. They identify it with a time of parental love, and they relate it directly to improvement of the baby. *"That sensation of holding her, of loving her a little..." "They were taking care of the baby, and you couldn't touch her (cries)"*.

They repeatedly refer to the high number of procedures and interventions that have to be performed on the baby during treatment with hypothermia. And they describe how they suffer due to the pain experienced by their children during those procedures and interventions. Especially, they recall the "multiple punctures" (in arms and feet), which leave marks that they can see later. *"Now we're going to give her an injection for this, now for that; maybe in one day they gave her shots twelve times"*. *"It's shocking to see him intubated and stretched out... they treat him as if he were a terminal patient; they had to give him massages to prevent sores"*. *"Everything is like a torture"*. *"When a normal baby is born, the first thing you do is hug him, and here's this baby with shots, tubes, injuries, sores, etc."*

6.1.4. Final decision about the strength and direction of the recommendation

Aspects that have determined the direction and strength of the recommendation:

Studies suggest that the aEEG has prognostic value for the combined outcome of death/disability, as well as for death, disability or cerebral palsy in different hours of life of newborns with HIE, treated or not with hypothermia. The quality of the evidence is better for the combined outcome of death and disability than for all other outcomes separately. No studies that assess epilepsy separately have been found.

The studies do not precisely specify how many of the patients that die do so as a consequence of adapting the therapeutic effort based on the information provided by the aEEG, which could alter the prognostic value of this test for death whenever death is evaluated ("self-fulfilling prophecy").

No major secondary effects from using this monitoring could be expected.

There seems to be a favourable cost-benefit ratio.

The preferences of the parents in this regard are unknown, or the potential impact on their stress during the intensive care of their child.

6.1.5. Summary of the evidence

6.1.5.1. Death or moderate/severe disability (own MA)[27, 123-135]

High quality	The aEEG predicts death or disability as from 6 hours of life in children not treated with hypothermia. There is predictive capacity in children treated with hypothermia, but it is much lower.
High quality	Hypothermia alters the predictive capacity of the aEEG, such that, in the event of an altered aEEG, similar positive posttest probabilities between patients that are and aren't treated with hypothermia are not obtained up to 48 hours of life. The maximum posttest probability is reached at 24 hours of life in children without hypothermia and at 48 hours in children with hypothermia. To predict death or disability, the diagnostic probability of the aEEG is maximum at 24 hours of life in children not treated with hypothermia. This predictive capacity remains similar at 36 and 48 hours of life. In children treated with hypothermia, the diagnostic probability of the aEEG is maximum at 48 hours of life in children treated with hypothermia, and it remains similar at 72 hours of life.

6.1.5.2. Death (own MA)[27, 123-135]

Low quality	The aEEG predicts death as from 6 hours of life in patients not treated with hypothermia.
Very low quality	The aEEG predicts death as from 6 hours of life in patients treated with hypothermia.
High quality	To predict death, the best time for interpreting the results of the aEEG is at 24 hours of life in children not treated with hypothermia (although it remains fairly similar at 36 and 48 hours of life, decreasing somewhat at 72 hours of life) and at 36 hours of life in children treated with hypothermia (it remains fairly similar at 48 and 72 hours of life). This is similar to what happens with the combined outcome of death or disability.

6.1.5.3. Cerebral palsy (own MA)[27, 123-135]

Very low qualtiy	The aEEG is predictive of cerebral palsy in the first 6 hours of life in patients either treated or not treated with hypothermia.

Very low qualtiy	The maximum difference between the pretest and posttest probability is reached at 48 hours of life in children treated with hypothermia. There are no data for this section separately from studies without hypothermia for 48 and 72 hours, wherefore we do not know if there is or isn't a difference in this aspect. In patients without hypothermia, the predictive capacity of cerebral palsy does not seem to be related to the hours of life (in fact, it is maximum at 6 hours). This could be due to the existence of a single study with data on this outcome separately.

6.1.5.4. Moderate/severe disability (own MA)[27, 123-135]

Very low quality	The maximum difference between positive pretest and posttest probability is reached at 36 hours of life in children treated and not treated with hypothermia. The maximum difference between negative pretest and posttest probability is reached at 36 hours of life in children not treated with hypothermia, but at 6 hours of life in children treated with hypothermia (a single study, and the reason is not clear).

6.1.6. Recommendations

Weak	We suggest the use of aEEG within the first 6 hours of life as a prognostic tool in newborns with HIE. The diagnostic OR is 30.69 (95% 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	We recommend 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%).

6.1.7. Implications for research

The number of patients assessed with aEEG and treated with hypothermia is still scarce. Future works that evaluate predictive capacity should include patients with this therapy, evaluated at different moments in life and with long-term neurological follow-up. Likewise, the expression of the results is very heterogeneous: area under the ROC curve, with others contributing only sensitivity and specificity. Rigorous studies are currently needed, in which a formal evaluation of long-term development is included. It is important that works include the percentage of patients who die due to therapeutic limitation in order to be able to better assess the predictive capacity of the aEEG in all outcomes that include death.

Future studies should study the potential impact on parental stress due to monitoring of electrocortical activity by aEEG during the intensive care of their child.

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

6.2.1. Introduction

Brain ultrasound is the first neuroimaging test that is done on any newborn with HIE due to its availability at the crib/incubator and its accessibility. In newborns with HIE, it allows discarding other pathologies, and it provides orientation about the moment when the hypoxic-ischaemic injury occurred and allows monitoring the injuries over time. Brain magnetic resonance (MR) imaging, unlike brain ultrasound, offers better visualisation of the injuries, allows more precisely determining their location, extent and severity and allows the detection of myelin. Therefore, this imaging technique constitutes the gold standard for studying brain injury in newborns with HIE. To answer the posed question, the authors of this guideline decided to analyse the prognostic value of the brain MRI in patients with HIE, treated or not with hypothermia, given that we consider that this to be the prognostic tool that is currently used on the majority of neonates with HIE. Even though numerous modes of MRI have been developed in the last decade (volumetric analyses, tractography, etc.), this review focuses on those that are used in clinical practice in our environment. Based on this criterion, the prognostic value of conventional sequences T1 and T2, of the diffusion-weighted sequence and of hydrogen spectroscopy have been analysed.

Very low quality

There are two MAs, one on the Apparent Diffusion Coefficient (ADC) (Coats, 2009[164]) and one on cerebral magnetic resonance biomarkers in neonatal encephalopathy (Thayyil, 2010[165]).

The MA by Thayyil[165] on the prognostic utility of cerebral magnetic resonance biomarkers in neonatal encephalopathy includes 32 studies (30 prospective and 2 retrospective), selected between 1990 and 2008, on newborns not treated with hypothermia (El Ayouty, 2007; Gire, 2000; Rutherford, 1998; Biagioni, 2001; Mercuri, 2000; Jyoti, 2006; Belet, 2004; Van Schie, 2007; Leisjer, 2007; Ricci, 2006; Barnett, 2002; Kuenzle, 1994; Hunt, 2004; Shanmugalingam, 2006; Amess, 1999; Robertson, 1999; L´Abee, 2005; Penrice, 1996; Boichot, 2006; Shu, 1997; Kadri, 2003; Cheong, 2006; Roelants-Van Rijn, 2001; Robertson, 2011; Zarifi, 2002; Brissaud, 2005; Peden, 1993; Barkovich, 1999; Hanrahan, 1999; Meyer-Whitte, 2008; Khong, 2004). This MA includes, among other analysed biomarkers, an assessment of conventional MRI sequences T1/T2: scoring systems of the severity of the injury, ratios of signal intensity and alteration of the signal within the PLIC. Patients with a gestational age of less than 35 weeks and with follow-up of less than 12 months are excluded. The results of the meta-analysis on the predictive capacity of neonatal death or of severe disability by an MRI taken in the first month of life are Se 91% (95% CI, 87% to 94%), Sp 51% (45% to 58%), PLR 1.71 (1.36 to 2.17) and NLR 0.25 (0.16 to 0.37). The consistency between the studies was low. Given that the prognostic value can depend on the age when the MRI is taken, in this MA the predictive capacity of the early MRI taken between days 1 and 7 [(6 studies), Se 0.84 (0.73 to 0.93) I2 = 24.6%; Sp 0.86 (0.70 to 0.95) I2 = 21.8%] and that of the late MRI taken between days 8 and 30 (5 studies) is analysed: [Se 0.99 (0.95 to 1) I2 0%; Sp 0.53 (0.41 to 0.64) I2 = 68.1%]. Unfortunately, this meta-analysis does not contribute the PLR, NLR or the OR.

Regarding the predictive results of the biomarkers used in the MRI, only the death or disability outcome is analysed. The most accurate biomarker according to this MA is the Lactate/NAA quotient measured in the basal ganglia or thalamus. Cut-off point (median and range): 0.29 (0.24 to 0.40), Se 0.82 (0.74 to 0.89), Sp 0.95 (0.88 to 0.99), LHR+7.84 (3.99 to 15.42), LHR-0.27 (0.18 to 0.39), DOR 45.56 (17.59 to 118.01), Q (SE) 0.88 (0.03), AUC (SE) 0.94 (0.03). Specificity inconsistency, 0%. Chi-squared, 6.27, gl 9. Sensitivity inconsistency, 20.1%. Chi-squared, 11.27, gl 9. For the ADC, the cut-off point (median and range) used to predict death or disability is 0.60 (0.55 to 0.90), Se 0.66 (0.52 to 0.79), Sp 0.64 (0.35 to 0.87), LHR+1.19 (0.48 to 2.93), LHR-0.56 (0.22 to 1.4), diagnostic OR of 2.24 (0.4 to 12.47), area under the curve of (SE) 0.66 (0.11). Some limitations are the fact that, out of 51 possible studies, only 32 are included (19 are excluded) due to not having access to 2-by-2 tables or due to the non-existence of information on the individual patients. Finally, the number of patients that die after adapting the therapeutic effort is not indicated. After analysing the included studies, Thayyil gives the following results for the death or severe disability outcome:

1. Predictive capacity of the adverse patterns of cerebral MRI in conventional sequences: Se 90.8% (86.4 to 93.8%), Sp 86.2% (82 to 89.5%), PPV 82.8%, NPV 92.7%, PLR 6.57 (5 to 8.65), NLR 0.11 (0.07 to 0.16), Accuracy 88.1%.
2. Predictive capacity of EARLY cerebral MRI (first week of life). Adverse patterns based on conventional sequences. Se 88.3% (80.2 to 93.3%), Sp 87.5% (80.9 to 92%), PPV 83%, NPV 91.5%, PLR 7.06 (4.5 to 11.09), NLR 0.13 (0.08 to 0.23), Accuracy 87.8%.
3. Predictive capacity of EARLY cerebral MRI (first week of life) in children with MODERATE HIE. Adverse patterns in conventional sequences: Se 78.63% (60.5 to 89.8%), Sp 84.2% (60.6 to 92.6%), PPV 78.6%, NPV 84.2%, PLR 4.98 (2.33 to 10.63), NLR 0.25 (0.12 to 0.53), Accuracy 81.8%.

However, there are several methodological limitations in this MA, which include:

- The bibliographical search was done in just two databases (Pubmed, Embase).
- Even though the quality of the studies was analysed overall according to QUA-DAS (Quality Assessment of Diagnostic Accuracy Studies), the quality of each one of the articles included is not assessed individually.
- There is notable heterogeneity in the population population of study, and the sample size of the studies is small; only in a small percentage did follow-up extend to 18-24 months. Nearly half the patients included were newborns with mild or severe HIE, in which establishing the prognosis is less complex. There is also notable heterogeneity in the evaluated NMRI studies regarding the equipment used, the magnetic fields of the same, the types of sequences, the echo times and the repetition times, as well as the days of life when the neuroimaging study is conducted.

– Many studies present possible biases (of both selection and by follow-up losses). Many of them only analyse the death or disability outcome, with the consequent risk of bias of the "self-fulfilling prophecy". As randomised studies on hypothermia have pointed out, the majority of deaths in newborns with significant HIE are secondary to limitation of the therapeutic effort. This decision is often based on the findings of the MRI. The studies do not precisely specify how many of the patients that die do so as a consequence of limitation of the therapeutic effort based on results such as the NMRI, which could alter the prognostic value of this test whenever death is evaluated.

– The analysis of the predictive value of the MRI is done by including any type of injury, regardless of their location and their extent. Various studies of conventional MRI, however, suggest that the evolution of newborns with minor injuries of the basal ganglia and thalamus or of white matter is drastically different from that from the newborns that show severe central injuries or overall injury patterns.

– The definition of the "adverse development" outcome for the meta-analysis is not clear. Different outcomes are classified as adverse or disabling based on the definition of each one of the studies. Thus, patients with moderate cognitive delay (development quotients < 1DE) or epilepsy and those with cerebral palsy without walking ability or with severe cognitive deficits (development quotients < 2DS).

Wilkinson, 2010[166] comments on and expands the MA by Thayyil to determine the prognostic value of the MRI for making decisions on limiting therapeutic effort. Wilkison adds to the analysis the study by Rutherford in 2010, which, in a sub-analysis of the newborns included in the TOBY, analyses the predictive value of the NMRI in patients treated with hypothermia, although it does not evaluate the quality of said study. It includes the studies of the MA by Thayyil, which evaluate the predictive value of the conventional MRI (given that it is what is used by clinicians to make decisions), and it also analyses their value in newborns with moderate HIE (insofar as this is the group for which it is most difficult to establish a prognosis). It does not specify the either the search sources or the inclusion or exclusion criteria, rather it is based on those of Thayyil. It selects those studies whose evaluated strategy is the conventional MRI (sequences T1 and T2), with a minimum follow-up on patients of 12 months.

Coats, 2009[164] conducts an MA on the value of the ADC. The bibliographical search is up to August 2007. Follow-up varies between 0 and 24 months. They present the data from 6 studies on newborns with HIE and pose the following values for a good prognosis (mean ± SE): basal ganglia, 91.7 ± 28.5 x 10-5 mm2/s; cortical grey matter, 123 ± 5.1 x 10-5 mm2/s; cortical white matter, 121.5 ± 33.2 x 10-5 mm2/s. The results of newborns with adverse results (significant differences) were: basal ganglia, 84.9 ± 15.1 x 105 mm2/s; cortical grey matter, 102.9 ± 4.9 x 10-5 mm2/s; cortical white matter, 115.3 +/- 13 x 10-5 mm2/s. Some limitations to the work include the different moments when the MRI is taken, the use of different MRI devices in the different works and variation of the measurement location. Moreover, another limiting factor is the variation in the follow-up period when assessing whether or not the patient does or doesn't have an "adverse" outcome, as the authors point out.

6.2.2. Outcomes

All were answered using the original MA prepared by the author group of this guideline. The lists of the works included in each time bracket, as well as the figures of true/false positives and negatives are included in the methodological material of this question.

For calculating the pretest probabilities for each one of the indicated outcomes, data taken from the recent MA on hypothermia published in 2012 by Tagin were used.[42] According to this MA, we have the following prevalences in children with moderate or severe HIE not treated with hypothermia: for death, 35.12%; for severe disability, 38.69%; for developmental delay, 34.71%; for cerebral palsy, 31.28%; and for death or disability, 63.17%. In children treated with hypothermia, these prevalences were the following: 26.23% for death, 26.26% for severe disability, 22.76% for developmental delay, 19.37% for cerebral palsy and 47.88% for death or disability.

After analysing the various described works, the development group of this guideline decided to focus on the prognostic value of conventional MRI sequences. The major heterogeneity existing between the works that analyse the biomarkers used in MRI makes it difficult to do an analysis beyond what was already analysed by the various authors.

To analyse the prognostic value of the conventional sequences of the MRI, the heterogeneity existing in the MA by Thayyil and the methodological limitations led the development group of this guideline to separately analyse each one of the included studies, in addition to incorporating works after the publication of those studies in order to respond to the posed question. Thus, a new MA was conducted, which was used to respond to the outcomes established by the group, thereby differentiating between patients that were treated and not treated with hypothermia. Only those studies that provided raw data were selected, to be able to:

- Analyse the newborns with an MRI taken in the first week of life separately from those that were taken between days 8 and 30.
- Classify and compare the findings of the MRI as significant (moderate or severe injury of basal ganglia and thalamus, absence of normal myelination of the posterior limb of the internal capsule or severe injury of white matter) and insignificant (normal MRI, isolated cortical highlighting, doubtful PLIC or mild/moderate injury of white matter).
- Evaluate the development of patients in those studies with a minimum follow-up of 12 months.

Moreover, in order to analyse the outcomes, the definition of severe disability used by the MAs was applied to assess the efficacy of therapeutic hypothermia: cerebral palsy with difficulty for or the impossibility of walking alone (GMFCS 3-5), developmental delay [score < -2 standard deviations (SD) in the Mental Development Index (MDI) of the Bayley II Infant Development Scale; the cognitive or language scales of the Bayley III Scale; the tests of Griffiths, Brunet-Lézine or Gesell], intellectual deficit [development quotient (DQ) < -2 SD], blindness (visual acuity < 6/60 bilateral) and neurosensory deafness requiring amplification.

Finally, 24 articles were included,[167-187] subsequently discarding 6 works after a complete reading.[188-194] Appendix 5 of the methodological materials shows the tables of works that were included, with the general characteristics, as well as the definition of the MRI findings deemed significant and that of moderate-severe disability for each study. The positive and negative true/false figures are also included, and the articles that were excluded from this MA are cited and the reasons are given, listing both some articles that were included in the MA by Tayyil and others that were published after it.

6.2.2.1. Death or moderate/severe disability

After conducting the MA, we observed that the MRI conducted within the first month of life reaches a posttest probability of 86% (95% CI, 80 to 90%) in normothermic newborns and 80% (95% CI, 74 to 86%) in newborns treated with hypothermia (Table 5 of Appendix 12).

If we separately analyse the predictive value of the NMRI taken in the first week of life (early MRI), the posttest probability is maintained, both for newborns not treated with hypothermia (posttest 84%; 95% CI, 76 to 90%) and for newborns treated with hypothermia (posttest 86% 95% CI, 62 to 96%). However, it is necessary to highlight that under hypothermia there are only two studies with 32 patients, and therefore the CIs are much broader.

The MRI taken between days 8 and 30 of life reaches a posttest probability of 88%, (95% CI, 68 to 96%) in normothermic patients and 73% (95% CI, 43 to 90%) in newborns treated with hypothermia.

For all other outcomes selected by the group, it was not possible to reach the predictive value of the MRI studies in newborns with HIE treated with hypothermia. Unfortunately, two studies had to be excluded (Shankaran, 2012, and Cheong, 2012), which conduct a secondary analysis of two multicentre, randomised and controlled trials on hypothermia: the NHICD trial and the ICE trial, respectively. Both studies include a high number of newborns and clearly defined inclusion and exclusion criteria, and they separately analyse the group of cooled newborns and the group of newborns not treated with hypothermia. However, they do not provide raw data that would allow separately analysing the early MRI studies versus those done between days 8 and 30 of life.

For all other outcomes, the data of newborns with HIE not treated with hypothermia were analysed in the MRI taken during the first month of life.

6.2.2.2. Death (pretest probability 35%)

The posttest probability of the MRI taken in the first month of life is 56% for predicting death (95% CI, 49 to 63%) in patients not treated with hypothermia. Said posttest probability is similar for the early MRI (55%, 95% CI, 49 to 60%) and for the late MRI (60%, 95% CI, 40 to 77%).

6.2.2.3. Severe disability (pretest probability 39%)

In patients not treated with hypothermia, the posttest probability of the MRI taken in the first month of life is 77% for predicting death (95% CI, 62 to 88%). Said posttest probability reaches 84% (95% CI, 52 to 96%) in the early NMRI and 87% (95% CI, 72 to 95%) in the late MRI.

For this outcome, the value of the absence in viewing the posterior limb of the internal capsule for predicting severe disability was analysed. It could only be analysed in the MRI taken during the first month of life. In patients not treated with hypothermia, the posttest probability is 78% (95% CI, 54 to 91%). The posttest probability in the only study on hypothermia that contributes raw data for analysis is 93% (95% CI, 71 to 99%), and the negative posttest probability is 10% (3.3 to 26.7%).

6.2.3. From the evidence to a recommendation

6.2.3.1. Quality of the evidence

Moderate quality	**Death or severe disability** – Few patients (fewer if early MRI is analysed separately from the late MRI). – There are only two studies with 32 patients (one of very low quality and with only 5 patients, and another of moderate quality) that analyse the predictive value of the early MRI for newborns treated with hypothermia. There is one study with 36 patients in hypothermia that analyses the value of the MRI between days 8 and 30. – Difficulty of knowing in how many patients death occurs after limiting the therapeutic effort in view of the prognostic value of the MRI itself. This is a limitation for evaluating the predictive capacity of all the outcomes that include death.
Low quality	**Death** – Few patients (fewer than for the combined outcome). There is only one study on hypothermia, which is of very low quality and which provides 5 patients. – Difficulty of knowing in how many patients death occurs after adapting the therapeutic effort in view of the prognostic information itself.
Very low quality	**Severe disability** – Due to the scare number of patients, it is not possible to differentiate between moderate and severe disability, as well as between different types of disability. – The pretest probability is of severe disability, while the MA itself analyses the outcome of moderate/severe disability. This means that the pretest probability would be greater than the one used. However, this should not affect the conclusions of this MA. – The pretest probability for disability by Tagin, 2012, is higher than that of the only study that measures disability in hypothermia (Thoresen, 2010): 32% in children without hypothermia and 16%% in children with hypothermia, versus 38% without hypothermia and 26% with hypothermia in the study by Tagin.
Very low quality	**Cerebral palsy and cognitive deficit** – There are only studies on newborns not treated with hypothermia. The number is more reduced, and moreover it is often difficult to determine the degree offunctional involvement of the cerebral palsy or the severity of the cognitive deficit.

6.2.3.2. Balance between benefits and risks

The MRI taken in the first month of life seems to be predictive of adverse development, in both patients treated with hypothermia and those not treated. There are still only a few studies that analyse if there are differences between the value of the early and late MRI. No risk from using the MRI could be expected, even if there is the risk inherent in moving any critical patient to the place where the equipment is located (above all if the equipment is not available in the centre where the patient is admitted). This risk could be greater in the first days of life in patients with haemodynamic instability.

6.2.3.3. Costs and use of resources

The use of the MRI is conditioned by the cost of the equipment, of monitoring and of specialised personnel for the interpretation thereof.

No economic evaluation studies that specifically analyse this subject were found. However, given the relatively low cost of the equipment and the predictive capacity shown in our meta-analysis, the cost-benefit balance must be clearly in favour of MRI monitoring in children with HIE.

6.2.3.4. Values and preferences of the patients

There are no specific studies. It has not been considered that the values and preferences of the parents of the patients regarding the use of MRI as a prognostic tool would be a determining factor for assessing the strength of the recommendation.

In all the qualitative study groups conducted for this CPG, the parents identify magnetic resonance as a very important test and a determinant for discarding brain damage. They do not know what it consists in exactly, and they refer to it as a tool for viewing the brain. *"It's a very important test. They're going to see the brain. Let's see if they see it well"*. They associate the term "dark spot" (frequently used by doctors to inform about the brain ultrasound) with the risk of injury. *"So you could see a small dark spot, but with the MRI you could rule out.."*. They place their hopes in it, and that gives it ambivalent meaning as a threat or reassurance. One the one hand, they want the moment of the test to arrive, and on the other, they fear that moment. Thus, they experience the test with stress. *"So, on the one hand there was the hope of saying 'Let's see if the results are good!', and on the other, just the opposite"*. They state the need to prepare psychologically when the test is going to be performed; and this is more difficult when the child has to be moved /(alone, without family) to a centre other than the one where the child is hospitalised. "I'm getting ready for the MRI"; *"we passed the test, breathe!"*.

6.2.4. Final decision about the strength and direction of the recommendation

Aspects that have determined the direction and strength of the recommendation:

Current scientific evidence shows that the brain MRI has prognostic value for the combined outcome of death/disability, as well as for death at various ages during the first month of life of a newborn, in neonates that are both treated and not treated with hypothermia. In newborns not treated with hypothermia, the MRI also seems to predict cerebral palsy or cognitive deficiency. The quality of the evidence is greater for the combined outcome of death and disability than for all other outcomes separately. No studies that assess epilepsy separately have been found.

There are no studies that precisely specify how many of the patients die as a consequence of limiting therapeutic effort based on the information provided by the MRI, which could alter the prognostic value of this test for death whenever death is evaluated ("self-fulfilling prophecy"). The aspects that have determined the direction of the recommendation the most have been the consistency between the results of the available studies, the total number of patients included in the analysis and the clear predictive capacity: magnitude of the diagnostic ORs.

No major secondary effects from using this technique of neuroimaging could be expected.

There seems to be a favourable cost-benefit ratio.

The preferences of the parents in this regard are unknown, or the potential impact on their stress during the intensive care of their child.

6.2.5. Summary of the evidence (own MA)[167–187]

6.2.5.1. Death or moderate/severe disability

Low quality	The conventional, EARLY cerebral MRI (sequences T1/T2), taken in the first week of life, shows an acceptable predictive value of death or severe disability of newborns not treated with hypothermia.
Moderate quality	The conventional, LATE cerebral MRI (sequences T1/T2), taken between days 8 and 30 of life, predicts death or disability in newborns not treated with hypothermia.
Very low quality	Therapeutic hypothermia does not seem to decrease, overall, the predictive value of death or disability of the MRI taken in the first month of life. When separately analysing the predictive value of the early MRI and the late MRI, hypothermia also does not seem to diminish it. However, there are still very few studies on hypothermia, and the number of included patients is still scarce, which could condition the fact that the CIs are broad.

6.2.5.2. Death

Very low quality	The early and late MRI are capable of predicting death in patients not treated with hypothermia.

6.2.5.3. Severe disability

Very low quality	The early and late MRI are capable of predicting severe disability at 12-24 months in patients not treated with hypothermia. There are no studies on hypothermia that allow an analysis of this outcome.
Low quality	The absence of normal myelination of the posterior limb of the internal capsule in an MRI taken in the first month of life is predictive of severe disability at 18-24 months. This is so in patients treated with normothermia and in patients treated with hypothermia.

6.2.6. Recommendations

Strong	We recommend 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, we recommend 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, we suggest 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.

6.2.7. Implications for research

The number of patients assessed using cerebral MRI and treated with hypothermia is still scarce. Future works that evaluate predictive capacity should include patients with this therapy, evaluated at different moments in life and with long-term neurological follow-up. It is very important to be able to separately analyse the MRI conducted in the first days of life from one taken after the first week, given that the early MRI tends to be used by clinicians as the basis for making decisions and for providing prognostic information to families. Even though the prognostic value of the conventional MRI has been analysed in this MA, in clinical practice it is usually evaluated together with other sequences, such as the HMRS and diffusion (in early studies, they would probably increase the predictive value of this imaging technique). Likewise, the published results are expressed very heterogeneously: area under the ROC curve, others contributing only sensitivity and specificity. It is currently necessary to conduct rigorous studies with a more precise methodology and uniform outcomes and with the specification of severity according to standardised classifications of the severity of the disability, such as the GMFCS or the score on the Bayley scale. It is important that works include the percentage of patients in which the MRI findings helped to establish the therapeutic limitation in order to be able to better assess the predictive capacity of the MRI in all the outcomes that include death.

The potential impact by the MRI on parental stress during admittance in Intensive Care Units should be explored in future studies.

6.3. What is the prognostic value of the biomarkers in blood, urine or CSF to predict death or neurodevelopmental problems in newborns with moderate or severe HIE, treated or not with hypothermia?

6.3.1. Introduction

In newborns with HIE, the prediction of death or severe disability has been traditionally based on the clinical severity of the HIE, on neurophysiological evaluations and on brain imaging studies. The first two approaches can be affected by medication and by therapeutic interventions, such as antiepileptic medication, sedatives and muscle relaxants. Thus, certain biomarkers of injury, generally more or less specific proteins of the nervous system, have been examined and used as an additional strategy for evaluating the severity of the damage and providing certain information about the prognosis. The main biomarkers of injury used have been neuron-specific enolase (NSE), protein S100B (S100B), the glial fibrillary acidic protein (GFAP), activin A and the lactate/creatinine ratio. Moreover, the incorporation of therapeutic hypothermia (as a specific neuroprotective intervention to reduce brain damage) could mean greater neuronal survival, as well as preservation of the blood-brain barrier, and this could give rise to lower NSE and S100B values in the body fluids of newborns treated with hypothermia. However, hypothermia, by dropping the body metabolism, can have an effect on the proteases that degrade these proteins, which could give rise to a more prolonged half-life of these proteins (NSE and S100B) in biological fluids. The effect by therapeutic hypothermia on the concentrations of NSE and S100B is unknown, and it is also unknown whether or not the therapy has changed the predictive capacity of these biomarkers. Wherefore, we have evaluated the available evidence on the predictive capacity of these biomarkers for the outcomes of death, adverse development (death or severe disability), cerebral palsy and epilepsy. After the original search of the prognostic value of the aforementioned biomarkers in biological fluids in children with HIE, a total of 31 publications that reported the determination of one or several of the biomarkers were identified. Of those publications, 12 did not refer to the development of the neonates beyond the first 6 months. Nine exclusively examined the relationship between the concentration of a biomarker in a biological fluid and the presence and severity of HIE, and they were excluded due to not responding to the posed outcomes (Nagdyman, 2001;[194] Dayioğlu, 2002;[195] Florio, 2004, 2007 and 2010;[196-198] Martins, 2006;[199] Gazzolo, 2004;[200] Bashir, 2009;[201] and Liu, 2010[202]). Two of the 12 publications that did not report on development used death and/or the brain damage detected by magnetic resonance imaging (MRI) during the neonatal period as the final outcome (Massaro, 2012,[203] and Ennen, 2011[204]), and they were included due to considering MRI to be a good predictive indicator of HIE.

The total number of publications that evaluated the predictive capacity of a biomarker and that were finally included in the study was 22. Of these, only one corresponded to an SR-MA about the predictive capacity of post-asphyxia brain damage for the following biomarkers: NSE, S100B, myelin basic protein, CK-BB, GFAP and interleukins IL6, IL8 and IL1 determined in the first 28 days of life in different biological fluids (Ramaswamy, 2009[30]). The review examined only prospective studies published in English that presented neurodevelopmental follow-up on patients until at least until 12 months of age. The study included 22 studies involving a total of 781 patients. The analysis strategy was to convert the results into units of mean and standard deviations and to then calculate the weighted means and standard deviations based on the measure-

ments expressed for each biomarker. Even though the quality of the included studies was evaluated (Newcastle-Ottawa Scale), it was not detailed for each study. Heterogeneity was measured using the I2. The results for each biomarker in the different biological fluids are presented below.

6.3.2. Outcomes

6.3.2.1. Death or severe disability

a) Neuron-specific enolase (NSE)

a.1 *NSE in CSF in patients not treated with hypothermia*

In the original search on the prognostic value of the concentration of NSE in children with HIE, a total of 7 articles were identified, plus the aforementioned SR. This systematic review (Ramaswamy, 2009[30]) included only 3 of the 7 identified publications that examined the relationship between the concentration of NSE and CSF and the development of the neonates with HIE (García-Alix, 1994;[18] Thornberg, 1995;[205] Blennow, 2001;[206] Ezgü, 2002;[207] Tekgul, 2004;[208] Jinqiao Sun, 2012;[209] Vasiljević, 2012[210]). Of these 7 publications, 6 correspond to cohorts of newborns with HIE without therapeutic intervention (no hypothermia), and one evaluated the value of this biomarker in a subgroup of newborns with HIE treated with hypothermia (Jinqiao Sun, 2012[209]). The SR by Ramswamy et al. included three studies (García-Alix, 1994;[18] Blennow, 2001;206 and Ezgu, 2002[207]). This SR did not provide a cut-off point, and no diagnostic efficacy values were given. The results were given as weighted means. The results, according to the outcome, were the following:

Low quality

- Abnormal development. Three studies that contributed 99 patients were included, with 26 patients showing abnormal development. The weighted mean difference (WMD) was 1.21 (95% CI, 0.04 to 2.38). The heterogeneity of the studies (I2) was 78.2%.
- Adverse development (death + abnormal development). They included the three indicated studies, hereby contributing 210 patients for this outcome (of which, 33 showed the adverse development outcome). The weighted mean difference (WMD) was 1.22 (95% CI, 0.32 to 2.12). The heterogeneity was 70.3%.

The conclusion of this SR was that the NSE concentration in CSF in the first 96 hours predicted death or adverse development.

Since this SR was published, 4 new studies have been incorporated in medical literature. Moreover, given the absence of cut-off points in this SR, and the absence of diagnostic efficacy values, the decision was made to conduct our own SR and MA to be able to respond to this question. The available studies up to December 2012 that contributed data about the predictive value of the concentrations of NSE in the first 72 hours of life and with follow-up of at least 12 months were considered. The bibliographic search that was performed is specified in the methodological manual of this guideline. Only publications in English or Spanish were included.

Seven publications met the initially established criteria, but two studies were excluded after a complete reading and after making the summary table. They were the following:

- Blenow, 2001.[206] A work coming from a single centre, which studied 30 neonates: 8 controls and 22 with HIE. The work points out that the concentration of NSE in CSF was related to only one neonatal death, but to with abnormal development. However, this work did not contribute raw data that allowed including its results in an analysis.
- Jinquiao, 2012.[209] This study coming from a single centre involves the 51 patients from that centre that were included in a multi-centre study on the efficacy of therapeutic hypothermia. 23 were assigned to the no-hypothermia branch and 28 to the hypothermia branch. It only contributes data for the group treated with hypothermia, which data are shown as the mean ± SD, and it is not possible to evaluate the predictive efficacy.

The five publications that were finally included contribute a total of 220 patients. To conduct the MA, an individual evaluation of the quality of each study was conducted, plus one of overall quality. The quality was initially considered to be high if the target population came from an RCT, if there was biochemical masking, if the outcomes were well-defined and if the statistical analysis included a cut-off point and an evaluation of predictive efficacy. The quality was lowered if the study was an observational prospective study, if the sample sizes were small, if the target population was not strictly defined and if the follow-up was not defined through specific evaluations for neurodevelopment, and it was considered very low if more than two of the preceding limitations were present and if the study was retrospective, as well as when no predictive efficacy data were provided (Table 6 of Appendix 7.2.).

For the adverse development outcome (death or severe disability), the results were those that are included in Table 7 of Appendix 7.2. The sensitivity, specificity, 95% CI and the PLR, NLR and OR for each study are shown in Table 8 of Appendix 7.2.

As we can see, in the 5 available studies, the concentration of NSE in CSF in the first 72 hours of life was capable of predicting adverse development in newborns with HIE. Two studies found that concentrations exceeding 25 ng/ml were associated with adverse development, while in another, the cut-off point was 60 ng/ml. Upon conducting the MA with the aforementioned data, it was determined that NSE in CSF had a PLR of 5.242 (95% CI, 3.159 to 8.697) and an NLR of 0.124 (95% CI, 0.049 to 0.314). The diagnostic OR was 49.378 (95% CI, 14.89 to 163.68). While in normothermia, the pretest probability according to the severity of the HIE or the basal risk is 63.1% (Tagin, 2012), the positive posttest probability in the case of high values of NSE in CSF is 90.0% (84.4% to 93.7%), and the negative posttest probability is 17.5% (7.8% to 35.0%). The I^2 of heterogeneity was 0%.

a.2 *Enolase in CSF of patients treated with hypothermia*

Only one publication has evaluated the value of this biomarker in a subgroup of newborns with HIE treated with hypothermia (Jinqiao Sun, 2012[217]). This study, which was part of an RCT, showed that hypothermia reduced NSE-CSF concentrations: the concentrations of NSE were significantly lower in the cooled group. However, the relationship between NSE concentrations and development was only in reference to the group subjected to hypothermia (they only provide the mean and SD for the group with good or bad development). Unfortunately, this study did not contribute data that would allow calculating the value of the concentrations of NSE in CSF to predict an alteration of neurodevelopment (MDI or PDI < 70) in newborns with HIE subjected to hypothermia.

Very low quality

a.3. *Enolase in serum in patients not treated with hypothermia*

Eight studies examined the relationship between the concentration of NSE in serum and the development of neonates with HIE (Thonberg, 1995;[205] Verdu, 2001;[211] Nagdyman, 2001;[194] Ezgü, 2002;[207] Tekgul, 2004;[208] Çeltic, 2004;[212] Roka, 2012;[213] and Massaro, 2012[203]). In six of them, the newborns with HIE did not receive any therapeutic intervention (hypothermia). Of these six, two studies were excluded from the analysis: one of them did not contribute data about concentrations in serum (Thorberg, 1995[205]) and the other (Ezgü, 2002[207]), even though it stated that there were not differences in the serum concentrations of NSE (an isolated determination in the first 72 hours) between newborns with normal or abnormal development at one year, did not contribute raw data, which prevents estimating the predictive value of this biomarker for the posed outcomes. Of the four studies, three contributed data for the combined outcome of death-severe disability (Verdu, 2001;[211] Tekgul, 2004;[208] Çeltic, 2004[212]) and one for the severe disability outcome (severe developmental delay) (Nagdyman, 2003[214]).

Low quality

The three studies that evaluated this outcome (Verdu, 2001; Tekgul, 2004; Çeltic, 2004) include 89 newborns with HIE, 13 of which died and 19 showed abnormal development. The main results are summarised in Table 9 of Appendix 7.2.

The studies were notably heterogeneous with respect to variables as important as the age in hours at the time of determination and how the severe disability outcome was evaluated, wherefore the disparity (inconsistency) of the results is not surprising, which makes it difficult to draw clear conclusions and does not allow an MA to be conducted, although everything seems to indicate a poor predictive capacity of NSE in serum during the first 72 hours of life.

a.4. *Enolase in serum in patients treated with hypothermia*

Of the eight publications that evaluated the value of the concentrations of NSE in serum, only two evaluated the value of this biomarker in newborns with HIE subjected to hypothermia.

Moderate quality

Roka et al.[213] evaluated the effect of hypothermia on the concentrations of serum NSE between 6 and 72 hours of life and the relationship that existed between these concentrations and adverse development (death or severe disability: PDI or MDI in Bayleys III < 70) in 24 newborns with HIE. This study, which formed a part of the TOBY RCT (sub-study) found no differences in the concentration of NSE between the group treated with hypothermia (n = 13) and the control group (n = 11) at any of the moments in time: 6, 12, 24, 58 and 72 hours. Upon evaluating the relationship between concentrations of NSE and development, they did not appreciate differences between the group with favourable development and the group with adverse development (death or severe disability), except at 24 hours (p = 0.036).

Massaro et al.[203] found different results with respect to the value of the NSE serum determination for predicting development. Their study examined the correlation between the concentrations in serum at the beginning of hypothermia and adverse development, defined as death or severe damage appreciated by MRI at 7-10 days. The serum samples were obtained at the beginning of hypothermia and at 12, 24 and 72 hours after it had begun. These authors found that the basal values (beginning of hypothermia) were the most predictive of adverse development. A cut-off point of 81 ng/ml had a sensitivity of 71%, a specificity of 83% and a PLR of 4.05. Even though the age (moment) of the first determination is similar among both studies (first concentration of NSE in serum at 4.7 hours in Massaro [interval of 0.4-6 hours] versus 6 hours in the study by Roka), they both examine different outcomes (death or Bayleys < 70 at 2 years in Roka and severe brain damage in MRI or death in Massaro et al.). The outcome of the study by Massaro et al. is the aspect that determines a reduction in the quality assessment of this very well designed study. While the cohort of patients studied by Roka is small, the study by Massaro et al. included 75 patients, which gives this study greater weight when evaluating the value of the utility of the serum concentration of NSE.

Low quality

b) S100B protein

b.1 *S100B protein in CSF*

Only two studies have examined the relationship between the concentrations of S100ß in CSF and some of the outcomes posed in this review (Blennow, 2001, and Jinquiao Sun, 2012).

Very low quality

The first (Blennow, 2001[206]) found that the group with adverse development showed higher concentrations than the patients with normal development, but this fact was at the expense of those that died. Since no raw data are provided, it is not possible to calculate the predictive value of death, adverse development or abnormal development.

The second (Jinquiao Sun, 2012[209]) was an RCT (sub-study) on hypothermia, and it found that the concentrations of S100ß in CSF at 72 hours after beginning treatment were lower in the treated group, and it found that the patients with adverse development showed higher concentrations than those that had favourable development. Unfortunately, the study did not estimate the predictive value of the concentration of S100ß and did not contribute raw data that allow estimating it.

Low quality

b.2 *S100B in serum in patients not treated with hypothermia*

Five studies have examined the relationship between the concentration of S100ß in serum and the development of newborns with HIE. Of these, three evaluated this marker in newborns with HIE not treated with hypothermia and two in newborns that received this therapeutic intervention.

Low quality (Nagdyman) and very low (Murabayasi)

The three studies that evaluated the predictive capacity of the serum concentration of S100ß in newborns with HIE that did not receive treatment with hypothermia include a total of 87 newborns with HIE, 34 of which showed adverse development (Nagdyman, 2003;[214] Thorngren-Jernek, 2004;[215] Murabayasi, 2008[216]). The results of the three studies are shown in Table 10 of Appendix 7.2.

The studies by Nagdyman and Murabayasi show notable methodological deficiencies [moment of determination, evaluation of the final outcome and sample size, 29 and 27, respectively, of which only 11 in the former and 3 in the latter had adverse development (death or abnormal development)].

The study with the greatest weight is the one by Thorngren-Jerneck, 2004,[215] who studied a population of 62 newborns with perinatal asphyxia, 57 of which showed HIE, and of those, 19 had adverse development. This study found that the serum concentration of S100B on the first and second day of life has limited predictive value (table). Moreover, the presence of HIE and acidosis showed a greater predictive capacity than the determination of S100B. However, the moment of determination was variable, insofar as the sample from the first day was obtained at between 1 and 19 hours, and this aspect is an important factor that could have an influence on the results and could therefore be an important factor of heterogeneity to be considered in this type of study.

Moderate quality

b.3 *100B in serum in patients treated with hypothermia*

Of the available studies, the first (Reka, 2012[213]) evaluated the value of this biomarker in a subgroup of newborns included in the RCT for assessing the neuroprotective efficacy of hypothermia. This studied showed that hypothermia reduced the concentrations of serum S100B versus a group with normothermia, but only significantly at 48 hours. The newborns of this study who showed adverse development (treated or not with hypothermia) showed higher concentrations of S100ß at each one of the moments between 6 and 72 hours of life. The highest significance was reached at 6 hours. This study did not report raw data to be able to calculate the predictive value of serum S100B.

Low quality

A different study (Massaro, 2012[203]) was the one conducted in a cohort of 75 newborns treated with hypothermia. These authors investigated the correlation between the concentrations in serum at the beginning of hypothermia and at 12, 24 and 72 hours after beginning hypothermia and adverse development (death or severe damage in MRI at 7-10 days). This study found that the basal values (at the beginning of hypothermia < 6 hours) were the most predictive of adverse development (death or severe damage in the MRI). A cut-off point of 0.7 μg/L had a sensitivity of 64%, a specificity of 84% and a PLR of 3.93. A cut-off point of 1.6 μg/L had a sensitivity of 40%, a specificity of 91% and a PLR of 4.3. Even though the age (moment) of the first determination is similar between both studies (first concentration of NSE in serum at 4.7 hours in Massaro [interval of 0.4-6 hours] versus 6 hours in the study by Roka), they both examine different outcomes (death or Bayleys < 70 at 2 years in Roka and severe brain damage in MRI or death in Massaro et al.). The cohort of patients studied by Roka is very small, while the one studied by Massaro has an adequate size (N = 75), which gives this study greater weight. The results of this study suggest that, also in newborns with HIE subjected to hypothermia, the concentration of serum S100B while still within the first 6 hours has very moderate predictive value.

Moderate quality

b.4 *S100B in urine*

The utility of determining the concentration of S100B in newborns with HIE has been evaluated in five studies. In two of the studies, the outcome was the relationship thereof to the severity of the HIE and, therefore, because they didn't contribute data on the development outcomes of death or disability, they were both excluded from this review. Another study was excluded because follow-up only reached six months, and moreover there was a high number of losses (only 46% of the newborns with HIE included in that study were followed up on).

Low quality

Only two studies of Gazzolo's Italian group tackled the outcomes that allow being evaluated for this CPG. One study of this group examined the capacity to predict development with the death or severe disability outcome (Gazzolo, 2003[217]). This study included 38 consecutive newborns according to perinatal asphyxia criteria, 12 of which showed moderate or severe HIE and 20 children with mild or no HIE, as well as a control cohort of 121 newborns, 96 of which were followed up on. The concentration of S100B in urine was determined in the first urination and at 12, 24 and 72 hours. The main results of this study are sown in Table 11 of Appendix 7.2:

This study reports that the three neonates that died showed the highest concentrations (values ≥ 3 μg/L).

This study has the limitation that the outcome at one year responds only to the neurological evaluation, and the classification of the disability is vague. For example, it points out that 18 of the neonates with adverse development showed hypo-hypertonia, but with no other specifications for establishing that they truly had a severe disability. The quality of this study is reduced due to the fact that the follow-up was not defined through specific evaluations for neurodevelopment. On the other hand, it is surprising that the study's results are notably different from the observed predictive capacity when S100B is determined in serum at similar times (Massaro, 2012;[203] Roka, 2012[213]).

The predictive capacity of the concentrations of S100B to predict death in the neonatal period has been examined as an isolated outcome only in one study, also from the Gazzolo group (Gazzolo, 2009[218]). This study included 60 newborns with perinatal asphyxia and HIE, 12 of which died in the first week of life. In this group, the concentrations of S100B increased at each determination until reaching their maximum value after 48 hours of life. In each one of the determinations in urine (first urination and after 24, 48 and 96 hours of life), the sensitivity, specificity, PPV and NPV were 100% for a cut-off point of > 1.0 μg/L.

High quality

c) Glial fibrillary acidic protein (GFAP)

c.1 *GFAP in CSF*

The glial fibrillary acidic protein (GFAP), also called glial filaments, is one of the fibrous proteins that form the intermediate filaments of the intracellular cytoskeleton, particularly glial cells as astrocytes. This specific protein of the cerebral tissue is not secreted in blood and is released only after the death of the astrocyte, wherefore it could pass to the blood stream due to an alteration of the blood-brain barrier.

Very low quality

Only two studies have examined the relationship between the concentrations of GFAP in CSF and development (Blennow, 1995;[219] 2001[206]).

In the first study,[225] the authors determined this biomarker in 21 newborns with HIE and in 10 normal controls between 12 and 48 hours of life (31 ± 4.8 in the group with HIE and 37.5 ± 10.5 in the control group). The neurodevelopmental outcome after the evaluation by a neuro paediatrician was classified as normal, suspect or abnormal based on the presence of neurological signs. Suspect children and those considered to be abnormal were grouped into a single category (abnormal development). The authors reported a sensitivity of 78% and a specificity of 75%, with a PLR of 3.12 for a cut-off point of 509 ng/L (no patient died).

In a second study of this same group,[205] the determination of said protein was between 6 and 89 hours of age, and unlike the first study, they found that its increase in the CSF of newborns with HIE and adverse development were only at the expense of those that died. Given that no raw data were provided in this study, it was not possible to calculate the predictive value of death.

Very low quality

c.2 *GFAP in serum*

Only a recent study has covered the relationship between the concentration of GFAP in serum and the presence of hypoxic-ischaemic injury in an MRI evaluation before discharge (Ennen, 2011[204]). The GFAP was determined in cord blood and in serum in the first 6 hours, as well as at 24, 48 and 72 hours and the first, second, third and fourth day post-hypothermia. This study showed a progressive increase in the concentrations of GFAP as from 24 hours, reaching the highest concentrations at the third day post-hypothermia. A value > 0.15 ng/ml showed an AUC of 0.718, with a sensitivity of 50%, a specificity of 84.6% and a PLR of 3.24. This study also examined the relationship between the concentrations of GFAP and death or early functional alteration (feeding disorder). Only one patient died, and even though the lack of raw data makes it impossible to evaluate the predictive capacity of this outcome, this neonate showed the highest concentration.

Low quality

d) Activin A in urine

There are three studies published on Activin A in newborns with HIE, and all three examine the relationship between this biomarker and the severity of the HIE, but not between it and the neurodevelopmental outcome. Therefore, they have not been included in the review, given that they do not answer the posed outcomes. The three studies showed that this biomarker is a good predictor of the severity of HIE in the neonatal period, but unfortunately, none of them examined the relationship between the concentrations in blood, CSF or urine and the subsequent development of the patients (Florio, 2004,[196] 2006[220] and 2007[197]).

e) Lactate/creatinine ratio in urine

Three studies have covered the utility of this ratio in urine to predict subsequent development in newborns with HIE (Huang, 1999;[221] Oh, 2008;[232] Liu, 2010[201]). One study was excluded because the follow-up reached only six months, and moreover only 46% of the newborns with HIE included in that study were followed up on. Low quality

The two studies that meet the criteria to be evaluated used a similar method of determination, but the moments are different. Huang et al. determined the lactate/creatinine ratio within the first 6 hours and OH et al. did so between 6 and 24 hours of life. The results of both studies are notably different (inconsistency) in the value of the lactate/creatinine ratio, and it is impossible to reach conclusions about its utility.

The study by Huang 1999[221] included 40 newborns with perinatal asphyxia, of which only 16 showed HIE, and there were 51 healthy newborns as the control group. It was not pointed out whether or not the follow-up was blind to the determinations. In the group with HIE, the lactate/creatinine ratio in the first 6 hours was 186 times higher than the ratio appreciated in the control group and 88 times that of the asphyxial newborns without HIE. 10 of the 16 neonates with HIE had adverse development (death in the first four months of life or disability). The lactate/creatinine ratios were significantly higher in those that had adverse development. The authors point out that only one of the newborns with adverse development showed values of less than 1.00, but they did not establish the cut-off point, and by presenting the values in a logarithmic scale, it is impossible to calculate the predictive values

The study by Oh, 2008,[222] included 58 newborns with HIE that participated in a multi-centre RCT to evaluate the efficacy of therapeutic hypothermia (28 in the hypothermia group and 30 in the control group). The lactate/creatinine ratio was determined between 6 and 24 hours and at 48 to 72 hours. For the data analysis, the newborns with the moderate or severe disability outcome and/or the death outcome were combined in one group and compared with those that showed normal development or mild disability. Even though the group with abnormal development showed significantly higher ratios, there was broad variation of the same and overlapping with the group with normal development. This conditioned the fact that, for the cut-off point of ≥ 25, the sensitivity was 33% and the specificity was 88%, while for a cut-off point of 50, the sensitivity was 25% and the specificity was 97%. After adjusting the results for hypothermia and the severity of the HIE, the lactate/creatinine ratio between 6 and 24 hours had a diagnostic OR of 5.52 (95% CI, 1.36 to 22.42, p = 0.02). High quality

6.3.2.2. Cerebral palsy

This outcome cannot be analysed separately for any of the described markers.

6.3.2.3. Death

This outcome cannot be analysed separately for any of the described markers.

6.3.2.4. Epilepsy

This outcome cannot be analysed separately for any of the described markers.

6.3.3. From the evidence to a recommendation

6.3.3.1. Quality of the evidence

Low quality	Death or severe disability. The quality of the evidence decreased when there was inconsistency (conflicting results), indirect evidence (only neuroimaging to establish the damage), inaccuracy of the results (small sample size), moments of determination with a broad range of hours or when the evaluation or classification of the neurodevelopment was imprecise or there was a risk of bias. Moreover, the quality of the evidence was reduced according to how the results were reported: no determination of the cut-off points using ROC curves or the data were shown as means and standard deviation.
Moderate quality	Death or severe disability. The quality of the evidence increased when the design of the study was specific for the question, when the sample size and the number of unfavourable outcomes allowed an adequate analysis and when the evaluated outcome variable was within an RCT for evaluating the efficacy of hypothermia, in which a specific evaluation of neurodevelopment was conducted, with adequate masking and scarce losses.

6.3.3.2. Balance between benefits and risks

While the determination of S100B in urine does not involve any risk, the serial determination of S100B or NSE in blood could involve the risk of anaemia or a reduction of the rate of circulating haemoglobin. The determination in CSF involves more risks, given that the lumbar puncture is not free from complications, and there is the possibility of destabilising the patient's homeostatis. Nevertheless, no study (NSE, S100B, GFAP) reported any problem related to the lumbar puncture for obtaining CSF, although it is probable that none would be recorded.

Any newborn with HIE should have access, during the neonatal period, to those diagnostic tests with proven capacity to establish the prognosis as accurately as possible. Given the apparent proven capacity of the determination of NSE in CSF, this test can be considered to be beneficial with acceptance of the risks. Nevertheless, it is necessary to make sensible use of this test, given that a lab test should not be performed on a newborn in an unstable situation or if they suffer from thrombocytopenia or coagulopathy that do not respond to active treatment - situations that are not infrequent in newborns with HIE. A lab test also shouldn't be performed if a newborn shows an increase in intracranial pressure due to obstruction of the circulation of CSF or stigmas suggesting

occult spinal dysraphism or tethered spinal cord. Therefore, this evaluation, like any other, must be individualised according to the patient's conditions.

In brief, in term or near-term newborns with HIE, which are stable and without refractory coagulopathy, the determination of NSE in CSF in the first 72 hours of life must be considered, particularly if additional information is needed to establish the prognosis or to make difficult ethical decisions.

6.3.3.3. Costs and use of resources

The determination of the NSE, S100B and GFAP biomarkers is relatively inexpensive, it is done using commercial ELISAs, and it is available at the vast majority of hospitals. Therefore, the cost has not been considered to be a determining factor in the decision-making for this question.

The determination of the lactate-creatinine ratio, due to being determined by magnetic resonance spectroscopy, places a notable limit on this biomarker, given that said tool is expensive and is not available in the vast majority of hospitals. Moreover, it must be kept in mind that the scarce predictive value of this ratio and the need for costly technology places a major limit on its clinical utility.

No economic evaluation studies that specifically analyse these biomarkers were found.

6.3.3.4. Values and preferences of the patients

No specific information about the values of the parents in this regard were found. However, it is obvious that obtaining urine for determining a biomarker makes this fluid preferable over blood, and more so over CSF.

6.3.4. Final decision about the strength and direction of the recommendation

Aspects that have determined the direction and strength of the recommendation:

References 231 to 247 were excluded from the MA due to not fulfilling the aforementioned inclusion criteria.

a) NSE

Current scientific evidence shows that the determination of the concentrations of NSE in CSF between 12 and 72 hours of life in newborns with HIE not treated with hypothermia predicts the risk of adverse development (death or severe disability). The aspects that have determined the direction of the recommendation the most were the consistency among the results of the five available studies [18, 205-207, 208, 210], the total number of patients included in the analysis and a clear predictive capacity: diagnostic OR of 49.378 (95% CI, 14.89 to 163.68) and a posttest probability of 90.0% (84.4% to 93.7%). No relevant adverse effects from a lumbar puncture to obtain this biological fluid are expected, as long as it is done following the standard of good clinical practice and assuring that there are no contraindications to performing it.

There is no evidence that hypothermia might modify the value of the concentration of NSE in CSF209 to predict death or adverse development (death or severe disability). No relevant adverse effects are expected from a lumbar puncture to obtain this biological fluid. Given the cost of the test, there should be a favourable cost/benefit ratio. The determination of NSE in serum during the first 72 hours does not seem to have an adequate predictive value of adverse development.

b) S100B

The scarce evidence available (two studies[206, 209]) does not allow establishing a predictive value for the concentration of S100B in CSF regarding adverse development. The determination of this biomarker in serum during the first 24 hours does not seem to have adequate predictive value. However, the heterogeneity between studies and moments of determination prevent a firm conclusion from being reached.

The determination of S100B in urine seems to accurately predict death in the first week of life, as well as adverse development.[217-218] However, the limited number of studies (one for each outcome) prevents firm conclusions from being reached. There are no studies about whether or not therapeutic hypothermia has an influence on the predictive value of the concentration of S100B in newborns treated with therapeutic hypothermia.

c) GFAP

The concentration of GFAP in CSF in the first days of life of newborns not treated with hypothermia seems to have scarce predictive value for disability at one year of life, but it could predict death during the neonatal period. Nevertheless, the data are clearly insufficient for reaching a firm conclusion. The available data (only one study[219]) prevent reaching conclusions about the predictive capacity of this biomarker in serum to predict adverse development, death, abnormal development, cerebral palsy and epilepsy.

d) Activin A in urine

No study has evaluated the predictive capacity of this biomarker in any of the body fluids.

e) Lactate-creatinine ratio

The lactate-creatinine ratio between 6 and 24 hours of life seems to have a limited capacity to predict the development of newborns with HIE.[221, 222]

6.3.5. Summary of the evidence

Moderate quality	In newborns with HIE not treated with hypothermia, the concentration of NSE in CSF between 12 and 72 hours of life shows an acceptable predictive value of death or serious disability at one year of life, with a diagnostic OR of 49.378 (95% CI, 14.89 to 163.68), a positive posttest probability of 90.0% (84.4% to 93.7%) and a negative posttest probability of 17.5% (7.8% to 35.0%) (own MA).
Low quality	In newborns with HIE not treated with hypothermia, the concentrations of both NSE and S100B in serum has a limited predictive value of death or of the combination of death or severe disability.[210, 216, 220-224] In newborns with HIE treated with hypothermia, the serum concentration of NSE or S100B in serum in the first 6 hours seems to have moderate predictive value with respect to the possibility of death or of presenting severe disability or severe damage in the MRI.[210, 216, 220-224]

Very low quality	The concentration of S100B in CSF between 6 and 89 hours can predict death during the first week of life.[206, 209] The concentration of GFAP in CSF between 6 and 89 hours in newborns not treated with hypothermia seems to have scarce predictive value for disability at one year of life, but it could predict death during the neonatal period.[219]
Moderate quality	The lactate-creatinine ratio in urine between 6 and 24 hours of life has a very limited value for predicting death or severe disability at one year of life.[221, 222]

6.3.6. Recommendations

Strong	In newborns with a gestational age of greater than or equal to 35 weeks with HIE, and they are stable and without refractory coagulopathy, the determination of 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.

6.3.7. Implications for research

The research on biomarkers with predictive capacity in newborns with HIE over the last 20 years is encouraging, but it is limited by small sample sizes (due to the studied population coming from single hospitals and not from multi-centre studies), by the existence of heterogeneity at the times of determination, due to using inaccurate classification measurements of neurodevelopment and due to non-masking and studies having a considerable risk of bias. Likewise, the expression of the results is very heterogeneous: area under the ROC curve in some, only sensitivity and specificity in others and occasionally only levels are provided, without measurements of diagnostic/prognostic capacity. It is currently necessary to have rigorous studies that follow a more precise methodology, as well as provide uniform outcomes and specify the assessment of development: score on development scales and significant delay of development assessed using standardised tests.

7. Follow-up

Questions to be answered:

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

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

7.1.1. Introduction

Even though the developmental consequences of perinatal hypoxic-ischaemic encephalopathy (HIE) are relatively well known at least during the first 2-3 years of life, up to now no study has been carried out that has evaluated the impact of different follow-up programmes on the health of children that had HIE in the neonatal period. Therefore, this question cannot be answered by applying the GRADE methodology, like the other questions asked in this CPG. We, the professionals who have prepared this guideline, are aware of the absence of research in this area and of the limitations that exist when establishing recommendations about follow-up. However, we also believe that care after discharge from the hospital must form a part of the comprehensive attention given to newborns with HIE and to their families.

Therefore, below we present a series of recommendations prepared with the consensus of the development group of this CPG, thereby encompassing the various aspects that we consider to be important in the follow-up on these patients.

7.1.2. Recommendations

√	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.
√	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.

8. Diagnostic and therapeutic strategies

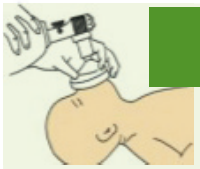
MANAGEMENT ALGORITHM FOR NEWBORNS AT RISK OF PERINATAL HYPOXIC-ISCHAEMIC ENCEPHALOPATHY

Caution! In the event of data that are compatible with a situation of intrapartum hypoxia-ischaemia

- Non-reassuring foetal status: bradycardia maintained, late decelerations, loss of beat-to-beat variability, meconium-stained amniotic fluid, scalp pH < 7.20.
- Dystocia
- Sentinel event: placental abruption, uterine rupture, umbilical cord prolapse, foetal-maternal transfusion.

Birth

Resuscitation



Evaluate! Status at birth

- Need for advanced resuscitation
- Apgar 5 < 5
- Umbilical pH in the first hour of life < 7.00

Do not use **Apgar 0 at 10 minutes** by itself to make the decision to limit therapeutic effort in the delivery room. ǂ

Do not begin administering **oxygen at 100%** ǂ

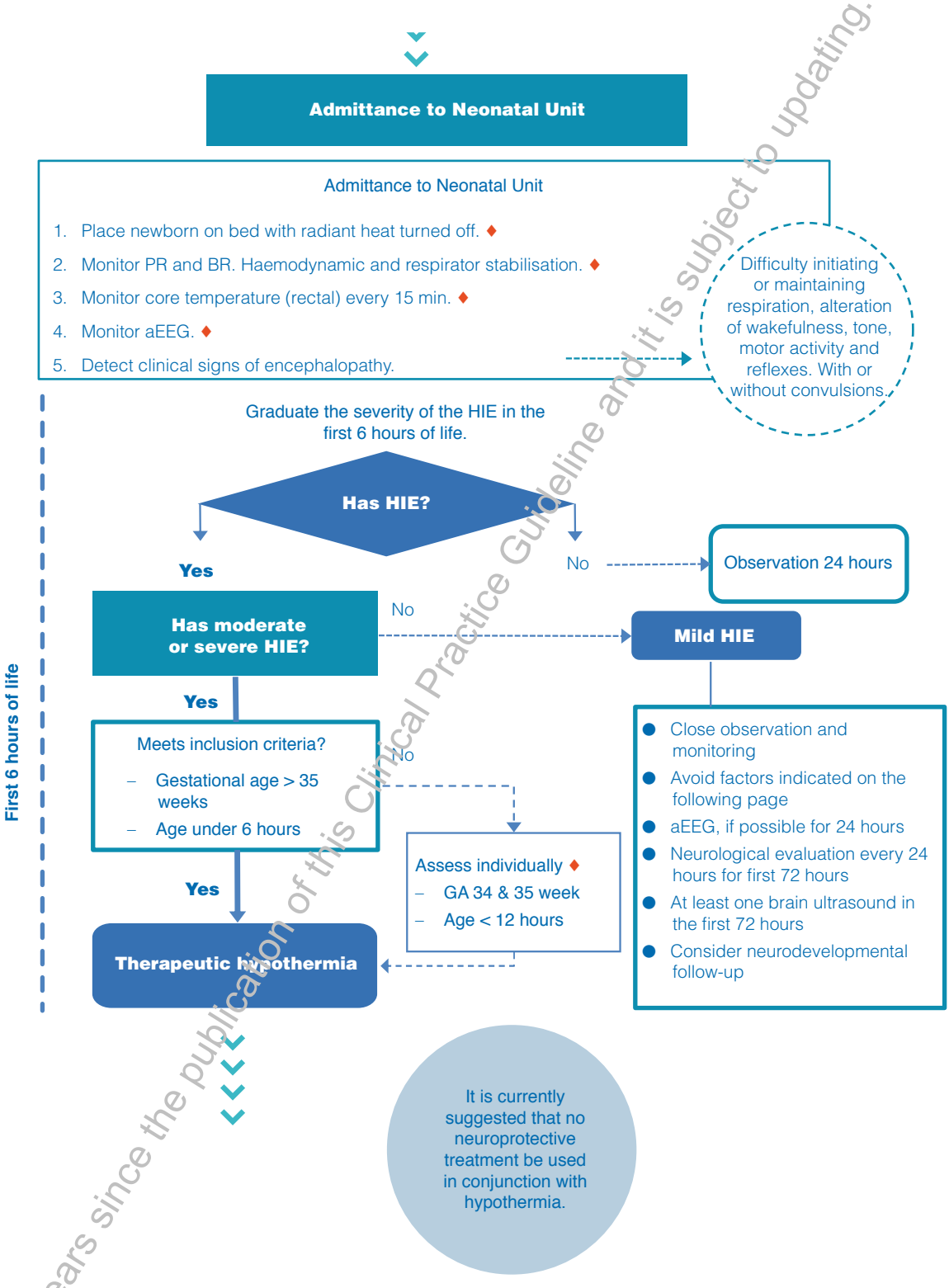
Measures to adopt in the delivery room

- **Turn on radiant heat, and monitor pre-ductal O2 saturation.** ♦
- **Begin resuscitation with ambient air and intermediate concentrations of O2. Modify FiO2 according to clinical response.** ♦
- **Avoid expansions** of volume and/or **bicarbonate.** ♦
- **Do not administer calcium.** ♦
- Take rectal temp: **avoid < 34° C and > 36° C.** ♦

Transfer

Admittance to Neonatal Unit

Strong evidence ⊙
Weak evidence ǂ
Good clinical practice ♦



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

Strong evidence ⊙

Weak evidence ǂ

Good clinical practice ♦

Therapeutic hypothermia ⊙

AVOID!

Hyperthermia in the first 72 hours ⊙

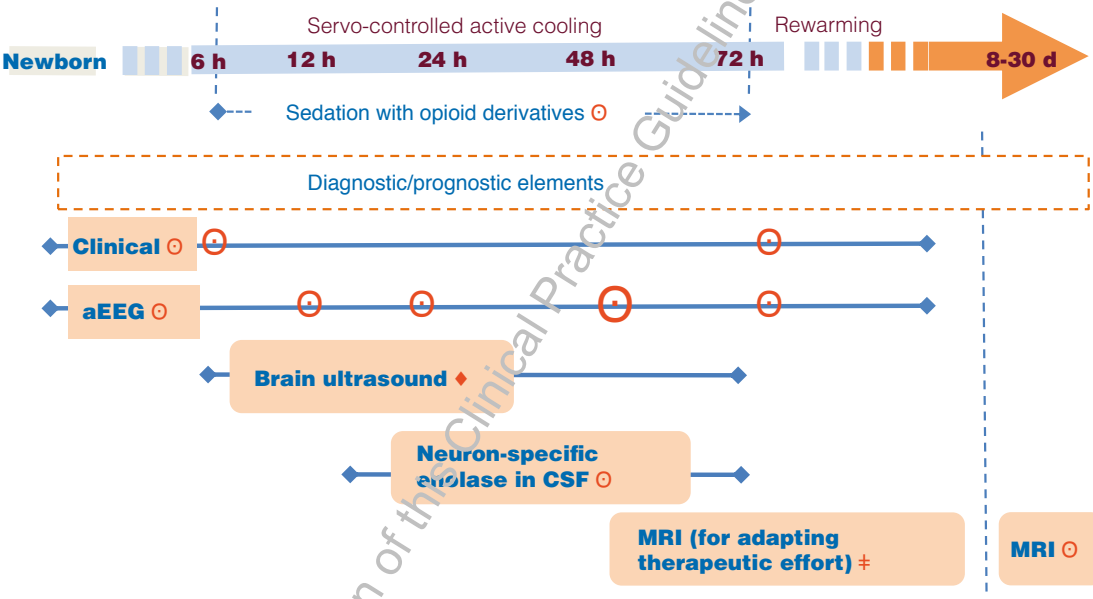
Severe hypocapnia (< 20 mmHg) in the first 24 hours ⊙

Hypercapnia in the first 24 hours ♦

Hypoglycaemia in the first 72 hours ⊙

Hyperglycaemia in the first 72 hours ♦

Maintained electrical seizures ⊙



FOLLOW-UP

The planning and duration of follow-up should be individualised, thereby considering the severity of the HIE and the type of brain injury in addition to family and social factors. ♦

Given the diversity and complexity of the problems that arise, a professional who is taking care of newborns with HIE during follow-up visits must be aware of these problems to allow a multi-disciplinary approach. ♦

Evaluations should be scheduled considering the age of appearance of each one of the complications and the specific risk that they might appear in each individual child. ♦

Both the children at a high risk of death after discharge from hospital and their families require special care targeted at anticipating the complications that lead to death, at optimising end-of-life care and at handling the family's needs regarding grief. ♦

Strong evidence ⊙

Weak evidence ǂ

Good clinical practice ♦

9. Dissemination and implementation

CPGs are useful for orienting professionals and patients in making decisions about healthcare, and they contribute to improving the health results of patients. The great challenge today is to achieve adherence by professionals and ensure knowledge for users and patients. A strategy of dissemination and implementation directed at overcoming the barriers that exist in the environment where CPGs are going to be applied is therefore essential.

9.1. Strategies for disseminating and implementing the CPG

The plan for disseminating and implementing the CPG on perinatal HIE in newborns includes the following interventions:

- Preparation of a summarised version and a quick guide (algorithms and annotations) in an on-line format.
- Promotion of the CPG by health authorities through media for healthcare professionals.
- Dissemination of the CPG on at least the official web pages of scientific companies that participate in reviewing the guide and on all others indirectly related to the health of newborns.
- Proposal for inclusion of the CPG in databases that compile guidelines at the state and international levels (National Guideline Clearinghouse: http://guideline.gov/).
- Distribution of a parents' guide among hospitals that provide therapeutic hypothermia.
- Free access to the various versions of this CPG at the following web pages: AQUAS (http://aquas.gencat.cat); Fundació Hospital Sant Joan de Déu (www.fsjd.org/es); the journal, Evidencias en Pediatría; and the web page of the Department of Health through Canal Salut (http://www20.gencat.cat/portal/site/salut/).
- Presentation of the results of the CPG in scientific activities (conferences, workshops, meetings) and particularly in professional education courses related to the handling of neonatal patients with HIE.
- Distribution of the CPG to professional bodies, health administrations, health centres and professional associations.
- Publication of information about the CPG in specialised journals and publications, particularly attempting to have it reviewed in Anales de pediatría, the most widely distributed national journal with the greatest weight within the professional scope of paediatrics.

9.2. Indicators and implementation plan

The application of the guideline's recommendations could be improved by measuring the adherence to and the implementation of those recommendations through monitoring and/or auditing. Implementation involves a planned process for the systematic introduction of an innovation or of changes of proven value, to be carried out in a specific environment at different decision levels (clinical service, organisation or health system). However, it has not been an objective of the authors of this guideline to propose indicators for the relevant recommendations or to design a specific implementation plan. In any event, when preparing the guideline, aspects that could have

an influence on adhesion by professionals to using the guideline have been taken into account, such as the broad representation of professionals in the development group and as reviewers of the guideline or the development of practical tools for application of the guideline (logarithms).

9.3. Keys to facilitating implementation of the CPG

The CPG includes questions regarding 4 broad areas related to the handling of children with HIE (risk factors, treatment, prognostic elements and follow-up), and it contains a large number of recommendations that respond to those questions. However, those who use the guideline need to organise and prioritise the recommendations to be implemented.

- The guideline belongs to the national CPG programme in the SNS, and it therefore does not deal with organisational aspects or required models of care to put the recommendations into practice. In any event, the group of authors has considered the efficient use of resources when formulating the recommendations. The moment when the CPG is adapted at the regional or local level is when the feasibility of the recommendations should be analysed, when the responsibilities of each professional regarding the care of each patient should be defined and when the scenarios or circumstances that require coordination or sequential action at the various care levels should be defined.
- The geographic representativity of the authors of the guideline and of those who have conducted the external review has contributed to qualifying the recommendations with knowledge of the context and environment where it is going to be applied (National Health System) and of the available resources (primary care, specialised care and social services).
- The identification and analysis of the particular context will contribute to the successful process of implementing the CPG, hereby understanding "context" as the set of influences at various levels: from the most external, determined by health policies in force (state, regional or local), to other, more specific influences, determined by the the specific professional organisation or professionals.

In this regard, developing comprehensive strategies in Spain is complex, given that the public SNS is composed of 17 health services that have different forms of management, regulation, planning and provision. Some autonomous communities have developed health plans (with specific prevention and care programmes for chronicity) and social-health plans that could facilitate the implementation processes. However, they are not uniform in the Spanish state as a whole. Nevertheless and as it can be seen in the make-up of the development, collaborator and reviewer group of the CPG and in the defined implementation actions, the intention is to implement this guideline throughout the (public) National Health System (SNS) as a whole. And given that this CPG is also targeted at professionals who work in the private sector, the interest in this CPG applies to the entire Spanish health system.

Even if healthcare for newborns with moderate or severe HIE is provided within the scope of level III neonatology services (public or private), the majority of patients are born at level II hospitals. Therefore, implementation should consider the possible differences between public and private healthcare, as well as the levels of care regarding the working methodology, structure and hierarchy. The different capacities of the various organisations to learn and to change must also be considered. And finally, we have also given major consideration to the fact that healthcare not only involves the health professionals, the patient with HIE and their family, but also the social and labour environments of the patient play an important role, as well as the services of the administration, social workers, psychologists and society itself. The role played by these elements in the success of effective implementation is far from trivial.

10. Future research lines

As we pointed out at the beginning of this CPG, both the diagnosis and treatment of children with HIE have experienced major advancement in recent years. In each clinical question, the authors of this CPG have indicated the current unknowns and lines of future research. They are all described below:

Risk / comorbidity factors

- There is a need for randomised and masked CTs that evaluate more adequate concentrations of oxygen and blood saturation to achieve a better response to the resuscitation measures of asphyxial newborns and to achieve lower mortality and better neurological development in the long term.
- More studies are needed regarding the risk of death and neurological morbidity associated with Apgar scores of 0, 1 and 2 in neonates that receive therapeutic hypothermia. Studies must differentiate between moderate and severe disability with greater precision, and they must separately show the outcomes associated with an Apgar score of 0, 1 or 2. The analyses of studies should not exclude either newborns deceased in the resuscitation room, or those that show clinical signs of apparent death or those that are admitted dying to intensive care units. The cause of death should be shown, and when it is due to having limited the therapeutic effort, the objective data based on which the decision is made should be shown (clinical, neuroimaging, electroencephalography, biochemical markers).
- More randomised and controlled studies or prospective cohort studies with a multivariate analysis of the diversity of potentially adverse factors on the nervous system in the first hours of life are required, while also considering the exposure time to the potential adverse factor. It is also necessary to correlate those factors with graduated and precise classifications of neurodevelopment.

Treatment

- Even though therapeutic hypothermia initiated in the first 6 hours of life has a proven neuroprotective effect in newborns with a gestational age of greater than or equal to 35 weeks with moderate or severe perinatal HIE, and it constitutes the only neuroprotective intervention that is used in clinical practice as of today, the beneficial effect is relatively modest, such that mortality is around 25% among treated patients, and approximately 20% survive with sequelae. Therefore, more research that leads to optimising this treatment is needed (for example, to answer the question if cooling should be deeper or longer). It is also very desirable to develop new interventions to be applied in combination with hypothermia in order to improve the neuroprotective effect. Moreover, as of today, there are no neuroprotective treatments that can be safely used on premature newborns with HIE. With respect to corroborating the benefit of hypothermia over a longer period (6-8 years), it is highly important to publish follow-up data at these ages from all the RCTs conducted. Research is being conducted in an RCT regarding whether or not cooling applied after the "window period" of 6 hours is beneficial in comparison with maintaining normothermia. It is in the best interest of this study that newborns of the control population receive strict monitoring of temperature and that hyperthermia be aggressively prevented or treated.

- Future research could help to clarify whether or not deeper or longer cooling could be accompanied by a more powerful neuroprotective effect. Likewise, it is very desirable to develop new interventions to be applied in combination with hypothermia, especially in newborns with severe HIE.
- Finally, an important limitation of hypothermia RCTs is the difficulty in preventing the hyperthermia described in the control groups, which could accentuate the protective effect associated with hypothermia. Given that therapeutic hypothermia initiated within the first 6 hours of life constitutes the standard treatment for newborns with moderate or severe HIE in our environment, it is highly unlikely that new trials might more accurately resolve if the severity of the encephalopathy conditions the effectiveness of treatment with hypothermia.
- Given that therapeutic hypothermia started within the first 6 hours of life constitutes the standard treatment for newborns with moderate or severe HIE in our environment, it is highly unlikely that new studies might help to clarify more precisely the prognostic value of the clinical categorisation of perinatal HIE in the absence of neuroprotective interventions and the role thereof in the selection of patients that could benefit from treatment with hypothermia.
- Given that therapeutic hypothermia constitutes the standard treatment for newborns with moderate or severe HIE in our environment, it is highly unlikely that new studies might help to more accurately answer this question, except for additional analyses of published RCTs or more longer term follow-up studies.
- Multicentre, randomised, controlled and blind trials that allow determining the effect of different drugs on mortality and on long-term neurodevelopment in newborns with moderate and severe HIE are necessary. In any event, these trials must be conducted in conjunction with treatment with hypothermia. In the treatments analysed in this guideline, it would be justified to conduct RCTs with more patients, given that the biological efficacy of these treatments has been proved in preclinical and experimental studies on animals, and there is certain evidence of a benefit in other groups of neonatal patients. Given the high number of treatments that could be used as therapy together with hypothermia, it is necessary to establish an ordered sequence based on experimental trials that would allow selecting, in the most efficient way possible, those with the most likelihood of success in the final phases of RCTs. In this regard, it would be desirable to have a multinational network that coordinated potential therapeutic trials and that publicised those treatments that were not successful in the more initial phases of application in order to gain in efficiency. The use of simple inclusion criteria, with uniform guidelines for administering the treatments and assessing disability using similar tests would facilitate a comparison of the results in future MAs. Newborns with moderate or severe HIE would be the candidates for participating in these RCTs, given the existing evidence that therapeutic hypothermia is beneficial in this group of patients. Given the existing limitations due to the narrow "therapeutic window" in this group of children (within 6 hours after birth), it would be recommendable to establish strategies that would allow informing parents before birth about the possibility of applying these therapies if they were necessary.
- It is necessary to conduct multicentre, randomised, controlled and blind trials with sufficient power to clarify the effect of different drugs in conjunction with treatment with hypothermia on mortality and on long-term neurodevelopment in newborns with moderate and severe HIE.
- There are some treatments whose biological efficacy has been proved in preclinical and experimental studies on animals, and there is certain evidence of a benefit in other groups of neonatal patients, wherefore it would be desirable to include them in pharmcokinetic and safety studies. Likewise, treatments such as EPO or topiramate, which point to evidence of safety, are potential candidates for being included in multicentre trials that determine death and long-term disability outcomes. Given the high number of treatments that could be used

as therapy together with hypothermia, it is necessary to establish an ordered sequence based on experimental trials in the laboratory and on animals that would allow selecting, in the most efficient way possible, those with the most likelihood of success in the final phases of clinical trials. In this regard, it would be desirable to have a network for coordinating potential therapeutic trials and publishing those treatments that were not successful in the more initial phases of application in order to gain in efficiency. The use of simple inclusion criteria, with uniform guidelines for administering treatments and assessing disability using similar tests would facilitate a comparison of the results in future meta-analyses. Newborns with moderate or severe HIE would be the candidates for participating in these trials, given the existing evidence that therapeutic hypothermia is beneficial in this group of patients. Given the existing limitations due to the narrow "therapeutic window" in this group of children (within 6 hours after birth), it would be recommendable to establish strategies that would allow informing parents before birth about the possibility of applying these therapies if they were necessary.

- Adequately masked, controlled and randomised studies with adequate power (sample size) are needed to examine whether or not the treatment of electrical seizures has a beneficial impact on neurological morbidity in neonates with HIE in treatment with hypothermia.
- More studies that evaluate the stress and discomfort associated with therapeutic hypothermia are needed, as well as the impact that they both have on both physiological stability and neurological morbidity. It is also necessary to learn if the systematic use of opioid derivatives in children with HIE has a neuroprotective effect. We recommend that studies that evaluate the neuroprotective efficacy of hypothermia indicate this variable and adjust the results in accordance therewith.

Prognostic studies

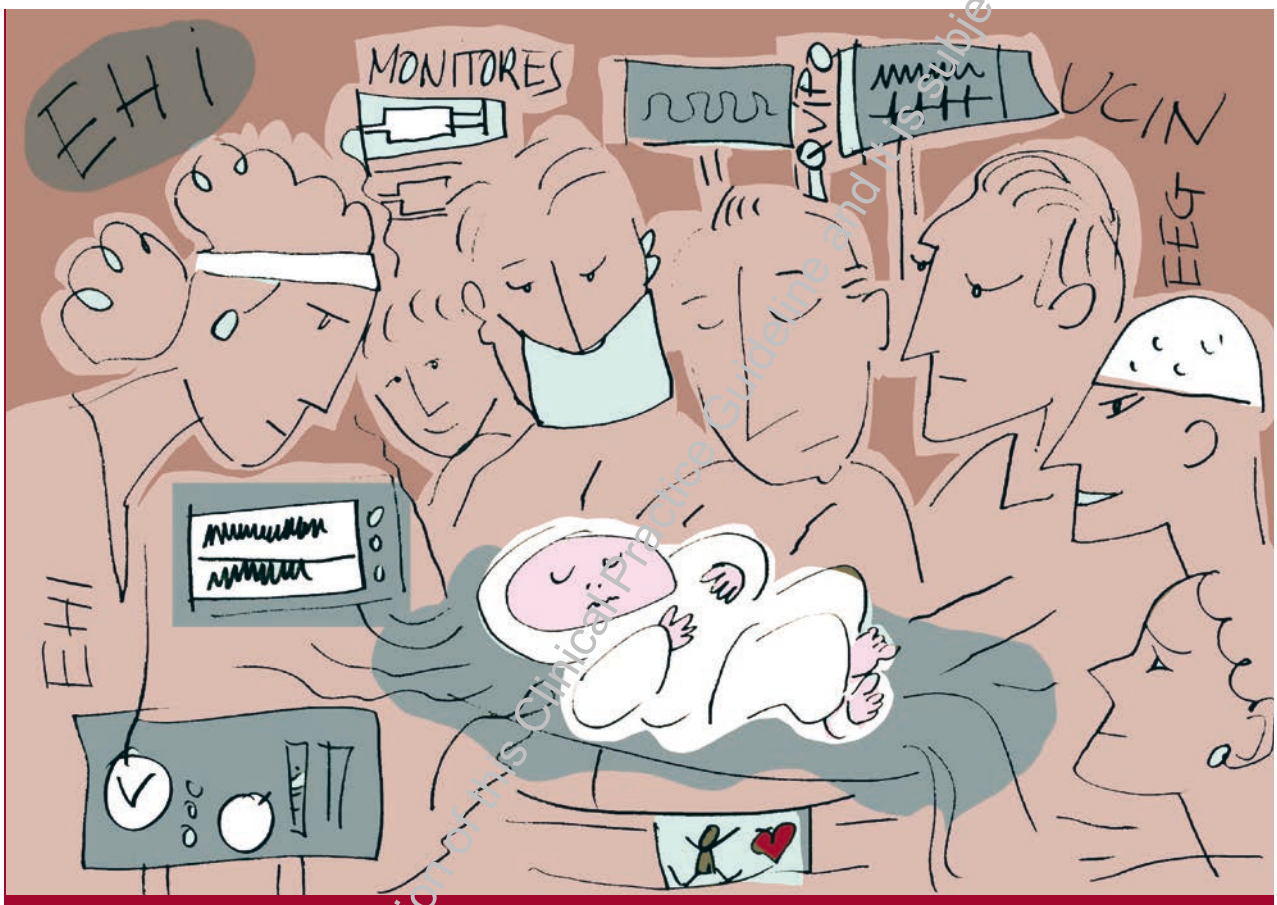
- The number of patients assessed with aEEG and treated with hypothermia is still scarce. Future works that evaluate predictive capacity should include patients with this therapy, evaluated at different moments in life and with long-term neurological follow-up. Likewise, the results are expressed very heterogeneously: area under the ROC curve, with other results contributing only sensitivity and specificity. Rigorous studies are currently needed, in which a formal evaluation of long-term development is included. It is important that works include the percentage of patients who die due to therapeutic limitation in order to be able to better assess the predictive capacity of the aEEG in all the outcomes that include death. Future studies should explore the potential impact on parental stress due to the monitoring of electrocortical activity by aEEG during the intensive care of their child.
- The number of patients assessed with brain MRI and treated with hypothermia is still scarce. Future works that evaluate predictive capacity should include patients with this therapy, evaluated at different moments in life and with long-term neurological follow-up. It is very important to be able to separately analyse an MRI taken in the first days of life and one taken after the first week, given that the early MRI tends to be used by clinicians as the basis for making decisions and for providing prognostic information to families. Even though the prognostic value of the conventional MRI has been analysed in this MA, in clinical practice it is usually evaluated together with other sequences, such as the HMRS and diffusion (in early studies, they would probably increase the predictive value of this imaging technique). Likewise, the published results are expressed very heterogeneously: area under the ROC curve, with other results contributing only sensitivity and specificity. It is currently necessary to conduct rigorous studies with a more precise methodology and uniform outcomes, including specification of the severity according to standardised classifications of the severity of the disability, such as the GMFCS or the score on the Bayley scale. It is important that works

include the percentage of patients in which the MRI findings helped to establish the therapeutic limitation in order to be able to better assess the predictive capacity of the MRI in all outcomes that include death. The potential impact by the MRI on parental stress during admittance in Intensive Care Units should be explored in future studies.

- The research on biomarkers with predictive capacity in newborns with HIE over the last 20 years is encouraging, but it is limited by small sample sizes (due to the studied population coming from single hospitals and not from multi-centre studies), by the existence of heterogeneity at the times of determination, due to using inaccurate classification measurements of neurodevelopment and due to non-masking and studies having a considerable risk of bias. Likewise, the expression of the results is very heterogeneous: area under the ROC curve, other results providing only sensitivity and stability and other occasions in which only levels are provided, without measurements of diagnostic/prognostic capacity. It is currently necessary to have rigorous studies with a more accurate methodology, as well as uniform outcomes with the specification of the assessment of development: score on developmental scales and significant delay of development assessed using standardised tests.

Appendixes

Appendix 1. Guide for mothers and fathers



Hypoxic-Ischaemic Encephalopathy and Therapeutic Hypothermia

GUIDE FOR MOTHERS AND FATHERS

This information for mothers and fathers forms part of the "Clinical Practice Guideline on Perinatal Hypoxic-Ischaemic Encephalopathy in Newborns". There is also a version in an on-line format
at the web page of GuíaSalud (http://www.guiasalud.es) and of Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS) (http://aquas.gencat.cat). At these web pages, it is also possible to consult the complete and summarised versions of the CPG.

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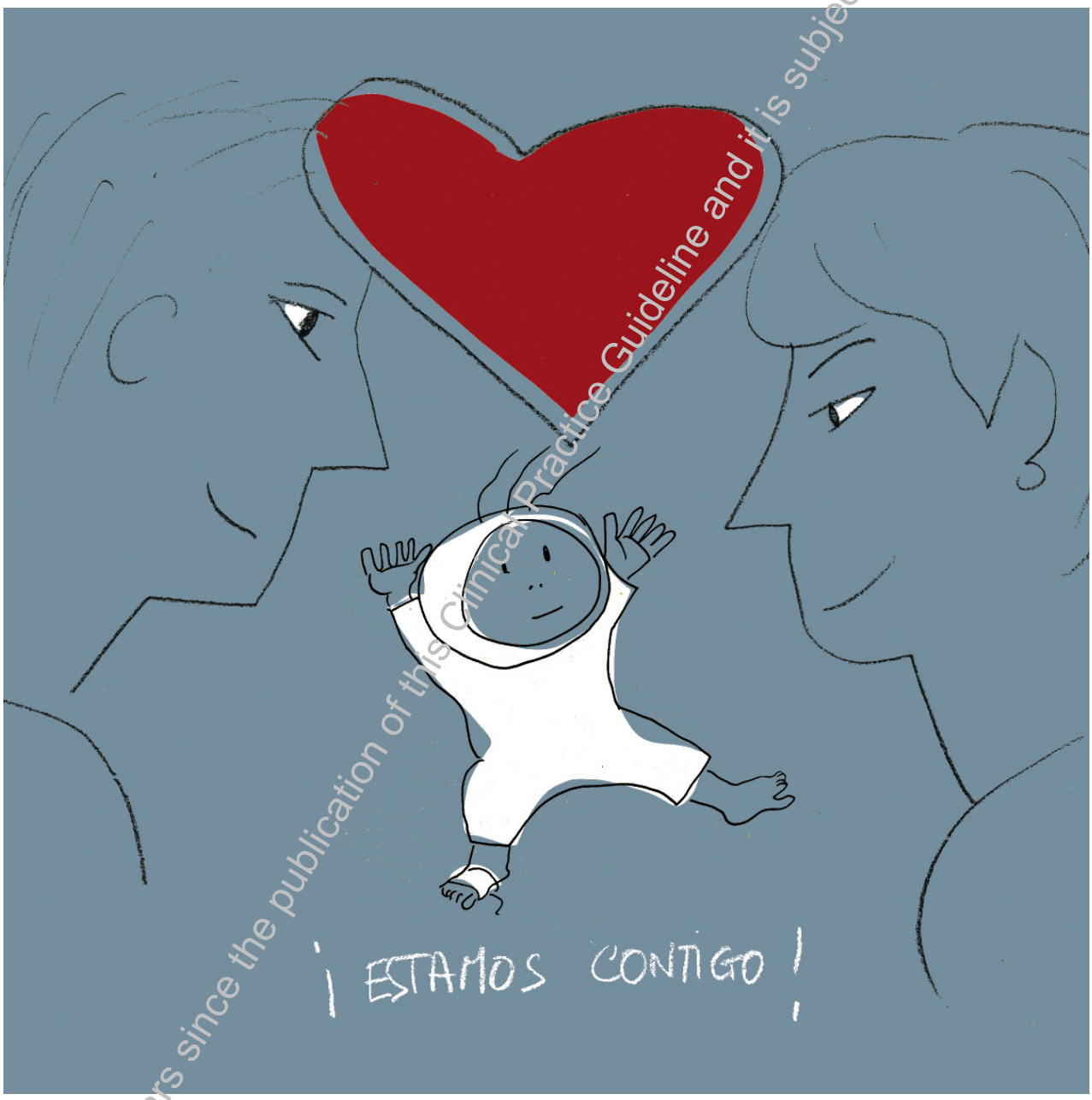
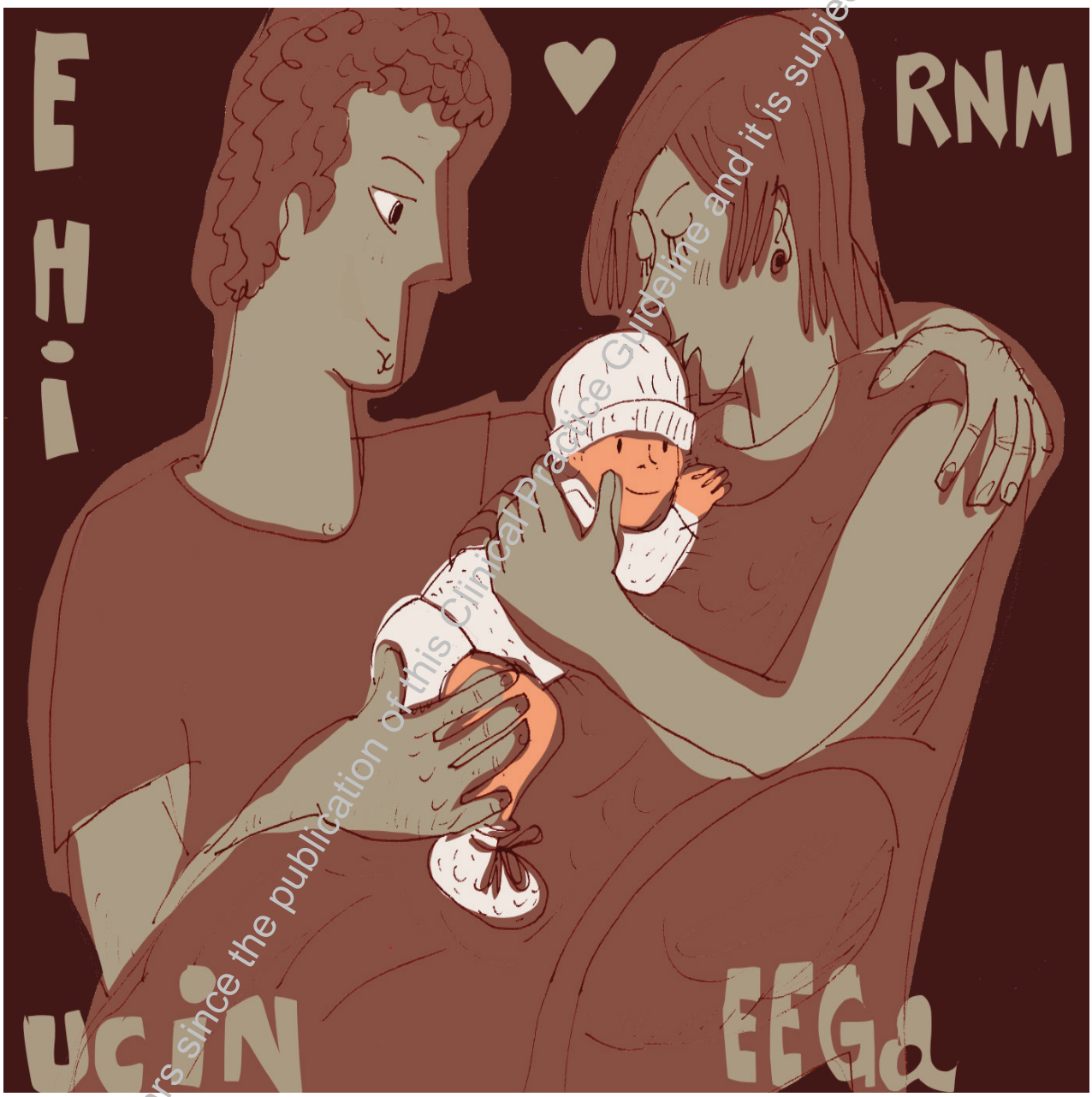


We're here for you!



- HIE - NMR - NICU aEEG

"You wish you had information; I wanted to know more."

"They tell you that your child is in hypothermia,
but you really don't know what it is."

"What I liked the most was all the happiness in there."

"The treatment was very caring,
it was really like being with family, and that helped too".

PROLOGUE AND INTRODUCTION

ABCs OF HYPOXIC-ISCHAEMIC ENCEPHALOPATHY

What is hypoxic-ischaemic encephalopathy?
How are the manifestations of HIE?
What could be the causes of HIE? Who form a part of the team taking care of the newborn? What happens during the first hours and days?
What information do we receive those first days?

TREATMENT AND CURES

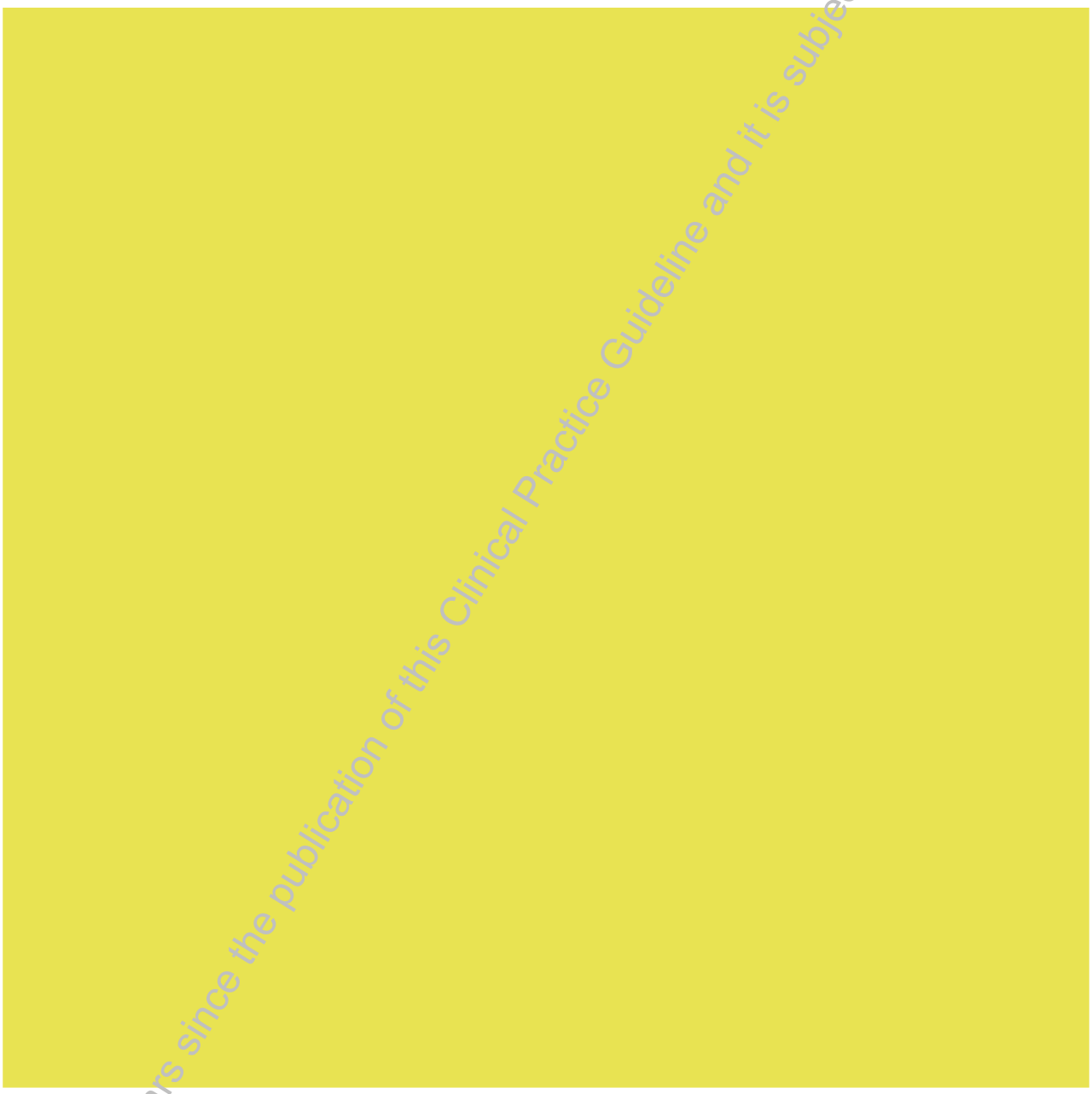
What is therapeutic hypothermia?
When could therapeutic hypothermia be necessary?
How is the temperature of a newborn decreased?
What other equipment is needed for a newborn for treatment with hypothermia?
Does the baby feel pain when in hypothermia? Where can hypothermia be applied? How is a baby moved urgently?

OUTCOME AND ASSISTANCE

What sequelae could be involved with hypoxic-ischaemic encephalopathy?
What happens when hypothermia treatment cannot help a baby?
What could help parents to face the difficult moments?

From A to Z

Adaptation of therapeutic effort; Enteral feeding; Oral feeding; Parenteral feeding; Analgesics; Antibiotics; Anticonvulsants; Early care; Catheter/access; Umbilical catheter; Informed consent; Vital signs; Convulsions; Brain ultrasound; Doppler ultrasound; Amplitude-integrated electroencephalography; Hypoxic-ischaemic encephalopathy; Cooling equipment; Team of care professionals; Scale for assessing hypertensive encephalopathy; Transport incubator; Inotropics; Cerebrospinal fluid; Brain metabolism; Cardiorespiratory monitoring; Nursery; Cerebral palsy; Lumbar puncture; Rewarming; Magnetic resonance; Respirator; Oximeter; Sedatives; Nasogastric tube; Urethral catheter; Decision-making; Muscle tone; Hypothermia treatment; Disproportionate treatment; Neonatal Intensive Care Unit (NICU)



PROLOGUE AND INTRODUCTION

Prologue

The aim of this guide for mothers and fathers of newborns with hypoxic-ischaemic encephalopathy (HIE) is to respond to the information and support needs of families while their child is hospitalised. Making them more familiar with the environment, the professionals and the care that their child is receiving could help them to better understand what is happening during the first days of hospitalisation. This guide is the result of the teamwork of a group of professionals from different disciplines and of the experiences of parents of newborns with HIE.

We hope that it might help you at these difficult times.

Clinical coordinator.
In representation of the Development Group of the Clinical Practice Guidelines on Perinatal Hypoxic-Ischaemic Encephalopathy in Newborns

Introduction for the parents

Perinatal hypoxic-ischaemic encephalopathy (HIE) is a major cause of mortality in the neonatal period and of permanent disability, and in Spain it affects one out every one thousand live newborns. Therapeutic hypothermia is an effective and safe treatment for decreasing the mortality and disability of newborns with moderate/severe HIE, and it is currently the standard treatment.

Your newborn child has an HIE, and the child is in the neonatal intensive care unit to receive treatment with therapeutic hypothermia. It is an unexpected and difficult situation, and everything happens very quickly: urgently admitting the baby, the severity of the situation, the invasive procedures, the decisions, the uncertainty due to the prognosis and what is going to happen...

With this guide, we'd like to smooth the way and provide you with information through the voices of parents who have experienced this same situation and have faced moments, questions and doubts similar to yours.

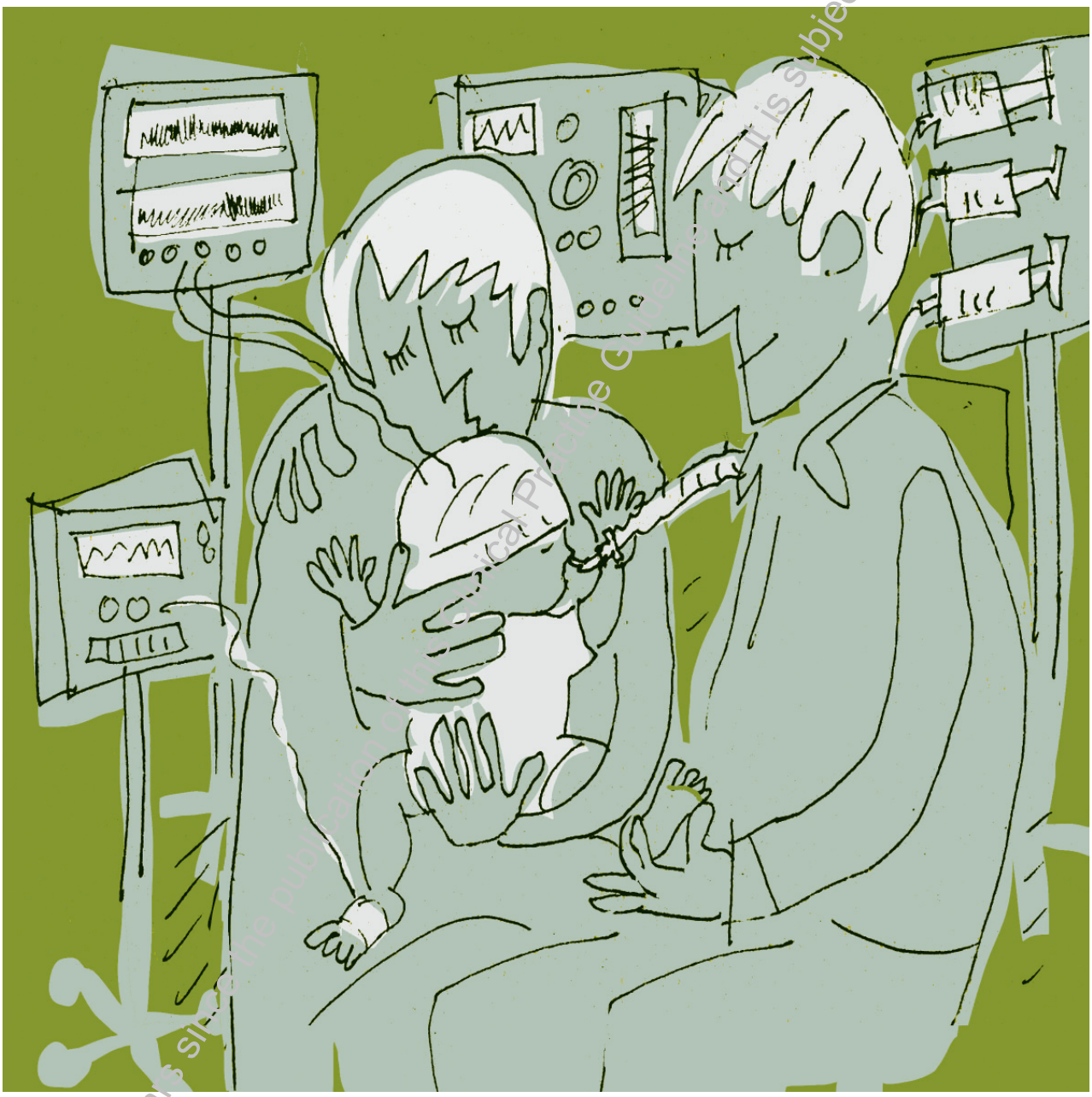
The guide is written in a simple style, and it is divided into four sections that are differentiated by colours.

The green-coloured pages help you to know what has happened to your baby; the maroon-coloured pages help you to understand what is helping your baby; and the orange pages help to better understand the present and the near future. The blue-coloured pages include explanations of the words that may be difficult to understand.

To conclude, we'd like to express our profound thanks to the families who, selflessly, have shared with us their experiences of having their children in the hospital, without which this guide would not have been possible.

Also, our gratitude to Dr Xavier Krauel for his artistic sensitivity in capturing the complexity and emotional world of families and in bringing it all together in the drawings that illustrate this guide. To Carlos Alaez, for his careful photography work, which made it easier for parents to talk about situations that are not always simple. And to Sara Pareja and her daughter Berta for their professionalism and commitment to designing and laying out the best of possible guides

Verónica Violant and Nuria Herranz



ABCs of
HYPOXIC-ISCHAEMIC ENCEPHALOPATHY

What is hypoxic-ischaemic encephalopathy?

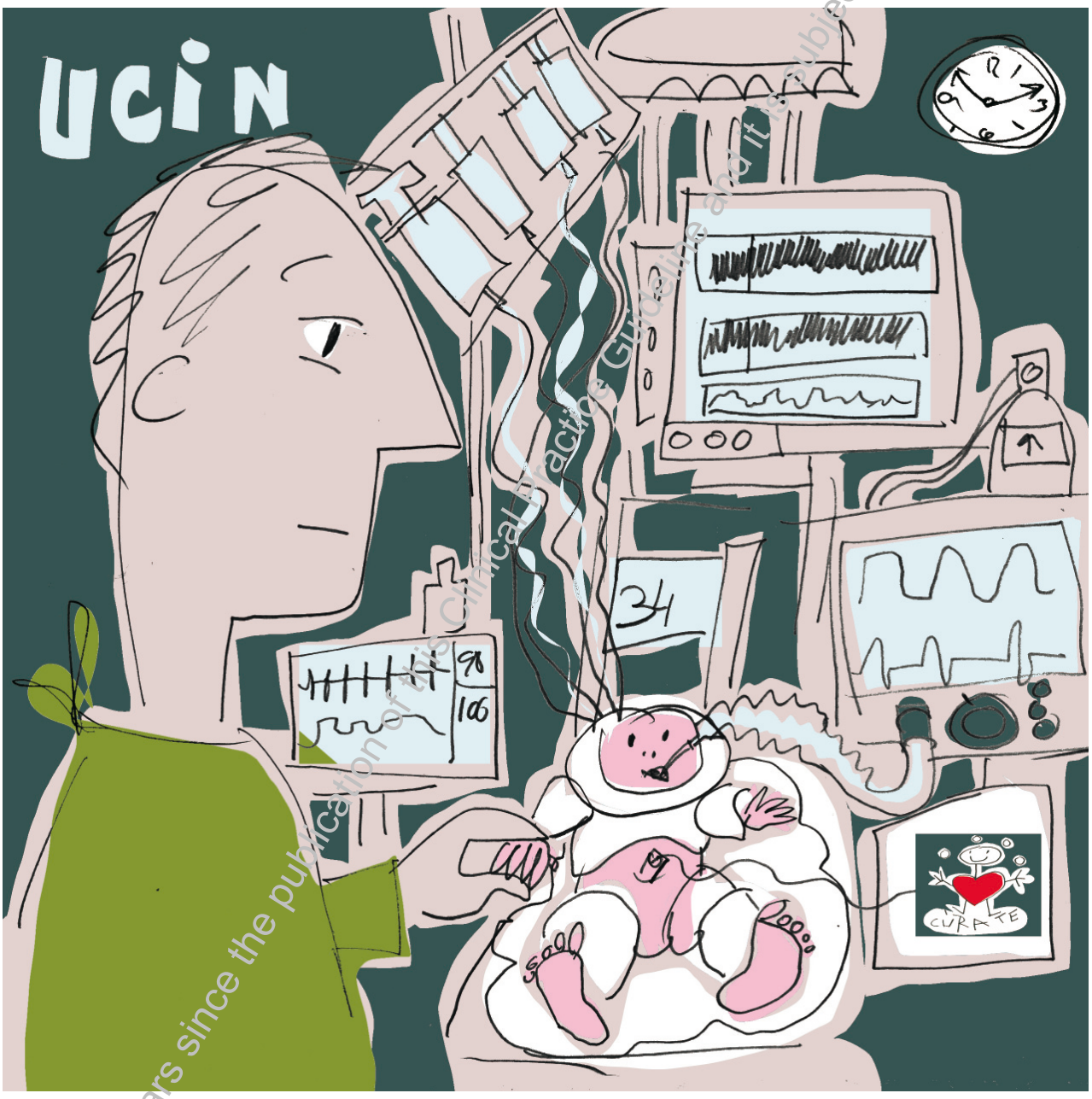
Hypoxic-ischaemic encephalopathy (HIE) is the clinical state that results from a lack of oxygen and blood in the brain immediately after or during birth. Depending on the intensity of this deficiency, it can also cause damage to other internal organs such as the heart, kidneys, liver and intestines.

How is HIE manifested?

HIE is manifested through a series of alterations that are observable in a newborn, such as: a lower ability to wake up and stay awake, an alteration of the *muscle tone* and posture, a low level of response to stimuli and, frequently, the appearance of convulsions. Based on these signs, it is graduated as mild, moderate or severe.

What could be the causes of HIE?

Any situation that might cause an interruption of the flow of blood and oxygen to the foetus. This could happen for several reasons: an anomalous passage of blood between the mother and the foetus, a detachment of the placenta, considerable compression of the umbilical cord or even a rupture of the uterus. But frequently, the cause of this deficit is never known for certain.



Why?

Placenta - Oxygen flow - Perfusion - Foetal well-being - bradycardia - Umbilical cord - Hypoxia-Ischaemia

Who form a part of the team taking care of the newborn?

The baby and the family receive care from various professionals at the same time (neonatologists, nurses, nursing assistants, neurologists, psychologists and early care specialists). They make up the team of professionals who take care of the newborn and work in continuous collaboration among themselves and with the family. This allows the best health results to be achieved, for both the newborn and the family

What happens during the first hours and days?

Many things happen in those first hours

Parents will be informed about the clinical situation of their baby and about the need to begin hypothermia treatment, and they must occasionally authorise an urgent move of the baby to another hospital.

Once treatment has begun, it is maintained for the next 72 hours. The newborn will remain in the same environment, where regular checks will be made and the necessary care will be given to ensure maximum stability. The information obtained from these procedures helps professionals to assess the situation of the newbornand to adapt the treatment to their needs.

After 72 hours have elapsed, the temperature of

"since it was my husband who was getting information from the doctors. I was in my room, because I was feeling down..."

"With the information we received, the truth is we felt more relaxed"

"They tell you that the baby is in hypothermia, but you really don't know what it is"

"You'd like to have information; I wanted to know more"

"I was never really clear about what this illness is; in other words, the starting point of everything that happened"

"Apart from the explanations, if you didn't understand something, they'd explain it to you again; sometimes I'd get lost with the technical terms"

"But here I'm the mother, I'm the father"

"I wanted to know what the problem is with my son and what exactly do I do with him right?"

the newborn will be increased slowly (0.5° C per hour) until the normal temperature of 36.5-37° C is reached. This procedure (known as *rewarming*) has an estimated duration of approximately 6 hours.

The first days involve the most stress, and at some point, if the father and mother are separated due to being at different hospitals, they can feel all alone. If this happens, sharing the process with someone you trust and/or with the team of professionals might help you to feel more assured.

What information do we receive those first days?

In general, there are three types of important information:

- During the first hours, a clinical evaluation of the neurological state and of the electrical activity of the brain is conducted *(amplitude-integrated electroencephalography, aEEG)*. Based on this evaluation, it is decided whether or not to apply *hypothermia treatment*.
- Over the next 72 hours, monitoring of the brain's electrical activity using the amplitude-integrated electroencephalography (aEEG) continues. Imaging studies (transcranial doppler ultrasound) and, occasionally, an analysis of the cerebral spinal fluid, obtained by a lumbar puncture, allow parents to be provided with information about the baby's level of severity.

- At one week of life, a brain imaging test is usually taken, which is called a magnetic resonance image, and it allows having more information about whether or not there is brain damage and, if there is any damage, information about the extent and severity.

During these first few days, parents and family could be overwhelmed and be overcome by various feelings at the same time, as if they were on an emotional roller coaster: anxiety, fear, ambivalence, happiness, confusion, incomprehension, uncertainty, tranquillity, rage, frustration, thanks and distrust, among others.

TREATMENT AND CARE

What is therapeutic hypothermia?

It is treatment that consists in decreasing the body temperature of a newborn down to 33-34° C, for the purpose of lower the brain metabolism. It has been proved that this therapeutic intervention improves the possibilities that a newborn will not have injuries and increases the probability that a newborn will survive without a disability.

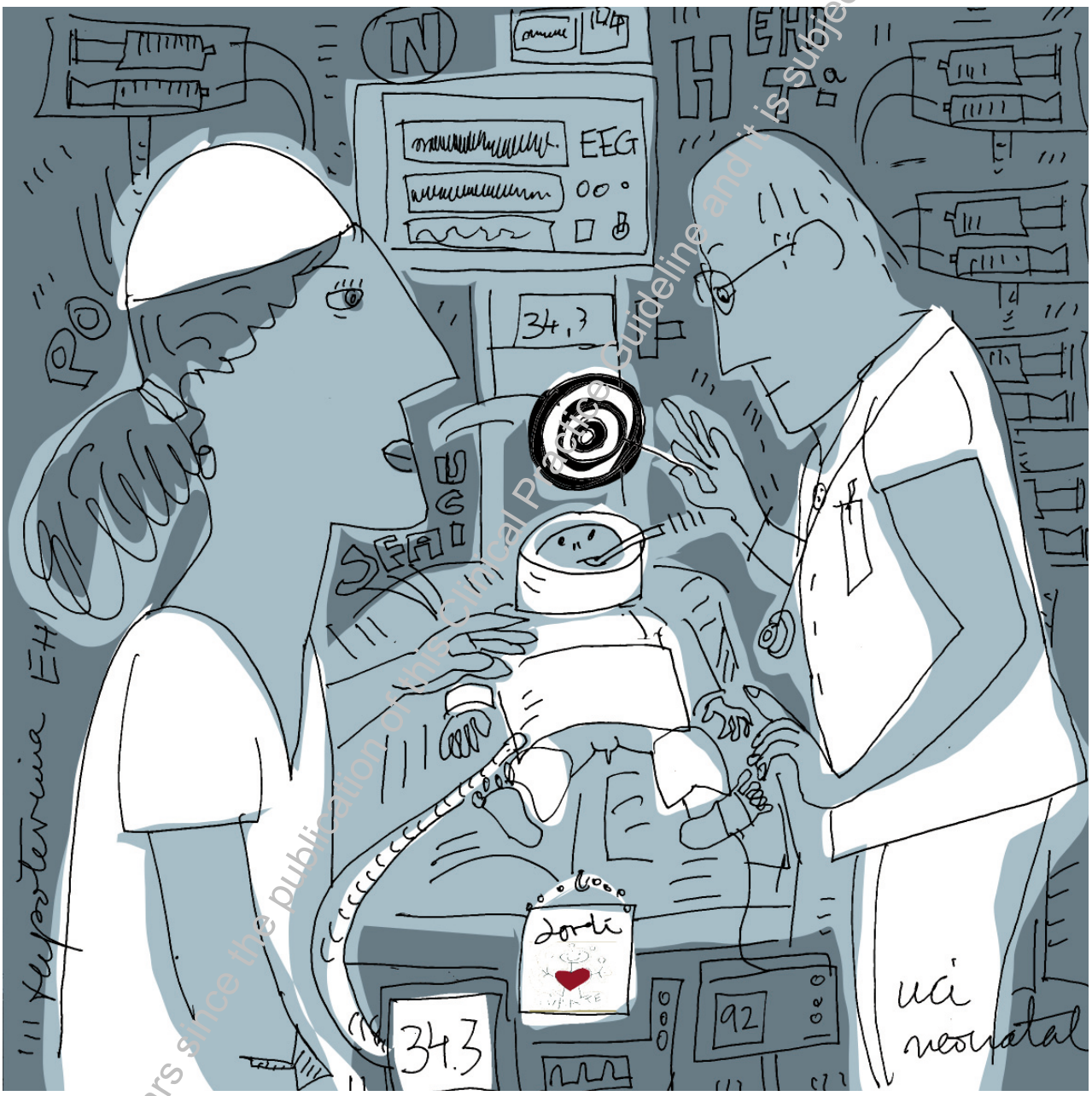
When could therapeutic hypothermia be necessary?

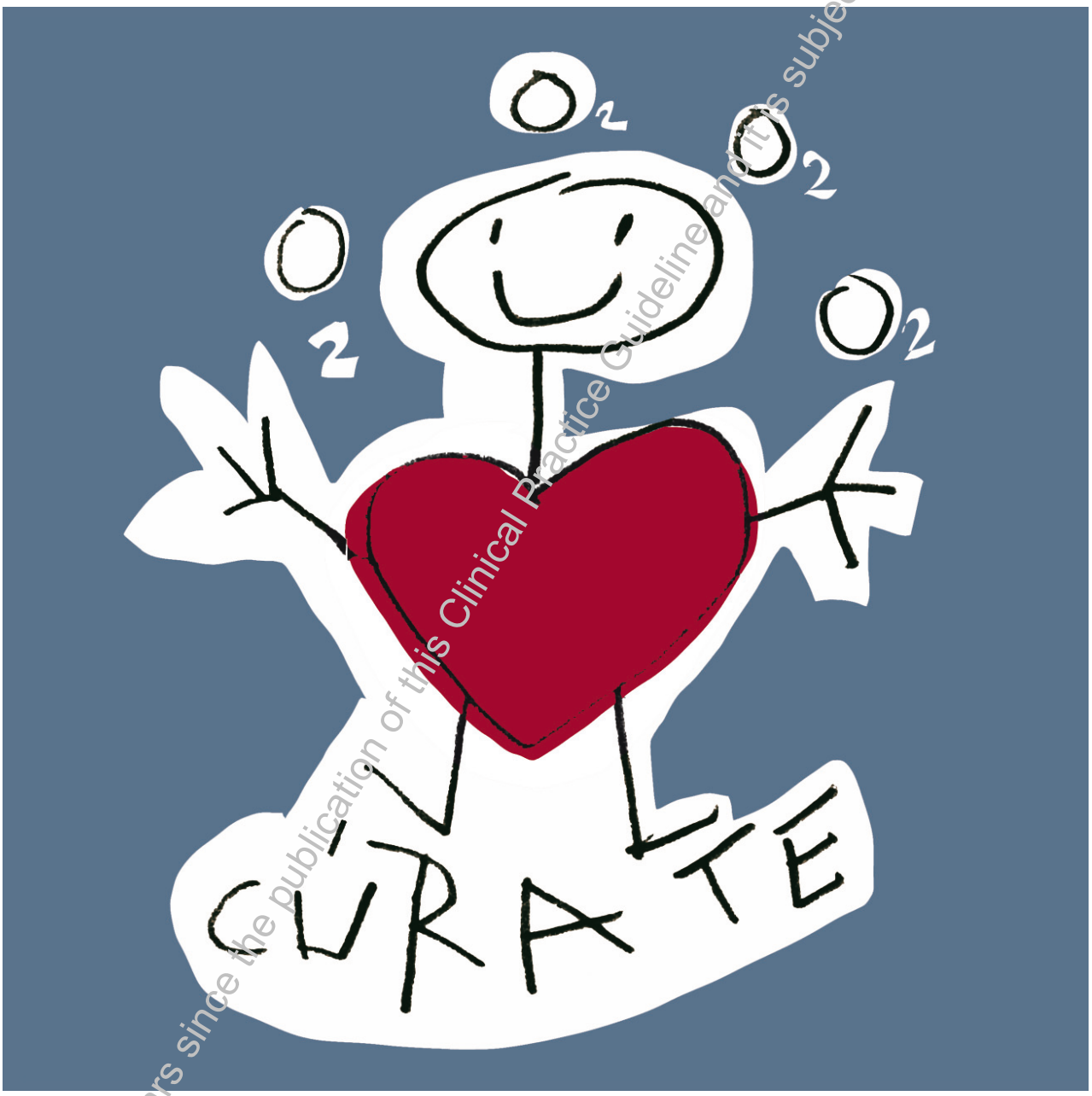
Soon after birth, in the first hours of life, if the newborn shows signs of hypoxic-ischaemic encephalopathy, the medical team will begin hypothermia treatment. This decision is made based on the baby's neurological state and the electrical activity of the brain.

How is the temperature of a newborn decreased?

There are several ways of decreasing the temperature of the newborn. They are all effective, and the application of one or the other depends on the equipment at each neonatal intensive care unit (NICU). All equipment works by circulating a cool liquid around the body or the head. The systems available at hospitals are the following:

- A special suit that envelops the body of the newborn
- A special mattress where the newborn lies down
- A special helmet placed on their head





Get better

What other equipment is required for treating a newborn with hypothermia?

In addition to the cooling equipment, the newborn needs to be closely monitored during the hypothermia period in the neonatal intensive care unit (NICU). They are surrounded by devices, cables and catheters. Some devices provide information about the vital signs (heart rate, blood pressure and oxygen saturation), and others help the newborn with breathing, hydration, nutrition and eliminating urine.

This information is needed, because the lack of oxygen or blood can not only affect the brain, but also other organs. On the other hand, in order to have more information about the electrical activity of the baby's brain, during the first 72 hours of life some very small needles are placed underneath the skin of the head, which are connected to a monitor called an amplitude-integrated electroencephalography (aEEG).

The equipment surrounding the newborn is very bulky and takes up a lot of the surrounding space. So much so that it can be hard for parents to see their baby this way, and it could cause feelings such as shock, anxiety, uncertainty, detachment, incomprehension, frustration, suffering displeasure, fear, vulnerability, distrust and inability to provide care. Sharing these feelings with close friends and/or with the professionals who are taking care of you will help to put a name to those feelings and thoughts and put them into perspective. The professionals are

"I saw him with all those electrodes on his head, over his whole body, everything with tubes: it leaves an impression, and I got a bit dizzy. I went up to my room, I relaxed and then I went back down"

"It hurt to see her that way, but what can you do?"

"She's suffering, and you're there (crying) and you think: but what do I do?"

"The image you hoped to see of your daughter isn't pretty: so many wires... above all the number of devices, all those little lights..."

"When a normal baby is born, the first thing you do is hug him, and nowhere's this baby with tubes, needles, wounds, sores, and you think..."

"Sleeping there. In the morning I come here and my two children who were at home are with my brother, since I'm alone"

the ones who can advise you the best and help you to understand everything about the baby and what it needs. "Don't hesitate to ask questions and clear up your doubts, and be sure that you have a good understanding of all the information".

Does the baby feel pain when in hypothermia?

During *hypothermia treatment*, as parents, feeling that your baby could be experiencing pain due to the cold, the equipment, the procedures or the care that he is receiving could be a source of stress.

Even through lowering the body temperature of the baby could cause discomfort, the baby receives a minimum dose of continuous *sedation* to favour the baby's comfort. The newborn is also placed in a *"cot"* so that their body feels protected and safe. The equipment does not cause pain, and it serves to monitor the brain's electrical activity and the *vital signs*.Painful or uncomfortable procedures and care are always performed with the administration of small doses of analgesics and sedatives to prevent and treat pain and favour comfort. During these procedures, if you wish and if the professionals think that it's appropriate, you can be with the baby, and you can participate in some simple treatment and hold their body (placing one hand on their head and the other on their flexed legs) to make them feel safe.

Where can hypothermia be applied?

This treatment is only carried out in NICUs that are qualified to provide this treatment, because they have both the cooling equipment and the monitoring equipment, as well as professionals trained on the comprehensive care of newborns with HIE.

When a hospital does not have this programme, the newborn is urgently moved to a qualified centre so that treatment can be initiated as soon as possible.

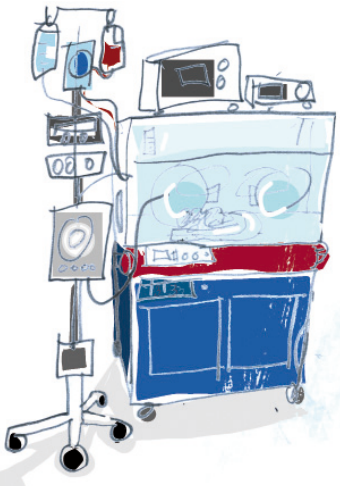
How is a baby moved urgently?

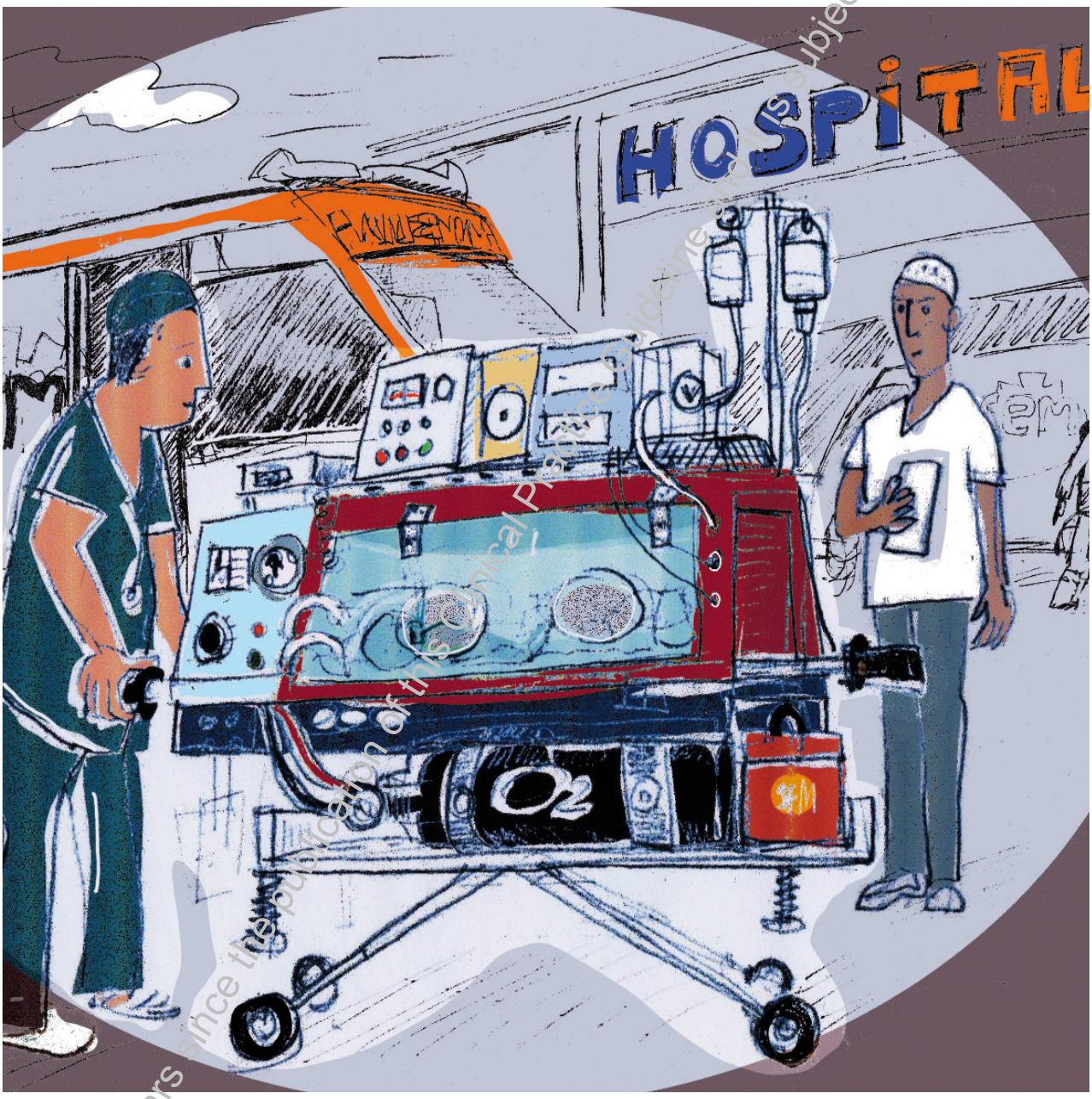
An urgent move assures that hypothermia treatment can begin in the first hours of life. Transport takes place under the control of a team of professionals who are specialised in transporting newborns. They begin passive hypothermia, which consists in getting the newborn to reach a temperature of 33-34° C by removing external sources of heat.In general, a baby is transferred by ambulance or helicopter without being accompanied by the parents. This means temporary separation from the baby, particularly if the mother remains admitted in the hospital where she gave birth. This situation can leave parents stunned. Externalising your thoughts and talking about it with someone you trust can help to clarify ideas and calm your nerves.

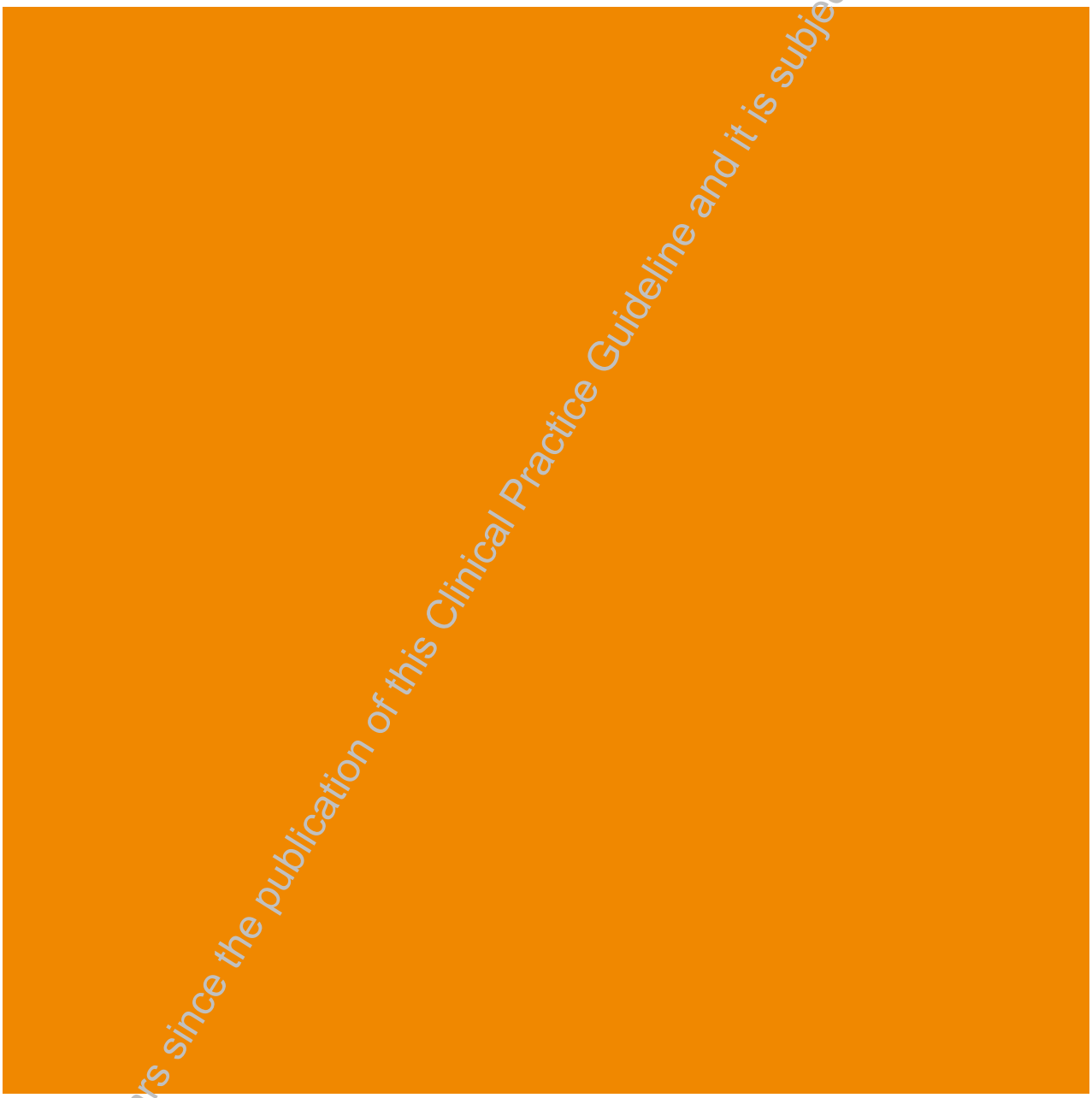
If the mother's health condition allows, professionals will assess the possibility of moving her to the hospital where the baby is. If it were not possible to move her, it is important for her to be accompanied by close friends or relatives.

If possible, having a photo of your baby will help to:

- Feel close to your child
- Stay rooted in reality
- Come up with questions that shared with professionals, will help emotionally and will prepare you for the encounter with the baby
- Share the situation with other children and/or close relatives.







OUTCOME AND ASSISTANCE

What sequelae could be involved with hypoxic-ischaemic encephalopathy?

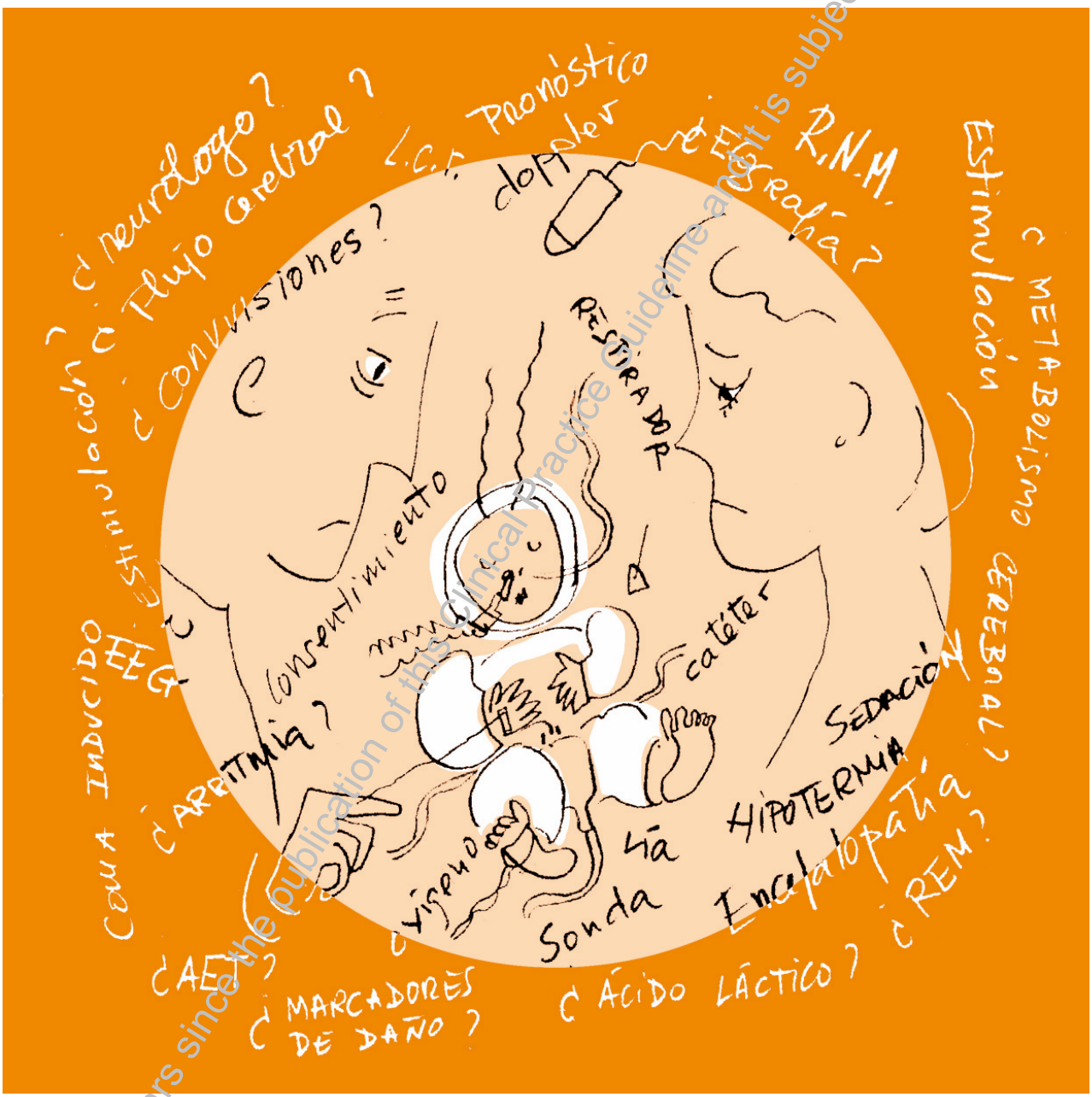
When the brain damage is severe, the baby could have movement, communication and learning disorders during childhood, in addition to eating difficulties or epilepsy. Movement and posture problems are frequently called cerebral palsy. This term indicates a

motor disorder. It can be mild or even affect the movement possibilities of a person. But the actual scope is difficult to predict when a baby is very small. The professionals who are taking care of the newborn will progressively provide you with information.

What happens when hypothermia treatment cannot help a baby?

Occasionally, the clinical condition of the newborn is so severe that it prevents applying or completing the hypothermia treatment, given that problems that threaten the baby's life are aggravated. This occurs particularly when there is very severe pulmonary hypertension or when the baby has a tendency to bleed and does not respond to treatment to prevent it.

Occasionally, either during or immediately after hypothermia treatment, the clinical data and imaging studies allow seeing that the baby has extensive and irreparable brain damage, with serious consequences for their future life. When this happens, the healthcare team will provide the family with a detailed explanation of the baby's condition and the possible consequences of this damage. If this is the case, the professionals and the parents can make a joint decision about not continuing with disproportionate treatment that does not provide the baby with any benefit and effectively prolongs their sufferingand the family's. This situation, within decision-making, is called adaptation of the therapeutic effort.



Neurologist? - Cerebral circulation? - CSF? - Prognosis - Doppler - Echography? - NMR - Stimulation? - Convulsions? - Respirator - Brain metabolism? - Consent - Sedation - Catheter - Arrhythmia? - Induced coma - Oxygen - IV line - Hypothermia - Encephalopathy - AET? - Injury markers? - Lactic acid? - REM?

Hypothermia

In these circumstances, when the end of the baby's life is near, all the efforts of the professional team are focused on preventing pain and ensuring the baby's comfort and providing individualised support for the family. In this situation, it is important to feel that the way in which we say goodbye to our child is how we really want it. The professionals will provide us with the resources and the necessary support to do so.

What strategies can help parents to face the difficult moments?

In general, the strategies that can help parents at the difficult moments throughout the process are:

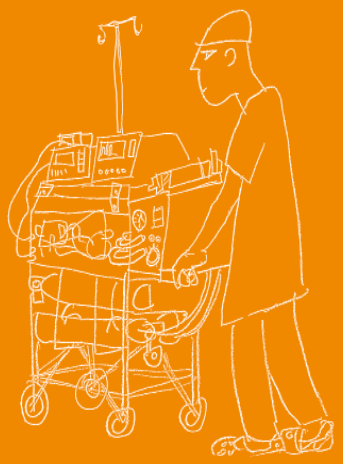
- Ensure that all the necessary information is available and that it is understood and that there is the opportunity to share it, if you wish, either with the professionals, with other parents who are experiencing a similar situation or with people who are close to you.
- Recognising that you are competent to be parents; "I feel capable of making decisions, of caring for, protecting and loving my baby".
- Being aware of the benefit that comes from feeling accompanied by family or friends. It can help to be with someone close when you are in situations that are new and/or difficult, such as: seeing our baby for the first time with hypothermia treatment, receiving critical information, facing a complex decision.

"What helped me the most personally was being able to talk with family, with friends... talking, talking..."

"What I liked the most was the happiness in there"

"Sometimes they took off the wires, because I was breastfeeding, like on the fourth day, and that feeling of holding her, loving her a little..."

"I felt that things weren't going well, in the incubator with the hypothermia, and I thought it was...well, between life and death, nothing else"



"It is essential to have the people you love very close by"

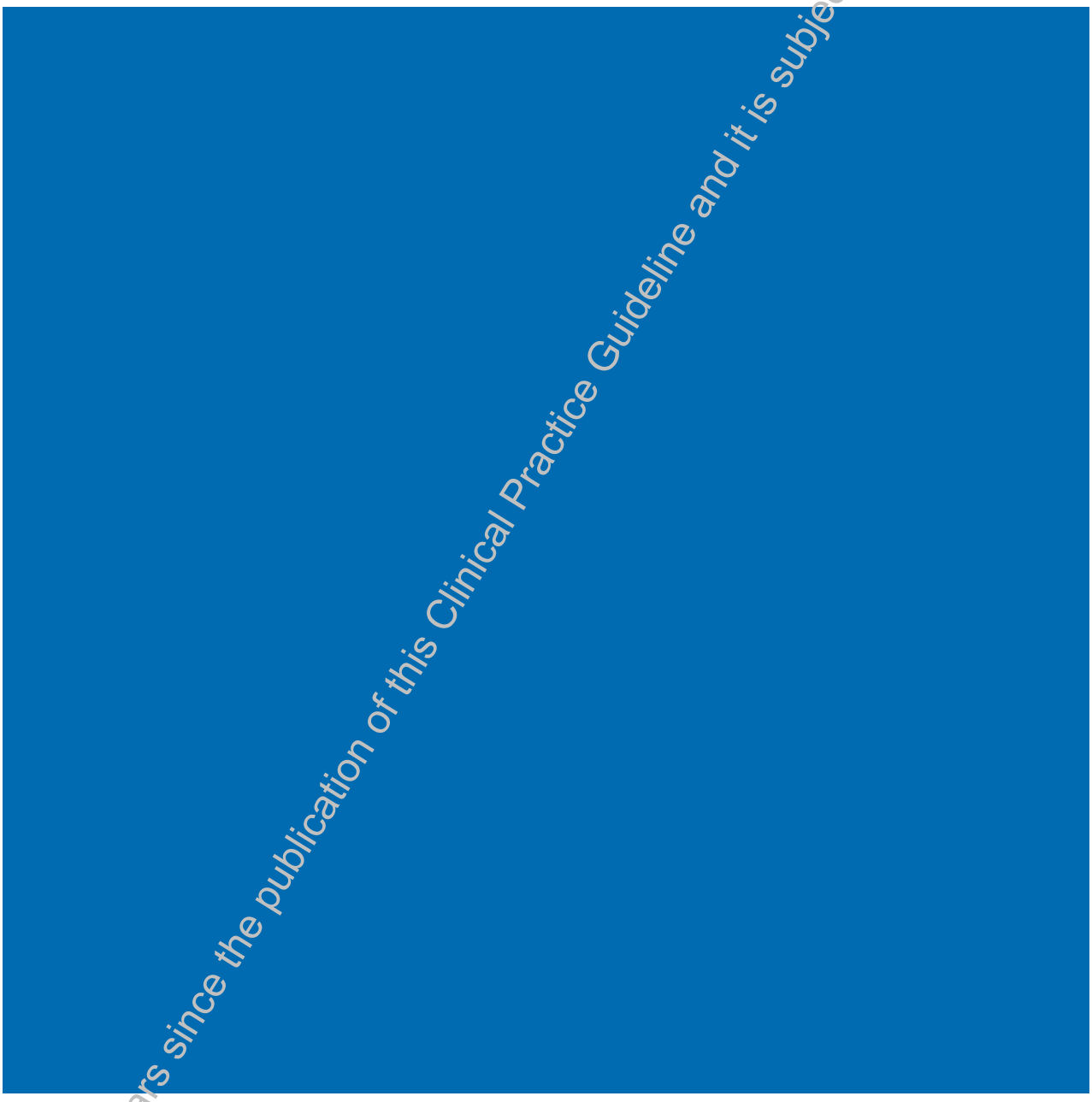
"It helped me... at the moment when you can hold him and change his diaper..."

"... The peace of mind and trust that we felt from the doctor..."

- During this time, you could have a number ofnegative sensations and feelings, which could be because you thought that you'd receive more support and understanding. It could help to try to look at things another way: try to put your expectations in order and also try to relax when you feel overcome by all these sensations and feelings.
- Knowing and using other resources can help in this situation. For example, those offered by the hospital (open access of the unit 24 hours a day; professionals such as psychologists, social workers and parental groups; spiritual services; associations and foundations), as well as other, outside resources (assistance therapy, community care services offered by a neighbourhood, etc.).
- Feeling that I provide care and that I take care of myself.

I provide care: by being with my baby; by participating in the care he receives; by pumping breast milk so that he can feed; by showing him my affection through the physical contact that my baby can tolerate; by providing a warm and personal environment around the baby through drawings of a brother or sister, a toy or some clothes; by informing my partner when he can't receive information first hand (information that generates security and trust).

I take care of myself: through feeling that other children are cared for and taken care of by me, by my partner or by people we trust; by staying well fed and hydrated; by resting the necessary number of hours; by sharing time together; by taking a few minutes for myself; by giving myself a brake during the time I'm in the unit, such as taking a short walk around the hospital or sitting outside to get some sun; by feeling that by taking care of myself, I am also taking care of my baby.



From A to Z

Adaptation of therapeutic effort

This involves the decision made jointly between the parents and the professionals to not apply or to remove any treatment due to considering that it will not provide any significant benefit to the newborn, and despite this, it could facilitate the newborn's natural approach to the end of life.

Enteral feeding

Milk feeding (mother's or bottled) that is fed to a newborn through a nasogastric or orogastric tube, which reaches the stomach directly.

Oral feeding

Milk feeding (mother's or bottled) that is ingested by a newborn directly from the mother's breast or through a bottle.

Parenteral feeding

Food consisting of proteins, hydrates, salts and fats that are given to a newborn through an intravenous line, thus reaching the blood directly. This procedure is used when a newborn cannot be fed through an enteral line.

Analgesics

They are medicines that prevent and treat pain.

Antibiotics

They are medicines used to prevent and/or fight infections caused by bacteria germs.

Anticonvulsants

They are medicines that prevent or limit the convulsions that can appear together with moderate or severe HIE.

Early care (or early stimulation)

It is the set of interventions targeted at the child population from 0-6 years of age, the family and the surrounding environment. These interventions respond as early as possible to the

temporary or permanent needs presented by children who have developmental disorders or who are at risk of suffering from such disorders.

Catheter/IV line

It is a thin, flexible and soft tube that is inserted in the veins of the arms and legs.

Umbilical catheter

It is a catheter that allows obtaining blood for analysis or introducing medicines without having to use a hypodermic needle on a newborn. This tube is inserted in the arteries or veins of the umbilical cord of a newborn baby.

Informed consent

This is a medical-legal document that explains the risks involved in the procedures that are going to be carried out on a newborn, which can range from surgery to

a complementary exam. This document is signed jointly by the parents and the medical care team that is taking care of the baby.

Vital signs

They include measurements of the heart rate, respiration rate, temperature and blood pressure.

Convulsions

They are uncontrolled movements manifested by the baby due to anomalous electrical discharges emitted by the brain. Their presence is an indicator of brain alteration, but they do not necessarily indicate that there is permanent brain damage.

Brain ultrasound

It is a test that visualises the baby's brain through an image. It is performed by the intensive care unit, thereby preventing the baby from having to be moved. It does not require sedation or any added monitoring, and the ultrasounds that are used do not cause any secondary effect for the newborn. Brain ultrasound uses the same ultrasound technology used on women when they are pregnant, in which the future newborn is observed through the abdomen. Visualisation of the brain using ultrasound is done through the anterior fontanelle (a zone

where the sutures of the skull come together and leave a gap without bone, which is a true window for accessing the interior), although if necessary, other fontanelles can be used.

Doppler ultrasound

It is a variety of ultrasound echography that measures the speed of the blood in the cerebral arteries.

Amplitude-integrated electroencephalography (aEEG)

It is a continuous record of the electrical activity of the cerebral cortex. It is also called the "brain function monitor", because it provides information about functional aspects of the bran and provides clues to the severity of injury, if there is any.

Hypoxic-ischaemic encephalopathy (HIE)

The clinical state that results from a lack of oxygen and blood in the brain immediatelyafter or during birth. Depending on the intensity of this deficiency, it can also cause damage to other internal organs such as the heart, kidneys, liver and intestines.

Cooling equipment

It is the technical equipment that allows reducing and maintaining the temperature of a newborn at 33.5-34° C and subsequently increasing it up to 36.5-37° C.

Team of care professionals

This is the group of professionals of various disciplines (neonatologists, nurses, nursing assistants, neurologists, psychologists, early care, etc.) who take care of the baby and their family.

Scales for evaluating encephalopathy

These scales allow assessing the severity of the encephalopathy by evaluating different signs, such as the ability to wake up and stay awake, alteration of the muscle tone and posture, response of the newborn to stimuli and the appearance of convulsions.

Hypotonia

This is a decrease of normal muscle tone. It is a characteristic of a newborn with hypoxic-ischaemic encephalopathy.

Transport incubator

It is a crib with a transparent cover that is used to move a newborn in isolation while guaranteeing heat and humidity, as needed. It can supply oxygen and mechanical ventilation (respirator) during the entire trip. Thus, it assures the best conditions for a newborn during a trip.

Inotropics

These medicines are administered to a newborn to help the heart pump blood more efficiently through the whole body.

Cerebrospinal fluid

This liquid bathes the brain and the spinal cord, and it serves, among other functions, to protect the brain, help eliminate its waste and maintain the intracranial pressure.

Brain metabolism

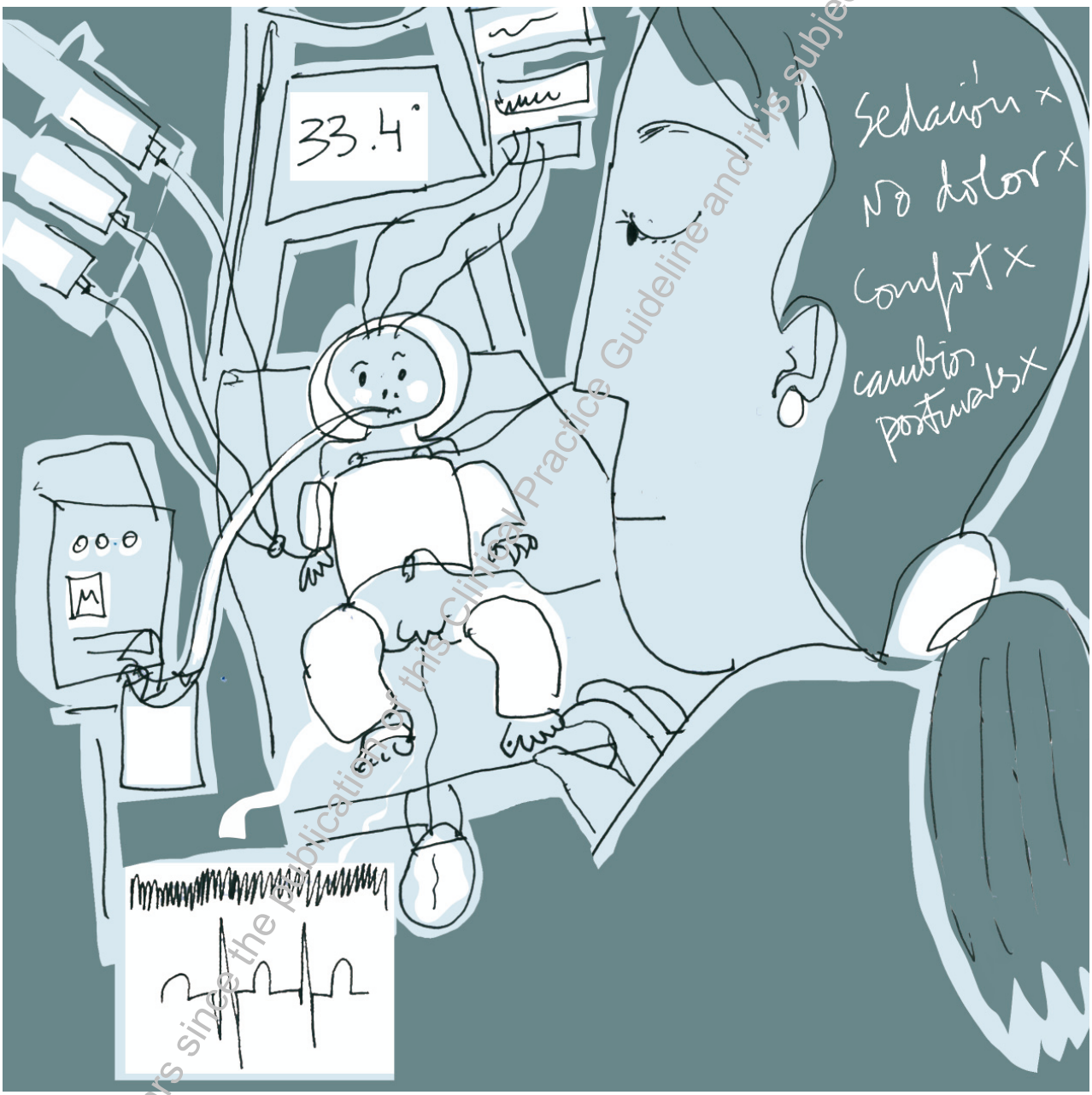
This is the set of biochemical reactions that fundamentally use oxygen and glucose and that allow the brain to perform its functions.

Cardiorespiratory monitoring

This procedure records the heart rate and the breathing rate through the application of adhesive sensors placed on the thorax of a newborn.

Nest

A circular and flexible role formed by towels and sheets, which we place around the body of a baby to help contain them and thus make them comfortable and feel safe.



Sedation - No pain - Comfort - Position changes

Cerebral palsy

A chronic motor disorder that, to varying degrees, affects the capacity to move, to maintain posture and/or to walk. Sometimes it is also accompanied by problems with learning, communication, perception and sometimes behaviour.

Lumbar puncture

A procedure that consists in introducing a special needle in the lumbar vertebral zone to obtain a small sample of cerebral spinal fluid to be analysed.

Rewarming

An action that consists in slowly rewarming a baby up to normal body temperature (36.5-37° C). The hypothermia equipment itself is used to perform this action.

Magnetic resonance

A diagnostic procedure that allows obtaining high-quality images of the brain in multiple planes. It also allows visualising some aspects of its functionality. It is a test that does not emit radiations, such as with X-rays or computerised axial tomography (CAT), but it requires that the newborn remain absolutely still for a few minutes, wherefore, to guarantee a good study, it is frequently necessary to give sedation.

Respirator

It is a device that provides air and oxygen to the lungs of a newborn when they cannot breath on their own.

Oximeter

A monitor that reports the heart rate and the oxygenation of the blood through a sensor, generally adhesive, which is placed on the toes and/or fingers. The maximum possible saturation value is 100%, although it could fluctuate, and there could be lower values.

Sedatives

They are medicines that have a tranquillising effect. Nasogastric/orogastric tube It is a silicone tube that is inserted through the nose or mouth of a newborn and reaches the stomach to provide food.

Urethral catheter

It is a very thin, flexible tube that is inserted through the urethra (which is the duct between the bladder and the exterior) to facilitate the elimination of a newborn's urine and allow collection and measurement of the urine.

Decision-making

It is the moment when we have to decide on the treatment and/or tests that are going to continue being conducted on a newborn. Sometimes making a decision is accompanied by the informed consent form.

Muscle tone

It is the tension of the muscle, which can range from very rigid (hypertonia) to very flaccid (hypotonia).

Hypothermia treatment

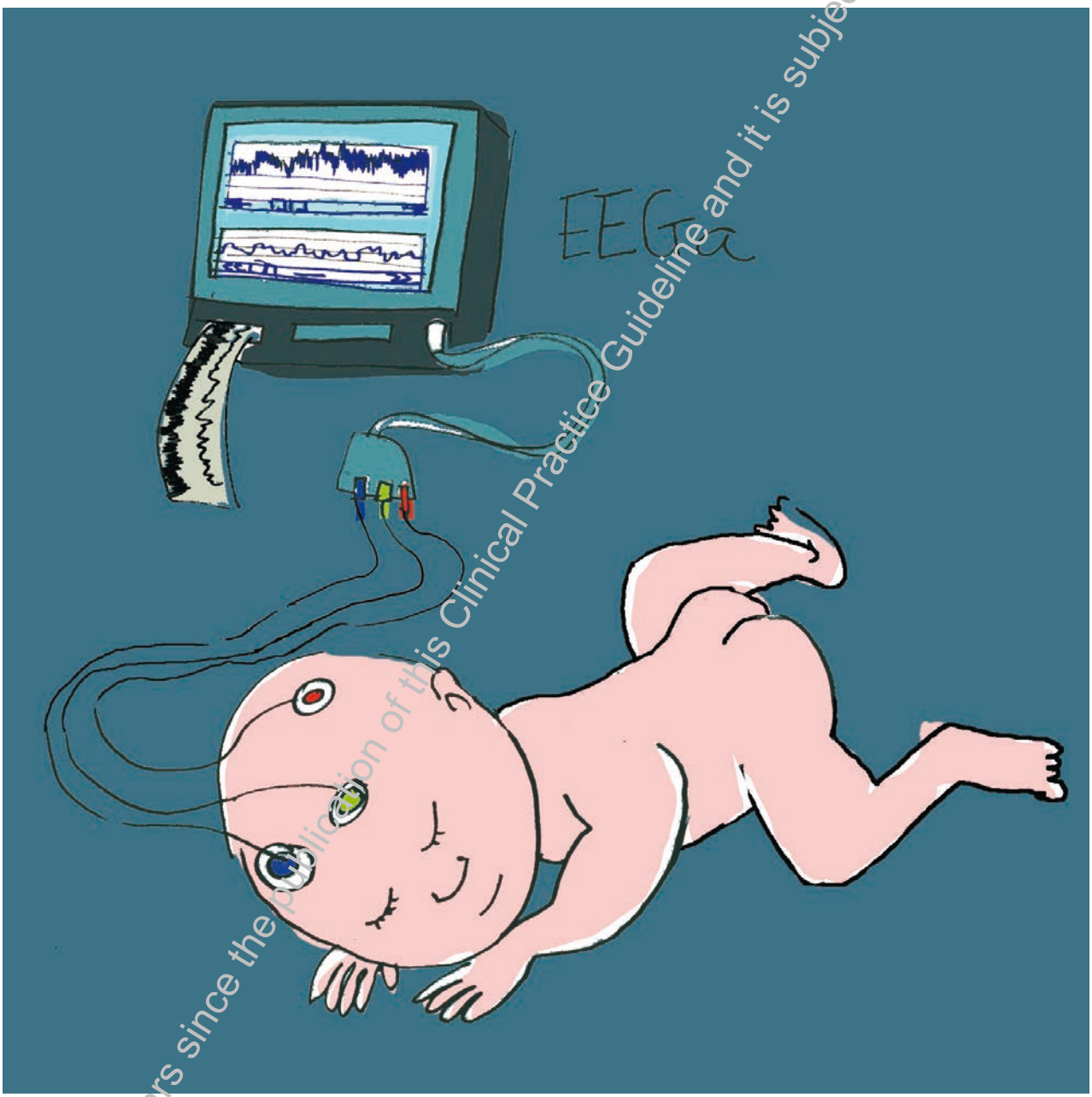
This is treatment that consists in decreasing the body temperature to 33.5-34º C. When it is applied in the first hours of life, it reduces the probability of death or of sequelae in subsequent stages related to encephalopathy.

Disproportionate treatment

These treatments include those such as ventilation with a respirator, the administration of certain drugs (inotropics, antibiotics or anticonvulsants) and interventions (analyses, imaging tests, cultures) that do not provide benefits to a baby, rather they could be extending the suffering of both the baby and the family.

Neonatal intensive care units (NICU)

A hospital zone within the neonatal unit where newborn babies are admitted, where, due to their health situation, they receive specialised treatment, constant controls and continuous monitoring.



aEEG

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Appendix 2. Search strategy

1. Quantitative search strategies for responding to the questions of the CPG

The following is indicated for each search:

- the PICO question to be answered
- the name of the consulted database
- the search strategy used
- the applied limits
- the number of articles/documents obtained

Apart from these initial searches, PubMed alerts were also generated, which provided 40 new articles

Question 1:

Does the administration of 21% oxygen versus concentrations above 21% during the resuscitation of newborns with asphyxia have an influence on neurological morbidity and mortality?

PubMed

("Asphyxia Neonatorum"[Mesh] OR "Asphyxia"[Mesh])) AND ("Oxygen Inhalation Therapy"[Mesh] OR "Oxygen"[Mesh])) AND ("Resuscitation"[Mesh] OR "Resuscitation Orders"[Mesh] OR "Cardiopulmonary Resuscitation"[Mesh])) AND (((disability OR "severe disability" OR "neurological morbidity")) OR ((("Cerebral Palsy"[Mesh]) OR "Brain Death"[Mesh]) OR ("Death"[Mesh] OR "Sudden Infant Death"[Mesh]))) AND (infant, newborn[MeSH])

Limits: newborn
5 articles
No reviews.

("Asphyxia Neonatorum"[Mesh] OR "Asphyxia"[Mesh])) AND ("Oxygen Inhalation Therapy"[Mesh] OR "Oxygen"[Mesh])) AND ("Resuscitation"[Mesh] OR "Resuscitation Orders"[Mesh] OR "Cardiopulmonary Resuscitation"[Mesh])) AND (((disability OR "severe disability" OR "neurological morbidity")) OR ((("Cerebral Palsy"[Mesh]) OR "Brain Death"[Mesh]) OR ("Death"[Mesh] OR "Sudden Infant Death"[Mesh]))) AND ((Meta- Analysis[ptyp] OR Review[ptyp]) AND infant, newborn[MeSH])

Limits: Meta-analysis, Review, newborn
6 articles

"Resuscitation"[Mesh])) AND ((("Oxygen"[Mesh])) OR ("Air"[Mesh]))) AND ((("Hypoxia-Ischemia, Brain"[Mesh])) OR ("Asphyxia"[Mesh] OR "Asphyxia Neonatorum"[Mesh])) AND ((Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp]) AND infant, newborn[MeSH])

39 articles

Cochrane English

(MeSH descriptor Cerebral Palsy explode all trees OR (cerebral palsy) OR (severe disability) OR (neurological morbidity)) AND (MeSH descriptor Death explode all trees OR MeSH descriptor Fetal Death explode all trees) AND (MeSH descriptor Resuscitation explode all trees) AND (MeSH descriptor Oxygen explode all trees)

0 results

Question 2:

Does an Apgar score of 0 at 10 minutes consistently involve severe neurological morbidity and mortality?

PubMed

"neurological morbidity" AND ("Apgar Score"[Mesh]) AND ("Morbidity"[Mesh] OR "Mortality"[Mesh] OR "Fetal Mortality"[Mesh] OR "Infant Mortality"[Mesh] OR "Perinatal Mortality"[Mesh])

2 articles

("Apgar Score"[Mesh] AND neurological morbidity AND "Asphyxia Neonatorum"[Mesh] AND infant, newborn[MeSH])

Limits: Newborn: birth - 1 month
23 results

(disability OR severe disability OR ("Cerebral Palsy"[Mesh]) OR ("Brain Death"[Mesh]^ OR "Death"[Mesh]) OR (neurological morbidity)) AND ("Apgar Score"[Mesh]) AND ("Asphyxia Neonatorum"[Mesh]) AND (Meta-Analysis[ptyp] OR Review[ptyp]) AND infant, newborn[MeSH])

Limits: Meta-Analysis, Review, Newborn: birth - 1 month
15 articles

Cochrane English

(MeSH descriptor Asphyxia Neonatorum explode all trees OR MeSH descriptor Asphyxia explode all trees)AND MeSH descriptor Apgar Score explode all trees AND neurological morbidity

19 results

(MeSH descriptor Cerebral Palsy explode all trees OR MeSH descriptor Death explode all trees OR neurological morbidity) AND (MeSH descriptor Asphyxia Neonatorum explode all trees OR MeSH descriptor Asphyxia explode all trees) AND MeSH descriptor Apgar Score explode all trees

1 result

Question 3:

Which of the following factors occurring in newborns with HIE during the first 72 hours of life are associated with greater neurological morbidity and mortality in the short and long term?

PubMed

(Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*)) AND ((((“Hypercapnia”[Mesh]) OR (“Hyperglycemia”[Mesh]) OR (“Hypoglycemia”[Mesh] OR “Persistent Hyperinsulinemia Hypoglycemia of Infancy”[Mesh]) OR (“Fever”[Mesh]))) AND ((((((disability)) OR (severe disability)) OR (“Cerebral Palsy”[Mesh])) OR (“Brain Death”[Mesh] OR “Death”[Mesh])) OR (neurological morbidity))

12 articles

((Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*)) AND ((((“Hypercapnia”[Mesh]) OR (“Hyperglycemia”[Mesh]) OR (“Hypoglycemia”[Mesh] OR “Persistent Hyperinsulinemia Hypoglycemia of Infancy”[Mesh]) OR (“Fever”[Mesh]))) AND ((((((disability)) OR (severe disability)) OR (“Cerebral Palsy”[Mesh])) OR (“Brain Death”[Mesh] OR “Death”[Mesh])) OR (neurological morbidity))) AND (infant, newborn[MeSH])

Limits: Newborn: birth - 1 month
3 articles

(Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*)) AND ((((“Hypercapnia”[Mesh]) OR (“Hypocapnia”[Mesh]) OR (“Hyperglycemia”[Mesh]) OR (“Hypoglycemia”[Mesh] OR “Persistent Hyperinsulinemia Hypoglycemia of Infancy”[Mesh]) OR (“Fever”[Mesh]))) AND ((((((disability)) OR (severe disability)) OR (“Cerebral Palsy”[Mesh])) OR (“Brain Death”[Mesh] OR “Death”[Mesh])) OR (neurological morbidity))) AND (infant, newborn[MeSH])

6 articles

Cochrane English

(MeSH descriptor Hyperthermia, Induced explode all trees OR MeSH descriptor Fever explode all trees OR MeSH descriptor Hypoglycemia explode all trees OR MeSH descriptor Hyperglycemia explode all trees OR MeSH descriptor Hypercapnia explode all trees) AND (MeSH descriptor Cerebral Palsy explode all trees OR MeSH descriptor Death explode all trees OR neurological morbidity)

Limits: Cochrane Reviews
5 results, 0 pertinent

(MeSH descriptor Hyperthermia, Induced explode all trees OR MeSH descriptor Fever explode all trees OR MeSH descriptor Hypoglycemia explode all trees OR MeSH descriptor Hyperglycemia explode all trees OR MeSH descriptor Hypercapnia explode all trees) AND (MeSH descriptor Cerebral Palsy explode all trees OR MeSH descriptor Death explode all trees OR neurological morbidity) AND (hypoxi* ischemi*)

0 results. Note: With HIE, articles are not recovered

Question 4:

Does hypothermia reduce the risk of mortality and/or of neurodevelopmental problems?

PubMed

(#31) AND #28 AND ((Meta-Analysis[ptyp] OR Review[ptyp]) AND "infant, newborn"[MeSH Terms])

Limits: Meta-Analysis, Review, Newborn: birth - 1 month
3 articles

Cochrane

(((((“Developmental Disabilities”[Mesh] OR neurodevelopment*[ti] AND ab)) OR (“Cerebral Palsy”[Mesh])) OR (“Infant Mortality”[Mesh] OR “Mortality”[Mesh] OR “Perinatal Mortality”[Mesh] OR “Mortality, Premature”[Mesh]))) AND (((Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields])) AND (“Hypothermia”[Mesh] OR “Hypothermia, Induced”[Mesh] OR Hypothermia[ti])) AND (infant, newborn[MeSH])

Limits: newborn, humans
31 results

Hypoxic*ischaemic*encephalopathy* AND hypothermia*

3 results

(Development* disabilit* OR neurodevelopment* OR cerebral palsy OR mortalit*) AND (hypoxi* ischemi*) and (hypotherm*) AND (newborn* OR infant* OR child* or neonat*)

13 results

Question 5:

Does the severity of HIE condition the efficacy of treatment with hypothermia?

PubMed

"Hypoxia-Ischemia, Brain"[Mesh] OR hypoxi*)) OR ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh])) AND (("Cerebral Palsy"[Mesh]) OR ("Death"[Mesh] OR "Brain Death"[Mesh]) OR ("Developmental Disabilities"[Mesh] OR "Disabled Children"[Mesh]) OR (cognitive disorder* OR cognition disorder*) OR ("Cognition Disorders"[Mesh] OR "Delirium, Dementia, Amnestic, Cognitive Disorders"[Mesh])) AND (((hypothermia OR "therapeutic hypothermia")) OR ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh])) AND ((Meta-Analysis[ptyp] OR Review[ptyp]) AND infant, newborn[MeSH])

Limits: Meta-Analysis, Review, Newborn: birth - 1 month
36 articles

("Hypoxia-Ischemia, Brain"[Mesh] OR (light hypoxi*) OR (medium hypoxi*) OR (severe hypoxi*) OR (acute hypoxi*)) AND ((hypothermia OR "therapeutic hypothermia") OR ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh])) AND (("Cerebral Palsy"[Mesh]) OR ("Death"[Mesh] OR "Brain Death"[Mesh]) OR ("Developmental Disabilities"[Mesh] OR "Disabled Children"[Mesh]) OR (cognitive disorder* OR cognition disorder*) OR ("Cognition Disorders"[Mesh] OR "Delirium, Dementia, Amnestic, Cognitive Disorders"[Mesh])) AND ((Meta-Analysis[ptyp] OR Review[ptyp]) AND infant, newborn[MeSH])

Limits: Meta-Analysis, Review, Newborn: birth - 1 month
22 articles

Cochrane English

((light hypoxi*) or (medium hypoxi*) or (severe hypoxi*) or (acute hypoxi*) OR MeSH descriptor Hypoxia-Ischemia, Brain explode all trees) AND (hypotherm*) AND (cerebral palsy) or (death) or (brain death) or (disabilit*) or (cognitive disorders)

Limits: Cochrane Reviews
41 results

Question 6:

Does the severity of HIE before initiating treatment with therapeutic hypothermia predict subsequent adverse evolution? Question 7. Has hypothermia changed the value of the clinical examination to predict neurodevelopmental disorders in a newborn with moderate or severe HIE?

PubMed

("Physical Examination"[Mesh] AND (infant, newborn[MeSH])) AND ("Developmental Disabilities"[Mesh] OR neurodevelopment*) AND (("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR hypothermia[ti] OR hypotermia[All Fields])) AND (Hypoxia- Ischemia, Brain[Mesh] OR hypoxi* OR ischemi*[ti] OR hypoxi* OR ischemi*[All Fields]) AND (infant, newborn[MeSH])

Limits: Newborn: birth - 1 month
12 articles

("Physical Examination"[Mesh] AND (infant, newborn[MeSH])) AND ("Developmental Disabilities"[Mesh] OR neurodevelopment*) AND (("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR hypothermia[ti] OR hypotermia[All Fields])) AND (Hypoxia- Ischemia, Brain[Mesh] OR hypoxi* OR ischemi*[ti] OR hypoxi* OR ischemi*[All Fields]) AND (infant, newborn[MeSH]) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* OR ischemi*[ti] OR hypoxi* OR ischemi*[All Fields])

Limits: Meta-Analysis, Review, Newborn: birth - 1 month
3 articles

Cochrane English

(hypoxi* ischemi*) and (hypotherm*) AND (Development* disabilit*) or (neurodevelopment*) AND MeSH descriptor Physical Examination explode all trees

7 results

(hypoxi* ischemi*) and (hypotherm*) AND (Development* disabilit*) or (neurodevelopment*) AND MeSH descriptor Physical Examination explode all trees

Limits: Economic evaluations 1 result

Question 8:

Are there pharmacological treatments that, initiated within the first 6-12 hours of life of a newborn with moderate or severe HIE, decrease the brain damage?

PubMed

(((((((("Drug Administration Schedule"[Mesh] AND (infant, newborn[MeSH]))) OR ("Drug Therapy"[Mesh])) OR ("Hypoxia-Ischemia, Brain/drug therapy"[Mesh] AND (drug*[ti] OR drug*[All Fields] OR pharmacolog*[ti] OR pharmacolog*[All Fields])) AND (infant, newborn[MeSH]))) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields]) AND (infant, newborn[MeSH]))) AND ("Brain Injuries"[Mesh] OR "Hypoxia, Brain"[Mesh]) AND (infant, newborn[MeSH])

(((((((((("Xenon"[Mesh])) OR ("Erythropoietin"[Mesh])) OR ("Allopurinol"[Mesh])) OR ("topiramate"[SupplementaryConcept]))OR("Phenobarbital"[Mesh]))OR("Thiopental"[Mesh])) OR ("Barbiturates"[Mesh]))) AND ((hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*) OR ("Hypoxia-Ischemia, Brain"[Mesh])) AND ((Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp]) AND infant, newborn[MeSH]) Randomized Controlled Trial,Reviwe, Meta-analysis, Newborn: birth-1 month

36 articles

Question 9:

Does the combination of hypothermia with topiramate, EPO, allopurinol or xenon reduce the risk of death-disability at 18-24 months in newborns with moderate or severe HIE?

PubMed

((("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR hypothermia[ti] OR hypothermia)) AND (("Allopurinol"[Mesh] OR allopurinol[ti] OR allopurinol[All Fields]) OR ("Erythropoietin"[Mesh] OR erythropoietin[ti] OR erythropoietin[All Fields]) OR ("topiramate"[Supplementary Concept] OR topiramate[ti] OR topiramate[All Fields]) OR "Xenon"[Mesh])) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields]) AND ((infant, newborn[MeSH] OR infant[MeSH:noexp] OR child, preschool[MeSH]))

Limits: Newborn: birth - 1 month, Infant: 1-23 months, Preschool child: 2-5 years
15 articles

((("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR hypothermia[ti] OR hypothermia)) AND (("Allopurinol"[Mesh] OR allopurinol[ti] OR allopurinol[All Fields]) OR ("Erythropoietin"[Mesh] OR erythropoietin[ti] OR erythropoietin[All Fields]) OR ("topiramate"[Supplementary Concept] OR topiramate[ti] OR topiramate[All Fields]) OR "Xenon"[Mesh])) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields]) AND ((Meta-Analysis[ptyp] OR Review[ptyp]) AND (infant, newborn[MeSH] OR infant[MeSH:noexp] OR child, preschool[MeSH]))

Limits: Newborn: birth - 1 month, Infant: 1-23 months, Preschool child: 2-5 years, review, meta-analysis
10 articles

(((((("Developmental Disabilities"[Mesh] OR neurodevelopment*[ti] AND ab)) OR ("Cerebral Palsy"[Mesh])) OR ("Infant Mortality"[Mesh] OR "Mortality"[Mesh] OR "Perinatal Mortality"[Mesh] OR "Mortality, Premature"[Mesh]))) AND (((Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields])) AND ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR Hypothermia[ti])) AND (infant, newborn[MeSH]) AND Search ("Allopurinol"[Mesh] OR allopurinol[ti] OR ("allopurinol"[MeSH Terms] OR "allopurinol"[All Fields])) OR ("Erythropoietin"[Mesh] OR erythropoietin[ti] OR ("erythropoietin"[MeSH Terms] OR "erythropoietin"[All Fields])) OR ("topiramate"[Supplementary Concept] OR topiramate[ti] OR ("topiramate"[Supplementary Concept] OR "topiramate"[All Fields]) OR ("Xenon"[Mesh] OR xenon))

0 articles

(("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR hypothermia[ti] OR hypothermia)) AND (("Allopurinol"[Mesh] OR allopurinol[ti] OR allopurinol[All Fields]) OR ("Erythropoietin"[Mesh] OR erythropoietin[ti] OR erythropoietin[All Fields]) OR ("topiramate"[Supplementary Concept] OR topiramate[ti] OR topiramate[All Fields]) OR "Xenon"[Mesh])) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields]) AND ((Meta-Analysis[ptyp] OR Review[ptyp]) AND (infant,

newborn[MeSH] OR infant[MeSH:noexp] OR child, preschool[MeSH])) AND ((Developmental Disabilities OR neurodevelopment) OR (mortality))

Limits: Newborn: birth - 1 month, Infant: 1-23 months, Preschool child: 2-5 years
1 article

Cochrane English

[(newborn*)or (infant*) or (child*) or (neonat*)] AND [(hypoxi* ischemi*) and (hypotherm*)] AND [(development* disabilit*) or (neurodevelopment*)or (cerebral palsy) or (mortalit*)] AND [(allopurinol) or (erythropoietin) or (topiramate) or (xenon)]

4 results

[(newborn*)or (infant*) or (child*) or (neonat*)] AND [(hypoxi* ischemi*) and (hypotherm*)] AND [(development* disabilit*) or (neurodevelopment*)or (cerebral palsy) or (mortalit*)] AND [(allopurinol) or (erythropoietin) or (topiramate) or (xenon)]

0 results

Question 10:

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

PubMed

("Brain Injuries"[Mesh] OR "Brain Damage, Chronic"[Mesh] OR "Hypoxia, Brain"[Mesh]) AND ((hypothermia OR "therapeutic hypothermia") OR ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh])) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*) AND ("Drug Therapy"[Mesh]) AND (infant, newborn[MeSH])

Limits: Newborn: birth - 1 month
8 articles. Without pharmacological treatment: 114 articles

("Brain Injuries"[Mesh] OR "Brain Damage, Chronic"[Mesh] OR "Hypoxia, Brain"[Mesh]) AND ((hypothermia OR "therapeutic hypothermia") OR ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh]) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*) AND ("Drug Therapy"[Mesh]) AND ((Meta- Analysis[ptyp] OR Review[ptyp]) AND infant, newborn[MeSH])

Limits: Meta-Analysis, Review, Newborn: birth - 1 month
4 articles

"Seizures"[Mesh])) AND ((("Hypoxia-Ischemia, Brain"[Mesh])) OR ("Asphyxia"[Mesh] OR "Asphyxia Neonatorum"[Mesh])) AND ((Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp]) AND infant, newborn[MeSH]

47 articles

Cochrane English

(hypoxi* ischemi*) AND (hypotherm*) AND (electrical seizures) AND (cerebral damage)

4 resultados

Question 11:

Does sedation with opioid derivatives in newborns with HIE decrease the risk of death or disability at 18-24 months?

PubMed

((“Analgesics, Opioid”[Mesh] OR “Analgesics, Opioid”[Pharmacological Action])) AND (((“Hypothermia”[Mesh] OR “Hypothermia, Induced”[Mesh] OR hypothermia[ti] OR hypothermia)) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields]))

5 articles

((“Analgesics, Opioid”[Mesh] OR “Analgesics, Opioid”[Pharmacological Action])) AND (((“Hypothermia”[Mesh] OR “Hypothermia, Induced”[Mesh] OR hypothermia[ti] OR hypothermia)) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields])OR brain injur* OR brain damage* Limits: Newborn: birth-1 month)

0 articles

((((Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields])) NOT (“Hypothermia”[Mesh] OR “Hypothermia, Induced”[Mesh] OR hypothermia[ti] OR hypothermia) AND (infant, newborn[MeSH]))) AND (“Analgesics, Opioid”[Mesh] OR “Analgesics, Opioid”[Pharmacological Action]) AND (infant, newborn[MeSH])

5 articles

(Search AND “Hypothermia”[Mesh] OR “Hypothermia, Induced”[Mesh] OR hypothermia[All Fields])) AND (((((“Analgesics, Opioid”[Mesh] OR “Analgesics, Opioid”[Pharmacological Action]))OR(“Morphine Derivatives”[Mesh]))OR(“Morphine”[Mesh]))OR(“Fentanyl”[Mesh])) AND ((Clinical Trial[ptyp] OR Meta- Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp]) AND (infant, newborn[MeSH])

6 articles

Cochrane English

(newborn*) or (infant*) or (child*) or (neonat*) AND (hypoxi* ischemi*) and (hypotherm*) and (brain damage) or (development* disabil*) or (cerebral palsy) AND MeSH descriptor Analgesics, Opioid explode all trees

0 results

Question 12:

What is the prognostic value of neurophysiological studies to predict neurodevelopmental problems in newborns with moderate or severe HIE? Has hypothermia changed the prognostic value of these tests?

PubMed

((("Diagnostic Techniques, Neurological"[Mesh]) OR "Electroencephalography"[Mesh] AND (infant, newborn[MeSH]))) AND (Developmental Disabilities OR neurodevelopment)) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields]) AND ((Meta-Analysis[ptyp] OR Review[ptyp]) AND infant, newborn[MeSH])

Limits: Newborn: birth - 1 month, review, meta-analysis
6 articles

PubMed

((((hypoxia ischemia)) OR ("Hypoxia-Ischemia, Brain"[Mesh])) OR (hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields]))) AND ("Electroencephalography"[M esh]) AND ((infant[MeSH] OR infant, newborn[MeSH]))

Limits: newborn, infant,
292 articles

(((((((hypoxia ischemia)) OR ("Hypoxia-Ischemia, Brain"[Mesh])) OR (hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields]))) AND ("Electroencephalography"[Mesh]) AND ((infant[MeSH] OR infant, newborn[MeSH])))) NOT ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh]) AND ((infant[MeSH] OR infant, newborn[MeSH]))

Limits: newborn, infant,
238 articles

(((((((hypoxia ischemia)) OR ("Hypoxia-Ischemia, Brain"[Mesh])) OR (hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields]))) AND ("Electroencephalography"[M esh]) AND ((infant[MeSH] OR infant, newborn[MeSH])))) AND ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh]) AND ((infant[MeSH] OR infant, newborn[MeSH]))

Limits: newborn, infant,
54 articles

Cochrane English

(Development* disabilit* OR neurodevelopment* OR cerebral palsy) AND (hypoxi* ischemi*) and (hypotherm*) AND (newborn* OR infant* OR child* or neonat*) AND MeSH descriptor Diagnostic Techniques, Neurological explode all trees

5 results

(Development* disabilit* OR neurodevelopment* OR cerebral palsy) AND (hypoxi* ischemi*) NOT (hypotherm*) AND (newborn* OR infant* OR child* or neonat*) AND MeSH descriptor

Diagnostic Techniques, Neurological explode all trees

3 results

(Development* disabilit* OR neurodevelopment* OR cerebral palsy) AND (hypoxi* ischemi*) and (hypotherm*) AND (newborn* OR infant* OR child* or neonat*) AND MeSH descriptor Diagnostic Techniques, Neurological explode all trees

Limits: Economic evaluations

1 result

Question 13:

What is the prognostic value of imaging tests to predict neurodevelopmental problems in newborns with moderate or severe HIE? Has hypothermia changed the prognostic value of these tests?

PubMed

("Developmental Disabilities"[Mesh] AND neurodevelopment*) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields]) AND (("Ultrasonography, Doppler"[Mesh] OR "Magnetic Resonance Imaging"[Mesh]) OR ("Ultrasonography"[Mesh] OR "ultrasonography"[Subheading])) AND (infant, newborn[MeSH]) NOT ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR hypothermia[ti] OR hypotermia[All Fields])

Limits: Newborn: birth - 1 month

12 articles

("Developmental Disabilities"[Mesh] AND neurodevelopment*) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields]) AND (("Ultrasonography, Doppler"[Mesh] OR "Magnetic Resonance Imaging"[Mesh]) OR ("Ultrasonography"[Mesh] OR "ultrasonography"[Subheading])) AND ((Meta- Analysis[ptyp] OR Review[ptyp]) AND infant, newborn[MeSH]) NOT ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR hypothermia[ti] OR hypotermia[All Fields])

Limits: Newborn: birth - 1 month, review, meta-analysis

0 articles

((((("Developmental Disabilities"[Mesh] OR neurodevelopment*)) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields])) AND (("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR hypothermia[ti] OR hypotermia[All Fields]))) AND (("Ultrasonography, Doppler"[Mesh] OR "Magnetic Resonance Imaging"[Mesh]) OR ("Ultrasonography"[Mesh] OR "ultrasonography"[Subheading]))

Limits: Newborn: birth - 1 month

7 articles

((((("Developmental Disabilities"[Mesh] OR neurodevelopment*)) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields])) AND (("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR hypothermia[ti] OR hypotermia[All Fields]))) AND (("Ultrasonography, Doppler"[Mesh] OR "Magnetic Resonance

Imaging"[Mesh]) OR ("Ultrasonography"[Mesh] OR "ultrasonography"[Subheading]))

Limits: Meta-Analysis, Review, Newborn: birth - 1 month
1 article

PubMed

("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR hypothermia[ti] OR hypotermia[All Fields])) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields])) AND ("Diffusion Magnetic Resonance Imaging"[Mesh] OR "Magnetic Resonance Imaging"[Mesh]) AND ((infant, newborn[MeSH] OR infant[MeSH]))

Limits: newborn, infant
31 articles

(Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields])) AND ("Diffusion Magnetic Resonance Imaging"[Mesh] OR "Magnetic Resonance Imaging"[Mesh])) NOT ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR hypothermia[ti] OR hypotermia[All Fields]) AND ((Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR systematic[sb] OR Meta- Analysis[ptyp]) AND (infant, newborn[MeSH] OR infant[MeSH]))

Limits: newborn, infant, meta-analysis, RCT, Reviews, systematic reviews
77 articles

(("Ultrasonography"[Mesh] OR "ultrasonography"[Subheading] OR "Ultrasonography, Doppler"[Mesh])) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields])) AND ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR hypothermia[ti] OR hypotermia[All Fields]) AND ((infant[MeSH] OR infant, newborn[MeSH]))

Limits: newborn, infant
7 articles

("Ultrasonography"[Mesh] OR "ultrasonography"[Subheading] OR "Ultrasonography, Doppler"[Mesh])) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields])) NOT ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR hypothermia[ti] OR hypotermia[All Fields]) AND ((Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR Meta-Analysis[ptyp] OR systematic[sb]) AND (infant[MeSH] OR infant, newborn[MeSH]))

Limits: newborn, infant, meta-analysis, RCT, Reviews, systematic reviews
32 articles

"Magnetic Resonance Spectroscopy"[Mesh])) AND ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR hypothermia[ti] OR hypotermia[All Fields])) AND (Hypoxia- Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields])

10 articles

"Magnetic Resonance Spectroscopy"[Mesh])) AND (Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields])) NOT ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR hypothermia[ti] OR hypotermia[All Fields]) AND ((Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR systematic[sb]) AND (infant, newborn[MeSH] OR infant[MeSH]))

Limits: newborn, infant, meta-analysis, RCT, Reviews, systematic reviews
23 articles

Cochrane English

(MeSH descriptor Ultrasonography, Doppler explode all trees or MeSH descriptor Magnetic Resonance Imaging explode all trees or MeSH descriptor Ultrasonography explode all trees) AND (hypoxi* ischemi*) not (hypotherm*) AND (Development* disabilit*) or (neurodevelopment*)

2 results

(MeSH descriptor Ultrasonography, Doppler explode all trees or MeSH descriptor Magnetic Resonance Imaging explode all trees or MeSH descriptor Ultrasonography explode all trees) AND (hypoxi* ischemi*) AND (hypotherm*) AND (Development* disabilit*) or (neurodevelopment*)

0 results

Question 14:

What is the prognostic value of the biomarkers in blood, urine or CSF to predict death or neurodevelopmental problems in newborns with moderate or severe HIE? Has this changed with hypothermia?

PubMed

((Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields]) AND ((“Hypothermia”[Mesh] OR “Hypothermia, Induced”[Mesh] OR hypothermia[ti] OR hypotermia[All Fields])) AND (“Biological Markers/blood”[Mesh] OR “Biological Markers/cerebrospinal fluid”[Mesh] OR “Biological Markers/urine”[Mesh])

Limits: Meta-Analysis, Review, Newborn: birth - 1 month
5 articles

((Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields]) AND (“Biological Markers/blood”[Mesh] OR “Biological Markers/cerebrospinal fluid”[Mesh] OR “Biological Markers/urine”[Mesh]) NOT (“Hypothermia”[Mesh] OR “Hypothermia, Induced”[Mesh] OR hypothermia[ti] OR hypotermia[All Fields])) AND ((Meta-Analysis[ptyp] OR Review[ptyp]) AND infant, newborn[MeSH])

Limits: Meta-Analysis, Review, Newborn: birth - 1 month
4 results

hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*) OR (“Hypoxia-Ischemia, Brain”[Mesh]))) AND (((((((“activin A”[Supplementary Concept])) OR (“Creatine Kinase, BB Form”[Mesh])) OR (“Myelin Basic Proteins”[Mesh])) OR (“Glial Fibrillary Acidic Protein”[Mesh])) OR (“S-100 calcium-binding protein beta subunit”[Supplementary Concept])) OR (neuron specific enolase)) AND (infant, newborn[MeSH])

newborn
59 articles

((Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields]) AND ((“Hypothermia”[Mesh] OR “Hypothermia, Induced”[Mesh] OR hypothermia[ti] OR hypotermia[All Fields]))) AND (“Biological Markers/blood”[Mesh] OR “Biological Markers/cerebrospinal fluid”[Mesh] OR “Biological Markers/urine”[Mesh])

Meta-Analysis, Review, Newborn: birth - 1 month
8 articles, 2 pertinent

((Hypoxia-Ischemia, Brain[Mesh] OR hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*[All Fields]) AND (“Biological Markers/blood”[Mesh] OR “Biological Markers/cerebrospinal fluid”[Mesh] OR “Biological Markers/urine”[Mesh]) NOT (“Hypothermia”[Mesh] OR “Hypothermia, Induced”[Mesh] OR hypothermia[ti] OR hypotermia[All Fields])) AND ((Meta-Analysis[ptyp] OR Review[ptyp]) AND infant, newborn[MeSH])

Limits: Meta-Analysis, Review, Newborn: birth - 1 month
5 articles, 1 pertinent

hypoxi* AND ischemi*[ti] OR hypoxi* AND ischemi*) OR (“Hypoxia-Ischemia, Brain”[Mesh]))) AND (((((((“activin A”[Supplementary Concept])) OR (“Creatine Kinase, BB Form”[Mesh])) OR (“Myelin Basic Proteins”[Mesh])) OR (“Glial Fibrillary Acidic Protein”[Mesh])) OR (“S-100 calcium-binding protein beta subunit”[Supplementary Concept])) OR (neuron specific enolase)) AND (infant, newborn[MeSH])

Limits: newborn
61 articles, 3 pertinent

Cochrane English

(hypoxi* ischemi*) not (hypotherm*) AND (Development* disabilit*) or (neurodevelopment*) AND MeSH descriptor Biological Markers explode all trees

2 results

(hypoxi* ischemi*) and (hypotherm*) AND (Development* disabilit*) or (neurodevelopment*) AND MeSH descriptor Biological Markers explode all trees

1 result

(hypoxi* ischemi*) not (hypotherm*) AND (Development* disabilit*) or (neurodevelopment*) AND MeSH descriptor Biological Markers explode all trees

Limits: 2011-2012, reviews only
12 articles

(hypoxi* ischemi*) and (hypotherm*) AND (Development* disabilit*) or (neurodevelopment*) AND MeSH descriptor Biological Markers explode all trees

Limits: 2011-2012, reviews only
3 articles

Cost-effectiveness, in general:

Cost_HIE_hypo

PubMed

((hypoxi*ANDischemi*[ti]ORhypoxi*ANDischemi*))OR("Hypoxia-Ischemia,Brain"[Mesh])))
AND ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh])))) AND (((cost[ti] OR costs[ti]
OR econom*[ti] OR reimburs*[ti] OR budget*[ti] OR expeditur*[ti])) OR (("Costs and Cost
Analysis"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Cost Allocation"[Mesh] OR "Cost of
Illness"[Mesh] OR "Cost Control"[Mesh] OR "Cost Sharing"[Mesh] OR "Cost Savings"[Mesh]
OR "Technology, High-Cost"[Mesh] OR "Health Care Costs"[Mesh] OR "Drug Costs"[Mesh])
OR "Health Expenditures"[Mesh]))

5 articles

Cost_HIE_hypo

NHSEED

hypothermia AND hypox*

3 results

HIE Outcomes, RCT review

PubMed

"Outcome Assessment (Health Care)"[Mesh] OR "Treatment Outcome"[Mesh] OR
"Fatal Outcome"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh]))
AND ((("Hypoxia-Ischemia, Brain"[Mesh])) OR ("Asphyxia"[Mesh] OR "Asphyxia
Neonatorum"[Mesh])) AND ((Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized
Controlled Trial[ptyp] OR Review[ptyp]) AND infant, newborn[MeSH])

96 articles

HIE hypothermia Outcomes, RCT review

PubMed

("Outcome Assessment (Health Care)"[Mesh] OR "Treatment Outcome"[Mesh] OR
"Fatal Outcome"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh]))
AND (("Hypoxia-Ischemia, Brain"[Mesh])) OR ("Asphyxia"[Mesh] OR "Asphyxia
Neonatorum"[Mesh])))) AND ("Hypothermia"[Mesh] OR "Hypothermia, Induced"[Mesh] OR
hypothermia[All Fields]) AND ((Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized
Controlled Trial[ptyp] OR Review[ptyp]) AND infant, newborn[MeSH])

49 articles

2. Search for qualitative studies

The bibliographic search responds to the general objective of the study: detect the impact that is caused to families whose children have had HIE and have required treatment with sustained, moderate hypothermia. In this regard, the search strategy centres on those descriptors related to encephalopathy, hypothermia and the family. In view of the non-existence of a specific bibliography, a search was conducted while considering both those concepts related to the clinical situation of urgency, the threat to life, parents-child separation and coping strategies experienced by families, as well as those related to the qualitative methodology itself.

The following is indicated for each search:

- the name of the consulted database
- the search strategy used
- the applied limits
- the number of articles/documents obtained

PubMed

Search Search (ischem*[TI] OR ischaem*[TI]) AND encephalopathy AND hypoxi*[TI] AND Search ((“Hypoxia-Ischemia, Brain”[Mesh]) OR “Brain Ischemia”[Mesh]) OR “Hypoxia, Brain”[Mesh]) AND (“Family”[Mesh] OR “Family Nursing”[Mesh] OR “Family Therapy”[Mesh] OR “Parents”[Mesh] OR “Single Parent”[Mesh]OR “Parenting”[Mesh])

33 articles, 9 pertinent

Search Search (ischem*[TI] OR ischaem*[TI]) AND encephalopathy AND hypoxi*[TI] AND Search ((“Hypoxia-Ischemia, Brain”[Mesh]) OR “Brain Ischemia”[Mesh]) OR “Hypoxia, Brain”[Mesh]) AND (“Family”[Mesh] OR “Family Nursing”[Mesh] OR “Family Therapy”[Mesh] OR “Parents”[Mesh] OR “Single Parent”[Mesh]OR “Parenting”[Mesh])

Limits: newborn (birth - 1 month)
12 articles, 0 pertinent

Search Search (ischem*[TI] OR ischaem*[TI]) AND encephalopathy AND hypoxi*[TI] AND Search ((“Hypoxia-Ischemia, Brain”[Mesh]) OR “Brain Ischemia”[Mesh]) OR “Hypoxia, Brain”[Mesh]) AND (stress[TI])

Limits: newborn (birth - 1 month)
13 articles, 0 pertinent. Neonatal stress

Search Search (ischem*[TI] OR ischaem*[TI]) AND encephalopathy AND hypoxi*[TI] AND Search ((“Hypoxia-Ischemia, Brain”[Mesh]) OR “Brain Ischemia”[Mesh]) OR “Hypoxia, Brain”[Mesh]) AND (family AND stress)

13 articles, 0 pertinent

Search Search (ischem*[TI] OR ischaem*[TI]) AND encephalopathy AND hypoxi*[TI] AND Search ((“Hypoxia-Ischemia, Brain”[Mesh]) OR “Brain Ischemia”[Mesh]) OR “Hypoxia, Brain”[Mesh]) AND (parent* AND neonatal intensive care)

5 articles

Search ("Intensive Care Units, Neonatal"[Mesh] Limits: Humans, Newborn: birth-1 month) AND Search ("Family Health"[Mesh]) OR "Family Nursing"[Mesh] Limits: Humans, Newborn: birth-1 month)

Limits: newborn (birth - 1 month)
50 articles

PsycINFO

hipoxic ischemic encephalopathy AND parents
2 articles, 0 pertinent

hipoxic ischemic encephalopathy AND family
4 articles, 0 pertinent

neonatal intensive care AND coping
52 artículos

Sibling AND Intensive care nursing AND newborn
0 artículos

Sibling AND Intensive care unit AND newborn
2 artículos, 2 pertinentes

family nursing AND Intensive care unit AND newborn
2 artículos, 2 pertinentes

family nursing AND Intensive care nursing AND newborn
0 artículos

parent stress index AND Intensive care nursing AND newborn
0 artículos

parent stress index AND Intensive care unit AND newborn
1 artículos, 1 pertinente

parents AND neonatal AND transport
5 artículos

parents AND critical neonatal AND transport
0 artículos

parents AND newborn AND transport
3 artículos

CINHAL

Parenting stress index AND Intensive care nursing AND newborn
3 artículos, 3 pertinentes.

Parenting AND Intensive care nursing AND newborn
23 artículos

Parenting AND Intensive care unit AND newborn
33 artículos

Sibling AND Intensive care nursing AND newborn
2 artículos, 2 pertinentes

Sibling AND Intensive care unit AND newborn
5 artículos, 5 pertinentes

critical neonatal AND transport
7 artículos

critical newborn AND transport
2 artículos

newborn AND transport AND parent
3 artículos

neonatal AND transport AND parents
20 artículos7 articles

Appendix 3. Glossary

Paroxysmal EEG activity. An electrical phenomenon that begins and ends abruptly, and it frequently shows a greater amplitude than the waves that constitute the base tracing.

Apnea. The absence or cessation of breathing movements.

Internal capsule. A dense sheet of white matter that is located between the thalamus and the caudate nucleus medially and the globus pallidus laterally. The IC has an anterior limb that contains thalamocortical fibres and frontopontines and a posterior limb (PLIC) that contains corticobulbar and corticospinal motor fibres.

Odds ratio (OR). A term used in diagnostic testing to indicate how much more probable a determined result of a diagnostic test is in a patient with a given illness, compared to a patient without that illness. Therefore, it compares the probability of obtaining a determined result in an ill individual against the probability of that same result in an individual who is not ill. ORs have the clinical utility of allowing an estimate of the change of probabilities attributable to a patient according to the result of a certain test. If the estimated probability before conducting the test and knowing its result (pretest probability) undergoes a considerable change upon learning the result and applying the corresponding posttest probability, then the test will be useful.

Clinical convulsion. A paroxysmal alteration in the neurological function (behavioural, motor or autonomic or a combination thereof).

Epileptic convulsion. A convulsion (see definition) that results from an uncontrolled electrical discharge of a population of neurons within the central nervous system (CNS).

Cerebral cortex. It is a thin sheet of grey matter (nerve tissue constituted by neurons) that covers the irregular surface of the cerebral hemispheres.

Cognitive disability (mental retardation). Slow and incomplete acquisition of cognitive skills during development. These children have intellectual functioning that is significantly below the mean, together with a limitation of adaptive behaviour, which is manifested in conceptual skills, social skills (communication) and practices (personal care, life at home, social skills, self-governance, health and safety). Intellectual disability is not a mental illness, but it is harder for these people to learn, comprehend and communicate.

Dystonia. Sudden, sustained and simultaneous contraction of agonist and antagonist muscles, thereby giving rise to unusual and bizarre postures that are maintained temporarily, as well as slow, spasmodic rotations (contortions).

Hypoxic-ischaemic encephalopathy (HIE). A clinical syndrome that results from an episode of hypoxia-ischaemia associated with perinatal asphyxia. The term "encephalopathy" denotes an acute neurological dysfunction of variable severity that is characterised by a difficulty to wake up or stay awake; difficulty to initiate or remain breathing (respiratory depression); an alteration of muscle tone, of motor responses, of responsiveness, of reflexes and of feeding ability; and frequently, convulsions. The nature and moment of origin of the encephalopathy determine what is called perinatal hypoxic-ischaemic encephalopathy (HIE).

Brain ultrasound. It is a safe, painless and non-ionising imaging technique that is performed on the head of a neonate, in which ultrasound is used to obtain images of the brain. This evaluation has high diagnostic performance, both of the pathology of brain development and of the pathology acquired during the prenatal, perinatal and postnatal periods.

Electroencephalogram (EEG). A neurophysiological evaluation that is based on the record of brain electrical activity under basal conditions of rest, alertness or sleep by applying numerous electrodes to the scalp and connected to electroencephalography equipment. The neonate has an EEG that differs from what is observed in another period of life, regarding both the bioelectrical rhythms and the organisation of the signal, which gives rise to a record that is unique to early infancy and specific for the post-menstrual age.

Amplitude-integrated electroencephalography (aEEG). A record of brain activity in which the activity is integrated for the amplitude of the voltage. In a newborn with hypoxic-ischaemic encephalopathy, the aEEG is mainly used to assess the activity of the base tracing, to detect sub-clinical convulsions, to evaluate the effect of antiepileptic drugs, to select those neonates that are apt for being included in neuroprotection strategies during the first 6 hours of life and, at an early stage, to establish a subsequent neurological prognosis.

Epilepsy. A chronic brain disorder that is manifested by epileptic seizures (convulsions) that recur during a period of time.

Spasticity. An increase of muscular resistance for movement in proportion to speed, which causes rigidity and a shortening of muscles and interferes with movement and with motor functions: walking, manipulation, balance, speech, swallowing, etc.

Magnetic resonance spectroscopy (MRS). A special MR sequence that allows detecting the concentration of different metabolites in a determined cerebral volume. The information is represented graphically and consists in a series of peaks at specific parts per million for each metabolite. The area of said peaks is proportional to the number of nuclei of the detected metabolite. Among the atomic nuclei that resonate and can be detected in MR, hydrogen (1H) and phosphorus are used the most.

Epileptic state. In a child, this term is used to indicate a clinical or electrical convulsive event that lasts for 30 minutes or when there are repeated convulsions without interictal recovery during 30 minutes. In a neonate, we talk about an epileptic state when the convulsions persist or recur during 15 minutes of direct observations or through monitoring with an EEG or aEEG.

Gross Motor Function Classification System (GMFCS). A classification of the degree of functional capacity of a child with cerebral palsy between 1 and 12 years of age. This classification describes the abilities in motor function observed in the daily life of children, with emphasis on sitting and walking.

Basal ganglia (BG). Grey nuclei in the interior of the brain, whose main components are: the caudate nucleus, the putamen and the globus pallidus. They are intimately related to each other, and they are involved in controlling posture and movement.

Therapeutic hypothermia (TH). The reduction of a baby's body temperature by between 3 and 4º C and keeping this target temperature stable for a period of 72 hours. The purpose of this intervention is to reduce the adverse impact involved with a hypoxic-ischaemic injury, and it is applied to those newborns with moderate or severe HIE.

Hypertonia. An increase in the muscular resistance to passive distension (see muscle tone).

Hypotonia. A decrease of the resistance of muscles to passive distension (see muscle tone).

Cerebral spinal fluid (CSF). A clear liquid that bathes the brain and the spinal cord. It circulates in the subarachnoid space, the ventricles of the brain and the ependymal canal.

Biochemical markers (Biomarkers). Metabolic products or molecules that indicate the depletion of tissue energy or the release of proteins, from neurons, the glial or the myelin when there is injury to the membrane or cellular necrosis. These "biochemical markers" spread to the interstitial space from the neural cells and from there to the CSF through the fenestrated epithelium of the central canal or to the blood due to malfunction of the blood-brain barrier. They are used to examine the gravity of an acute hypoxic-ischaemic injury.

Myelin. A sheath of proteins and phospholipids forming a thick layer around the axons of the neurons. In the central nervous system, they are cytoplasmic extensions of the oligodendrocytes. Its insulating effect allows the rapid transmission of nervous impulses between the different parts of the body.

Number Needed to Treat (NNT). A number that translates how many patients will have to be treated in order to prevent an event, which responds to the formula of 1/absolute reduction of the risk.

Odds Ratio (OR). It is an estimator of risk for which there is no well-accepted term in Spanish. It is a way to represent the risk that a health condition or illness might appear in one population group versus the risk that it might occur in another. It is obtained based on the "odds" quotient in each group. The "odds", occasionally called "advantages", are the quotients of the frequency of an event versus its complement, meaning the number of times that an event might occur versus how many times it doesn't occur. Thus, "odds" of 5 indicates that 5 patients will suffer the event versus 1 who will not. If the "odds" of the group, object of study, is greater than that of the control group, we will obtain an OR of greater than 1, which will be greater to the extent that the difference is greater; if the "odds" in the group, object of study, is less than the control group, we'll obtain an OR of less than 1. The OR is used in epidemiological studies of control cases, and in logistic regression analyses and meta-analyses.

Cerebral palsy (CP). A non-specific term that refers to the existence of a permanent and non-progressive disorder that affects tone, posture and movements, and it is due to an injury to the developing brain. CP is a highly variable disorder with respect to its aetiology, type, distribution and, above all, regarding its severity, which is expressed according to the degree of functional capacity (GMFCS).

Dyskinetic cerebral palsy. CP that is characterised by a fluctuation and abrupt change in muscle tone, the presence of involuntary movements and a persistence of primitive reflexes. It is the form of CP that is related the most to perinatal factors such as

HIE. Depending on the predominating signs, different clinical forms are differentiated: a) choreoathetoid (choreo, athetosis, tremors); b) dystonic, y c) mixed, associated with spasticity. The underlying injuries of the brain selectively affect the basal ganglia.

Spastic cerebral palsy. CP that is characterised by an increase in the muscular resistance, with movement proportional to the speed. Children with spastic CP can show different forms: tetraplegia (the most severe form, affecting the four extremities and generally related to extensive brain damage), diplegia (predominantly affecting the upper extremities) and hemiplegia (affecting a body half, almost always with a predominance of the upper extremity).

Lumbar puncture (LP). A procedure that is carried out to collect a sample of cerebral spinal fluid to conduct a biochemical or microbiological analysis.

Developmental delay. In this CPG, it refers to the alteration of or a delay in a child's overall acquisition of skills, which are directly observable or measurable within the context of their natural progress.

Brain magnetic resonance (MR). A non-invasive neuroimaging technique that allows obtaining high-resolution images, in multiple planes of the brain (sagittal, coronal, transversal or axial) and of the spinal cord (transversal and longitudinal), without ionising radiation (unlike computerised tomography) and without the need to change the patient's position. It is used to confirm the existence of an injury to the brain, and to characterise the severity, extent and topography thereof.

Diffusion-weighted magnetic resonance imaging (DWI). A special sequence of MRI that uses echo planar technology and is capable of detecting and quantifying the physiological movement of the molecules of free water in brain tissue. It allows obtaining images and a quantitative measurement of diffusion: the apparent diffusion coefficient (ADC). Its sequence is highly useful in the study of recent ischaemic injuries, and also in the early diagnosis and characterisation of many pathologies.

Absolute risk. It measures the incidence of an event or damage in the total population. In other words, the absolute risk is the probability that a subject suffers an event over time.

Relative risk (RR). A statistical measure that compares the frequency at which an event occurs among those that have the risk factor and those that do not have it. It therefore indicates how much more probable it is that an event will occur in one group of patients versus another.

White matter (WM). White matter is the tissue that is in the brain underneath the cerebral cortex and surrounding the central grey nuclei, and it is formed by the axions of the neurons (nervous fibres), mainly myelinated or in the process of myelination in the newborn.

Grey matter (GM). It is the part of the central nervous system (CNS) where the neuronal bodies, dendrites, axonal terminals, neuronal synapses, glial cells and abundant capillaries are grouped together (these capillaries are the reason for its darker, "grey" colour). Grey matter can be found forming the cerebral cortex and the cerebellum, and also forming the nuclei of the interior of the brain (thalamus and basal ganglia).

Thalamus. A grey nucleus that constitutes the largest portion of the diencephalon, and it forms a part of the lateral wall of the third ventricle. It has extensive connections with the cerebral cortex and plays an important role in both sensory functions and in cognitive and motor functions.

Muscle tone. The tension of a muscle at rest, which conditions the resistance of the muscle to passive distension. To a large extent, it conditions the body posture at rest and the resistance to changes in the position of a part of the body.

Nerve pathway. A bundle of nerve projections (axons) that have the same origin and destination.

Oromotor disorder. Problems with oral feeding due to the involvement of the orofacial musculature. It tends to be present in children with cerebral palsy secondary to injury in the nuclei of the basal ganglia and thalamus.

Base tracing in the aEEG or the EEG. Activity in the EEG that represents the base of activity

according to which normal or abnormal patterns are identified, over which the transitory waves stand out as sharp waves, peaks and interictal spikes.

Brain stem. A part of the brain in the form of a stem, which connects the cerebral hemispheres to the spinal cord. This structure consists of three parts: the medulla oblongata, the pons and the midbrain.

Appendix 4. Abbreviations

ADC	Apparent Diffusion Coefficient
DFLE	Disability Free Life Expectancy
PLIC	Posterior limb of the internal capsule
IbCC	Iberoamerican Cochrane Centre
IQ	Intelligence Quotient
NLR	Negative Likelihood Ratio
PLR	Positive Likelihood Ratio
Sp	Specificity
DWI	Diffusion-weighted magnetic resonance imaging
RCT	Randomised clinical trial
EEG	Electroencephalogram
aEEG	Amplitude-integrated electroencephalography
GA	Gestational age
HIE	Hypoxic-ischaemic encephalopathy
NSE	Neuron-specific enolase
EPO	Erythropoietin
BG	Basal ganglia
GMFCS	Gross motor function classification system
GRADE	Grading of Recommendations Assessment, Development and Evaluation
CPG	Clinical Practice Guideline
PMRS	Proton magnetic resonance spectroscopy
TH	Therapeutic Hypothermia
IBECS	Spanish Bibliographic Index in Health Sciences
CI	Confidence Interval
ILCOR	International committee responsible for coordination of all aspects of cardiopulmonary and cerebral resuscitation worldwide

IME	Spanish Medical Index
CSF	Cerebral spinal fluid
MA	Meta-analysis
MDI	Mental development index in the Bayley test
MRS	Magnetic resonance spectroscopy
NNT	Number Needed to Treat
O_2	Oxygen
OR	Odds Ratio
CP	Cerebral palsy
PDI	Psychomotor development index in the Bayley test
PECOT	Patient-Exposure-Comparison-Outcome-Time
LP	Lumbar puncture
GFAP	Glial fibrillary acidic protein
QDA	Qualitative Data Analysis
ARR	Absolute risk reduction
MR	Magnetic resonance
NB	Newborn
RR	Relative risk
RRR	Relative risk reduction
SR	Systematic review
Se	Sensitivity
WM	White matter
GM	Grey matter
SNS	National Health System
S100β	S100Beta protein
TP	Topiramate
NPV	Negative predictive value
PPV	Positive predictive value

Appendix 5. Declaration of interests

Guideline Development Group of the CPG on perinatal HIE

Thais Agut Quijano, Ana Alarcón Allen, Gemma Arca Díaz, Juan Arnáez Solís, Albert Balaguer Santamaría, Dorotea Blanco Bravo, 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

María José García Borau, Olga Artiñano Cuesta, Javier Soriano Faura, Enrique Salguero García, Fermín García-Muñoz Rodrigo, María Teresa Moral Pumarega, Antonio Losada Martínez, Máximo Vento Pérez, José Quero Jiménez, Sergi Cabré Gili, María Luz Ruiz Falcó and Pau Ferrer Salvians declared no conflict of interests.

Appendix 6. Important aspects about follow-up on children with HIE

Introduction

The consequences of neonatal hypoxic-ischaemic encephalopathy (HIE) are permanent and are expressed intensely during infancy and childhood. The introduction of treatment with hypothermia has meant a decrease in the number of children with this illness who die or who show severe disability in follow-up,[87] and it is currently deemed that this therapy must be offered in our country to all children with moderate or severe HIE.[43] However, and despite this important therapeutic advance, HIE currently continues to be a major cause of mortality and of neurological disability, and this situation is not expected to change substantially in the upcoming years. Therefore, all children with HIE, whether or not they have received treatment with hypothermia in the neonatal period, must be included in a follow-up programme until a minimum of two years of age.

Children with HIE need the care of a multi-disciplinary team, but it is always advisable for one member of this team to be in charge of coordinating follow-up and to be the person who establishes a more frequent and closer relationship with the family. This professional could be a general paediatrician, a neonatologist or a neuro paediatrician, depending on how the neonatal follow-up unit is organised at each hospital and on the experience of the various members of the group regarding this illness. Moreover, it must be kept in mind that the problems faced by these children are not exclusively neurological and that these families benefit from a comprehensive and holistic approach. If there isn't an appropriate follow-up programme for children with HIE at a hospital, the family must be referred to another centre that does have one, in the same way that it is now mandatory that all newborns with HIE susceptible to treatment with hypothermia must be sent to a centre of reference that offers this therapy, regardless of their place of birth. All children with HIE and their families have the right to continue receiving appropriate care after being discharged from the hospital.

Follow-up on children with HIE must be individualised and be adapted to the changing needs of the child and their family. The first step to offering a follow-up plan that is efficient and that responds to the real needs of the patient is to establish a prognosis that is as accurate as possible at the time of discharge.

Main problems during follow-up

1. A motor disorder that is secondary to neonatal HIE: cerebral palsy

The term cerebral palsy is non-specific, and refers only to the existence of a permanent and non-progressive disorder that affects tone, posture and movements and is due to an injury to the developing brain.[240] However, the degree of functional capacity, established according to the Gross Motor Function Classification System (GMFCS),[241] can be highly variable (Table 1). This classification was designed and originally standardised for children with cerebral palsy at between 1 and 12 years of age. Its purpose was to describe abilities in motor function observed in the daily life of children, with an emphasis on sitting and walking.[241, 242] The level of functional capacity affects not only motor skills per se, it is also related to the frequency and severity of other problems associated with CP, such as feeding and language disorders, visual alterations and epilepsy (Figure

1). [243,244] Therefore, for all children who are diagnosed with CP, it is necessary to determine not only the type and distribution of the motor disorder, but also the functional level. The diagnosis of cerebral palsy in a child who had HIE, without providing other data, says very little about their abilities and limitations and about the repercussion of the illness on their health, on their quality of life and on their possibilities of social involvement. [244, 245]

In general, children with isolated injuries in the basal ganglia and thalamus tend to have dyskinetic (dystonic and/or athetoid) cerebral palsy. This form of CP, even though it is highly debilitating due to the presence of abnormal movements, dystonia and oromotor involvement (in the majority of cases, the degree of functional involvement is between levels II and IV of the Gross Motor Function Classification), it can and usually is accompanied by an intellectual level within the normal range. Unfortunately for many of these children, the motor and communication difficulties prevent them from showing their true cognitive capacity. The development level or intellectual level in these patients must be evaluated by professionals who are familiar with these types of problems, and the tests that are used must be especially designed for children with motor and communication disabilities (as from 4-5 years of age), or they must be appropriately adapted (before this age, there are no specific development tests for this type of patient).

Highly extensive injuries to the basal ganglia and thalamus, especially if they are accompanied by damage to the white matter, are more frequently associated with spastic cerebral palsy and severe functional involvement (levels IV-V of the Gross Motor Function Classification).[246] In these cases, the level of intelligence is more variable, although once again it tends to be underestimated in children with major motor limitations.

In the few children with isolated damage to the white matter and/or cortex who develop CP, it is usually spastic and has a pattern of involvement that prefers the lower extremities. The majority of these children have a mild or moderately mild degree of involvement (levels I-III of the Gross Motor Function Classification), and they are capable of reaching independent walking, although it may take them a long time to do so.

Children with significant spasticity have a high risk of developing subluxation or even complete dislocation of the hips. This risk is maximum in non-ambulatory children, in which the prevalence of this painful and serious complication is around 50%. A subluxation of the hips can be detected on time through X-ray programmes, which have proved that they can reduce the incidence of dislocation and the need for salvage surgery. All children with CP and significant functional involvement (levels II-V of the Gross Motor Function Classification) should have hip X-rays annually as from 2 years of age and earlier or at a greater frequency if subluxation is suspected.[247] In the event of any doubt, the opinion of a paediatric traumatologist will always be useful. Other musculoskeletal complications include scoliosis, osteoporosis and contractures, and they usually appear in older children.

In brief, in all children in which CP is diagnosed during follow-up, it is necessary to establish the type, distribution and functional level using the GMFCS. Moreover, if it hadn't been done before, these children must be referred to a paediatric neurologist for the specific handling of spasticity, of dystonia and of medical complications associated with the motor disorder.

2. Feeding and language disorders

Children with cerebral palsy secondary to injury in the basal ganglia and thalamus can have oral feeding problems and spoken language problems due to the involvement of the orofacial musculature. The prevalence of these problems is not well known, but they seem to affect a significant number of these children, and they are related to the severity of the motor disorder.[248] In fact, these disorders are not exclusive to children with HIE, rather they also occur in children with PC of different origins.[249,250]

Oral feeding problems have serious consequences for the life of children with HIE, and it is a factor that, together with gastric reflux and aspiration pneumonia, contributes to their malnutrition, with all the deleterious effects that this involves.251 Other consequences of oral feeding disorders are the extended meal times and the consequent exhaustion of both the child and the care givers.[252] Moreover, the administration of drugs may not be reliable, which has major repercussions for children who need to take medication such as antiepileptics.249,253 Oral feeding disorders tend to become complicated, because it is hard for parents to admit that they exist, and unless they are asked directly and repeatedly and there is a high degree of suspicion by the professionals who are taking care of them, parents tend not to mention it or to minimise it during doctor visits, which leads to making the situation worse[254] (Table 2). Feeding problems are a source of embarrassment for many families. Moreover, oral feeding has a strong symbolic component, and many parents are reluctant to admit that they cannot continue "feeding" their children. Professionals who treat these families need to be empathetic and compassionate in order to bring to light the existence of these disorders and manage them appropriately.[253, 255, 256]

Children with oral feeding disorders must receive intervention at two levels. On the one hand, they can benefit if they receive rehabilitation by a speech therapist specialising in orofacial practices,[257] and on the other, they must be routinely assessed and monitored in a paediatric gastroenterology and nutrition service in order to optimise their nutrition and assess if feeding through a gastrostomy tube is necessary.[251] The need for this is relatively frequent in the most severe cases, due to the complete inability of these children to take food orally and/or due to the danger involved with safety of the airway. Even though the insertion of a gastrostomy tube is a safe technique that assures improvement of the nutritional condition and quality of life of the child and family, [249, 250] parents are very often opposed to surgery, because they consider it unnatural, because they fear social rejection and/or because they feel that they are depriving their children of one of the few pleasures that they can enjoy. [243, 251]

Alterations in language can be as frequent or more so than feeding problems, and their origin is the same as in the preceding case.[250] An oromotor alteration causes dysarthria, and children with dyskinetic CP can also have altered facial expressiveness. All this affects their communication capability and makes it seem that they have a lower intellectual level than what they actually have. Children with oral communication problems must be evaluated by professionals who are experts in these types of problems, given that many improve their skills with adequate rehabilitation, and others can benefit from alternative/augmentative communication systems.[258]

3. Visual disorders

Alterations of the visual function to differing degrees are frequent after neonatal HIE.[260] Children with severe injuries to the basal ganglia and thalamus and/or with extensive injuries to the white matter are those at a greater risk of having a visual disability.[260] In children with HIE, injuries of the ganglia and thalamus (specifically the posterolateral region of the putamen) are more highly associated with visual alterations than damage to the occipital cortex.[261] Therefore, it is advisable for these children to be evaluated during the first year of life and then regularly thereafter by paediatric ophthalmologists who are familiar with these alterations.

4. Hearing loss

The frequency of this problem is estimated at around 5%.[31, 32, 34] Even though the prevalence of this sequela is low, the figures are considerably higher than in the general population (5/1000 newborns), which leads to the conclusion that perinatal hypoxic-ischaemic injury can have permanent effects on hearing in some cases. Although it is a controversial subject, the presence of significant neurosensorial hearing impairment as the only sequela of perinatal hypoxia-ischaemia

is an exceptional event. The majority of children with hearing loss also have significant alterations in other areas of their development. Nevertheless, it seems prudent to examine the hearing function of all children with a history of HIE in the first year of life (regardless of the neonatal screening test) and subsequently if there are clinical suspicions.

5. Epilepsy

The risk of developing epileptic seizures after HIE is not well known, but it is calculated that 10-20% of all children with HIE will show it throughout infancy.[31, 32, 34, 36] It tends to appear during the first year of life (50% of cases), although sometimes the appearance is delayed until 5-10 years. The most important risk factors are the severity of the encephalopathy; the presence, severity and duration of convulsions in the neonatal period; and extensive injury to the basal ganglia and/or to the white matter and cortex.[271] In children with major motor involvement in which the clinical manifestations may not be evident, conducting a periodic electroencephalography could be useful.

6. Cognitive deficit and behavioural problems.

It is not easy to know the scope of these sequelae, especially in the first two years of life. Studies on the evolution of children after HIE, mainly in clinical trials that have evaluated the therapeutic effect of hypothermia, report figures of psychomotor delay (considered as scores in development tests that are inferior to two standard deviations below the mean of the normal population) in 25-35% of children with moderate and severe HIE.[31, 32, 34, 36, 37] These figures are very similar to the global prevalence of CP in this population, and in many cases they probably reflect the motor disability of these children more than an intellectual deficit per se.

Despite the aforementioned, a cognitive delay and difficulties in learning after neonatal HIE are more frequent than what was thought up to now, and they show up even in the absence of cerebral palsy.[264] Contrary to motor disability, cognitive alterations seem to be notably dependent on the family and the social environment. The level of maternal education and the level of family income have been associated with significant differences in the incidence of neuropsychological deficiencies during childhood in children with neonatal HIE.[265]

Even though conventional developmental tests could be useful for the subgroup of children with HIE who do not develop severe CP and for comparing results in research studies, they should not be used in clinical practice to assess the intelligence or the degree of cognitive development of a child with HIE and significant injury to the ganglia or thalamus. These children could have considerable motor disability that also affects their communication capacity, wherefore the results obtained using these tests do not reflect their intellectual level or their general level of development. In particular, Bayley's test[266] is not designed to be used in children with a physical and/or neurosensorial disability, and it should not be applied routinely to these children. If it is applied, the results should be interpreted with considerable prudence.1 Unfortunately, there are no developmental tests for small children that take into account the impact by motor disability on the remainder of the neurodevelopment. More important than obtaining an intelligence quotient or a development quotient is evaluating which developmental areas of a child require greater attention and what the child's strong points are. This is especially important when the child joins the education system, to determine if they have special educational needs or if they need adaptations to the educational curriculum.

In children with HIE evaluated during school age, behavioural and social alterations have been reported, especially anxiety, lack of attention / hyperactivity and aggressiveness. One population study has even indicated a greater frequency of autism with respect to the general population, but in said work the evaluated patients had not only had HIE, but also other types of neonatal encephalopathy not due to perinatal asphyxia, and the percentage of children with genetic disor-

ders was considerable.[267] The frequency and range of the behavioural problems in children with HIE are not well known, but it is a subject that is stirring up growing interest and concern.

Follow-up programme for newborns with HIE after discharge from Neonatology

Tables 3 and 4 show how follow-up on children with HIE can be organised according to their prognosis. This schematic is a guideline, and it does not in any event replace an individual assessment of the needs of each patient and their family. Different families can have different needs, even when the degrees of involvement of their children are apparently similar. The prognosis, as it has been previously explained, is based on a combination of the clinical data and of the results of complementary tests, mainly imaging tests. Any child with significant HIE (moderate or severe) must have a brain MRI, ideally between 7 and 21 days of age, but if this is not possible, then at any other time during the neonatal period. In children with mild HIE who show rapid recovery, who have a normal neurological screening exam at the time of discharge and in which the brain ultrasounds have been repeatedly normal, the MRI is not essential.

A prognosis should never be established based exclusively on the results of the MRI or of any other complementary test. If there is a discrepancy between the clinical state and the neuroimaging, it will be necessary to review the diagnosis and assure the reliability of the images (including the time when they were taken) before giving the family the prognosis. In the event of any doubt, it is better to wait and repeat the test to see how the injuries have evolved.

A. Children with mild HIE and normal neuroimaging tests or isolated, mild-moderate damage to white matter

In these children, the motor prognosis is very good, and it is an exceptional case when a child develops cerebral palsy. The development of these children during the first two years of life is normal in the majority of cases, and they do not need therapeutic or rehabilitating interventions or specialised care. These children can be seen between 9 and 12 months of age, and if everything goes well, once again at two years. As from two years, this group of children can show behavioural problems with a greater frequency than the general population. If there is no specific follow-up programme beyond this age, the family should be informed about the possibility that these problems might appear, and they should know what socio-educational resources they can use. Ideally, these children should be evaluated during school age to detect memory and learning difficulties and the need for educational support, and to detect behavioural and social-emotional alterations. In any event, it is advisable for the primary care paediatrician to know the perinatal history of these children and to be able to refer them to specialised centres if necessary.

B. Children with mild or moderate HIE and mild injuries to the basal nuclei and thalamus

This group of children is very similar to the preceding group, but they can have mild motor disorders in 10-20% of the cases, wherefore they need closer monitoring during the first year of life. In the majority of cases, they can be evaluated at 6 months, and if everything goes well, once again at two years. If the exploration at 6 months is not completely normal or if there is another reason for concern, a new visit at 12 months could be useful. Almost all cases of CP secondary to neonatal HIE will have appeared before this date.

Subsequent follow-up on this group can be done as with children of the first group.

C. Children with moderate or severe HIE and extensive injuries to white matter

This group has a slight but significant risk of developing CP. In the majority of cases, it is in the form of mild, spastic diplegia or tetraplegia that usually allows independent walking. The biggest challenges faced by these children, however, are cognitive and language delays, behavioural disorders, visual problems and the development of epilepsy. The high frequency of visual problems in this group of children justifies evaluating them as from 6 months by an ophthalmologist who has experience with the visual sequelae of this illness. Depending on this first exam, specific and subsequent ophthalmological follow-up must be scheduled. It is advisable to be very receptive to the possible behavioural problems that parents could report, given that as from the second year of life and in the event that there are suspicions, an evaluation by a child psychiatrist and/or a specialised psychologist could be very helpful.

In these children, the growth of the head circumference during the first months after discharge is an indicator of the loss of volume and therefore of the extent of the damage to white matter, and it can be used to identify children who are at a greater risk of showing neurodevelopmental disorders in the medium to long term.[170]

D. Children with moderate or severe HIE and moderate-severe injuries to the ganglia and thalamus, with or without mild-moderate damage to white matter.

In this group of children, the prevalence of cerebral palsy is very high, greater than 50%, and it is related directly to the extent of the damage to the ganglia and thalamus. Feeding and communication disorders are frequent as a consequence of alterations to the oromotor function. Signs of motor involvement and oral feeding difficulties appear very early and almost without exception before the end of the first year of life, which justifies more frequent and closer follow-up during the first few months after discharge than in the preceding groups.

In this group, a first visit at 3 months of age will allow knowing the level of the child's adaptation to the family home and knowing what problems have arisen since discharge from the hospital. The most severe children will already show signs of motor involvement at this time, and it is advisable that they begin rehabilitation therapy as soon as possible. It is therefore a good time for them to be re-admitted to rehabilitation and physical therapy, if this wasn't done before discharge. It is necessary, as from this very moment, to begin assessing the possibility that oral feeding disorders might appear and, if there are suspicions, to begin exploring the feelings and attitudes of the parents regarding these problems. Throughout the second semester, it is advisable to evaluate vision and hearing. It is during the second year of life, generally after having tackled any problems of oral feeding, when communication and language disorders in these children become more evident.

As from 18 months of age, the remainder of the visits can be scheduled according to the family's needs and the problems that arise. Probably, if the parents are satisfied with the care that the child is receiving from the multi-disciplinary team, the work of the coordinator will be less necessary.

E. Children with severe HIE, moderate-severe injuries to the ganglia and thalamus and extensive damage to white matter

In this group, the presence of severe CP, oromotor involvement, visual impairment and epilepsy are the norm, and also the mortality rate during infancy is considerable. These children should be seen for the first time at an age of 3 months or earlier, depending on the condition of the child and the family's level of concern. Some children in this group are sent home with a nasogastric tube

due to the impossibility of receiving food orally and due to the difficulty of managing secretions. It is highly improbable that these problems will get better, wherefore it is mandatory to monitor growth and the nutritional condition, as well as early referral to gastroenterology and nutrition. Most of the considerations that have been made for the preceding group are also applicable to these children, with the additional consideration of the risk of death. This is discussed in more detail in the following section.

Mortality during follow-up. Palliative care

Severe HIE is associated with high mortality in the neonatal period, which can reach 25-30%.[266, 267] Among survivors with severe HIE, a significant number of children die during infancy, frequently during the first year of life.170, 268 The children who die have not only previously had a severe motor disability, but also, with a high frequency, they have also had problems with feeding, visual impairment and epilepsy. The most frequent causes of death are primarily respiratory problems, including pneumonia and aspiration pneumonitis, and secondly, there are refractory epileptic seizures.[269]

In the majority of cases, the best place for the child to die is in their home with their family,[270] and this option should be facilitated as much as possible whenever this is what the parents want. In some autonomous communities, paediatric palliative care units have been developed. These units offer the ideal framework for caring for these children. The purpose is to favour the care of a child at their own home and to prevent emergency calls or hospital admissions, whenever possible. Ideally, in the days or weeks prior to death, the potential treatments that the family would be willing to accept for their child and under what circumstances should be agreed upon with the family. If it is considered necessary, this can be put in writing to facilitate the process for other health professionals who didn't previously know the child, so that they can provide the most appropriate care when the time comes.

The death of a child who had HIE is devastating for a family, regardless of the child's degree of disability. For many parents, death is the extension of the grief that began with the birth and ensuing loss of the healthy child they expected. Handling the grief of not only the parents but also the siblings and other members of the family must form a part of the medical care that is offered to these patients.

Other aspects of care for follow-up on children with HIE

The relationship that is established with families during follow-up after discharge from neonatology places paediatricians in a privileged position, not only with respect to learning first-hand about the difficulties of these families in their daily life but also with respect to being participants in other, more intimate concerns. It is not infrequent for many families, once the acute period of the illness has passed, to begin re-experiencing the time around the birth of the child and to think about the causes that led to the illness of their child. Sometimes parents can even feel guilty, thinking that some attitude or decision of theirs during pregnancy or delivery could have caused this outcome. It is necessary to be sensitive to these concerns and be alert to signs that indicate that the parents still have unresolved doubts. It's never to late to go back over what happened, even though the child may have died, and it can sometimes be very beneficial in such conversations to include the participation of the obstetrician who took part in the birth. Parents who would like to have more children need to know the risks of something similar happening again, and they need to discuss the possible options that exist to minimise them. A new pregnancy could mean a source of stress for both parents, especially as the time of birth approaches. Even though another pregnancy may not be strictly high-risk for medical reasons, the emotional circumstances of the parents make it a high-risk pregnancy, and it should be managed as such.

If the development of a child with HIE is not what is expected and it is suspected that some factor other than the perinatal hypoxic-ischaemic episode could have caused or contributed to the brain injuries, the initial diagnosis must be reconsidered and a complete study must be conducted according to the new circumstances. Cooperation with paediatric neurologists, geneticists and other specialists could be very valuable.

Lawsuits due to supposed obstetric or perinatal negligence are very frequent after the birth of a child with HIE who subsequently shows sequelae. In 2001, the compensation for cases of obstetric malpractice made up 60% of the total compensation that the British health system had to cover.[271] And even though there are no comparable data in our country, it is very likely that the figures are similar. This means that it is very possible that during the follow-up on these patients, we might find out that the family has filed a lawsuit, and this could give rise to an uncomfortable situation in our relationship with the parents. In these cases, it is best to talk about the subject directly with them. We have to keep in mind that the majority of parents do not want to harm the medical team who took care of them, but they need to understand what happened: if the damage could have been avoided and if measures have been taken so that a similar episode doesn't happen again. In these circumstances, when the conflict threatens the professional relationship, it might be better for both the family and the professionals to refer the patient to another centre to continue with care and follow-up. But in no event should the existence of a lawsuit jeopardise the quality of the care that the patient receives or constitute a barrier to our communication with the parents.

The financial load and workload represented by caring for a child with a disability is a subject that we health professionals pay scarce attention to. The needs of these children are incomparably greater to those of children with normal development, and they normally increase with the passage of time. Many children would benefit from special equipment and devices that are not generally covered by the state or that are only partially covered, and due to their price, they are inaccessible for a large number of families. These include wheelchairs, orthopaedic devices, communication support devices and architectural adaptations in the home.[272] It is important for social workers to form a part of the multi-disciplinary team that is caring for these children in follow-up. We paediatricians can help by transmitting these needs to the corresponding agencies and, in general, by contributing to making these problems more visible in society.

Table 1. Gross Motor Function Classification for children from 0 to 2 years with cerebral palsy

Level	Description
I	The child is capable of sitting and remaining seated on the floor with both hands free to handle objects. The child crawls on hands and knees, stands up and takes steps while holding onto furniture.
II	The child remains seated on the floor but may need their hands for support and to maintain balance. The child wriggles or crawls with hands and knees. The child can stand up and take a few steps holding onto furniture.
III	The child remains seated on the floor with back support. The child can wriggle and turn over.
IV	The child needs support of the torso to remain seated. Head control is sufficient. The child can turn over to supine, and sometimes to prone.
V	There is no head control or of the torso against gravity, either prone or sitting. The child needs the help of an adult to turn over.

Figure 1. Alterations in a child with CP and follow-up

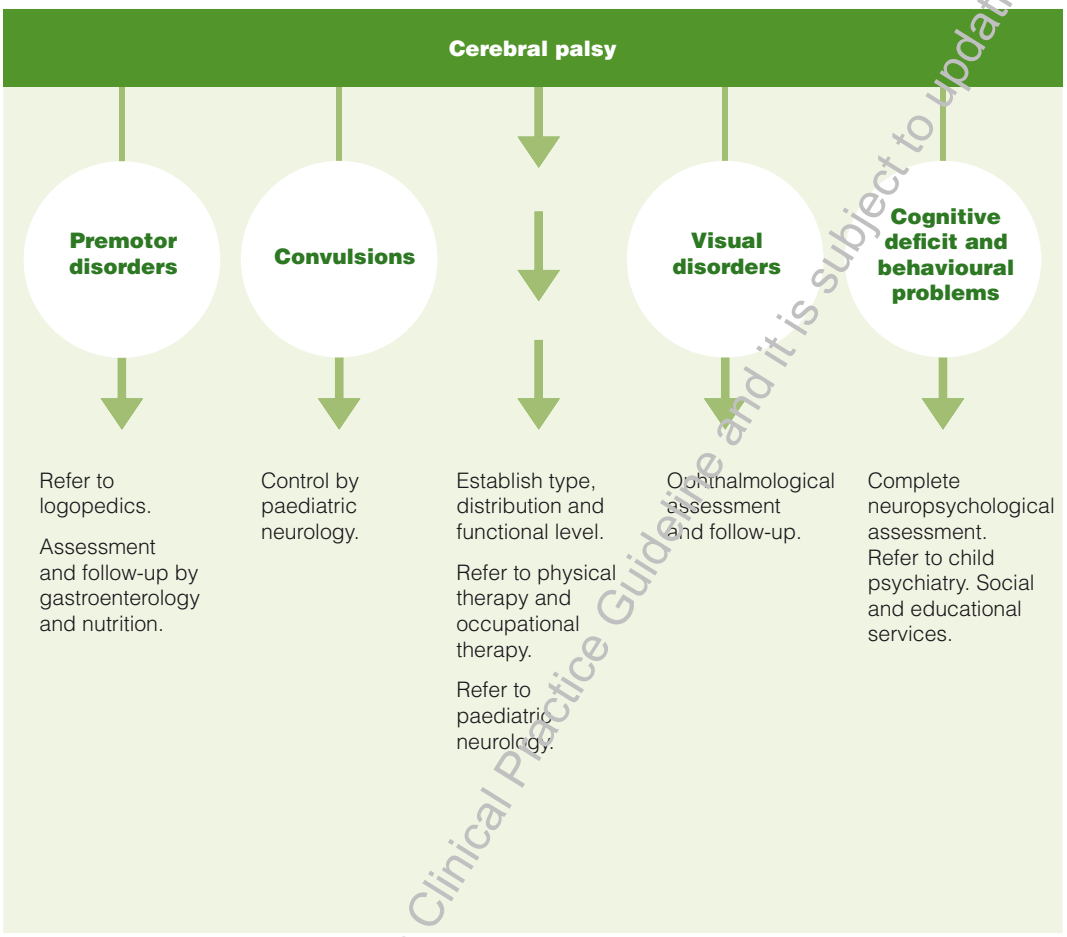

Tabla 2. Problemas de alimentación

Children at risk of showing oral feeding disorders during follow-up
– Children with severe HIE – Children with extensive involvement of the ganglia and thalamus, especially if it includes the brain stem – Children who have not succeeded in establishing normal oral feeding at the time of discharge.
Warning signs
– Meals that take too long, breast feeding babies and children who show stress before feeding (try to observe a feeding during a doctor's visit) – Liquids have to be thickened – Children who are not able to eat solid foods after one year of life – Choking (with liquids and/or solids) – Persistent cough – Frequent respiratory infections – Gastric reflux, constant vomiting – Slow growth, less than optimal nutritional state – Difficulties in the development of spoken language – Excessive salivation for the age

Table 3. Follow-up calendar for children with HIE

Estimate of the prognosis at the time of discharge						
Group		1*	2	3	4	5
Degree of encephalopathy		Mild	Mild/ moderate	Moderate/ severe	Moderate / severe	Severe
Neuro-imaging	Ganglia/ thalamus involvement	No	Mild	No	Moderate / severe	Moderate / severe
	WM involvement	No / mild-moderate	No / mild-moderate	Extensive	No / mild-moderate	Extensive
General prognosis		Very good Discrete increase of the risk of learning and behavioural problems in school age	Good Mild CP in 10-15% Discrete increase of the risk of final motor impairment, learning problems and behavioural problems in school age	Intermediate Mild CP in 15-25% Significant risk of cognitive delay, visual impairment and behavioural alterations, microcephaly and epilepsy	Adverse Moderate-severe CP in 50-75% Frequent feeding and communication disorders; visual impairments and epilepsy	Very adverse Moderate-severe CP in > 90% Very frequent feeding and communication disorders; visual impairments, microcephaly and epilepsy. High mortality, especially if there is brain stem injury
Postnatal age		Follow up planning				
3 months					General and neurological evaluation. Assessment of feeding and nutrition Refer to NRL and multi-disciplinary team	General and neurological evaluation. Assessment of feeding and nutrition Refer to NRL and multi-disciplinary team Assessment of threat to life
6 months			General and neurological evaluation. Refer to NRL and rehabilitation of motor signs	General and neurological evaluation (head circumference!) Assessment of visual function Refer to NRL and rehabilitation if motor signs	General and neurological evaluation. Assessment of feeding and nutrition Assessment of visual function	General and neurological evaluation. Assessment of feeding and nutrition Assessment of visual function Assessment of threat to life
9 months - 1 year		General and neurological evaluation Consider a hearing assessment	Repeat evaluation if examination not entirely normal at 6 months. Refer to NRL and rehabilitation if motor signs Hearing assessment	General and neurological evaluation. Hearing assessment	General and neurological evaluation. Assessment of feeding and nutrition Hearing assessment	General and neurological evaluation. Assessment of feeding and nutrition Hearing assessment Assessment of threat to life
18 months				General and neurological evaluation. Formal assessment of neurodevelopment. Psychological and psychiatric assessment if behavioural alterations	Continue with visits every 6-9 months following the same scheme, according to family needs Evaluation of communication and language disorders Evaluation of the cognitive level and educational needs (Do not use developmental or intelligence tests without adapting) Evaluation of social resources	
24 months		General and neurological evaluation. Formal assessment of neurodevelopmen				

Table 4. Proposal of follow-up on children with HIE according to the prognosis

Evaluation	What it includes	When
General evaluation	General state of health, health problems since the last visit, usual medication.	In all visits
Neurological evaluation	Neurological examination, including measurement of the head circumference Guided interview: appearance of convulsions since last visit; tolerance of / adverse effects from anticonvulsant drugs, such as those used for spasticity and dystonia (assure regular follow-up by the paediatric neurologist) In some children with CP: functional repercussion according to the classification of the gross motor function; early detection of subluxation of the hip and other painful musculoskeletal complications	In all visits
Neurological evaluation	Assessment of the nutritional state Guided interview: what does the child eat? how long do meals take? does the child have a good appetite? is the child happy when it's meal time? does the child like different textures and flavours? does the child frequently choke? is it hard for the child to drink? does the child continuously cough? how many times in the last 6 months has the child had any respiratory infection? did the child need to be admitted to hospital for this reason? has the child ever been diagnosed with aspiration pneumonia? does the child have signs of gastric reflux? does the child take any medication for the reflux? is the child constipated? Observe a feeding/meal directly during the doctor's visit whenever possible	In all visits of children with a motor disorder of any degree
Assessment of communication disorders	Guided interview: does the child speak; how many words does the child use? is the child understood well, including people who don't know the child well, or just the child's family? does the child use any other means to communicate - indicating with their eyes or finger, different intonations, shouts or gestures? is the child capable of transmitting their likes, needs and mood? can the child express when they have pain? Directly observe how the child communications with us and with their relatives	In all visits of children with a motor disorder of any degree
Evaluation of visual function	Once before one year of age in all children with moderate or severe HIE (consider for children with mild HIE if they show other risk factors or there is clinical suspicion)	As from 6 months in children with significant ganglia and thalamus injury and or extensive injury to white matter
Evaluation of hearing function	Once before one year of age in all children with moderate or severe HIE (consider for children with mild HIE if they show other risk factors or there is clinical suspicion)	As from 6 months in children with significant ganglia and thalamus injury and or extensive injury to white matter
Evaluation of neurodevelopment	Evaluation of development through observation during the doctor's visit and information provided by the parents. Formal evaluation (development test) around 2 years of life. Any development test (Bayley, Brunet-Lezine, Batelle, others) with which the examiner is familiar. Do not administer without adapting to children with a motor and/or neurosensorial disability.	In all visits Developmental test: 2 years

Appendix 7. Others

1. Report from the Clinical Research Ethics Committee

REPORT FROM THE CLINICAL RESEARCH ETHICS COMMITTEE

Dr Pablo Ferrer Salvans, Secretary of the Clinical Research Ethics Committee (CEIC), Fundació Sant Joan de Déu, Esplugues de Llobregat (Barcelona), hereby

CERTIFIES

That in the meeting of the Clinical Research Ethics Committee of Fundació Sant Joan de Déu held on 24 October 2013, the "Guide for parents: Hypoxic-Ischaemic Encephalopathy and Hypothermia" was assessed, which has CEIC code PIC-108-13 and whose principal investigator is Dr Alfredo Garcia-Alix Pérez.

The CEIC has examined the submitted project, and it found no ethical objections to the development thereof.

Which I sign in Esplugues de Llobregat (Barcelona), 22 November 2013.

Signed:

Dr Pablo Ferrer Salvans

Secretary of the CEIC of the SJD Foundation

2 Descriptive tables of the results of the included studies

Table 1. Included studies, pre- and posttest probabilities and diagnostic ORs of the aEEG for death or moderate/severe disability broken down by hours of life

	No Hypothermia				Hypothermia			
	Pre- Prob. 63.17%				Pre- Prob. 47.88%			
	Studies (Newborn)	Positive post Prob. (95% CI)	Negative post Prob. (95% CI)	Diagnostic OR (95% CI)	Studies (Newborn)	Positive post Prob. (95% CI)	Negative post Prob. (95% CI)	Diagnostic OR (95% CI)
6 hours	10 (464)	89.9% (80% to 95.2)	28.3% (18.2 to 38.2)	30.69 (10.09 to 93.31)	5 (144)	59.4% (53.5 to 64.9)	11.4% (3.5 to 31)	12.74 (3.24 to 50.16)
24 hours	5 (267)	97.55 (93.3% to 99.1)	21.5% (15.9 to 29.2)	237.61 (56.47 to 999.89)	3 (78)	76.7% (66.4 to 84.5)	7.6% (1.8 to 27.4)	41.87 (7.01 to 250.02)
36 hours	3 (76)	97.1% (87.3% to 99.49)	26.5% (13.4 to 45.7)	104.25% (16.55 to 656.74)	3 (66)	89.1% (57 to 98.1)	9.2% (2.7 to 25.4)	115.21% (16.562 to 801.44)
48 hours	3 (77)	96.6% (85.5% to 99.3)	30.8% (21.5 to 43)	76.88 (12.72 to 464.89)	2 (65)	96.9% (81.7 to 99.6)	16.8% (8.4 to 30.2)	157.76 (16.59 to 1499.9)
72 hours	3 (64)	90.7% (73.9% to 97.1)	35.4% (24.6 to 47.1)	42.68 (7.97 to 261.57)	2 (66)	95.8% (75.6 to 99.4)	28.3% (16.8 to 43.8)	60.29 (6.74 to 539.48)

Table 2. Included studies, pre- and posttest probabilities and diagnostic ORs of the aEEG for death, broken down by hours of life

	No Hypothermia				Hypothermia			
	Pre- Prob. 35.11%				Pre- Prob. 26.23%			
	Studies (Newborn)	Positive post Prob. (95% CI)	Negative post Prob. (95% CI)	Diagnostic OR (95% CI)	Studies (Newborn)	Positive post Prob. (95% CI)	Negative post Prob. (95% CI)	Diagnostic OR (95% CI)
6 hours	8 (360)	70.2% (58.3 to 79.9)	5.1% (2.1 to 11.1)	59.18 (21.28 to 164.55)	3 (65)	32.9% (26.8 to 39.5)	11.6% (2.8 to 39.7)	3.89 (0.61 to 24.87)
24 hours	5 (267)	79.8% (53.9 to 93)	4.6% (1.1 to 17.1)	116.95 (19.15 to 714.10)	3 (65)	39.8% (26 to 55.4)	7.6% (1.7 to 27.9)	9.61 (1.52 to 60.62)
36 hours	2 (56)	69.6% (54.7 to 81.2)	7.5% (2.1 to 22.9)	29.69 (5.56 to 158.52)	1 (43)	65.1% (47.2 to 79.5)	2.1% (0.4 to 23.8)	90.00 (4.59 to 1762.85)
48 hours	2 (47)	64.5% (49.9 to 77.2)	8.4% (2.6 to 25.7)	19.42 (3.55 to 106.29)	2 (53)	64.4% (43.4 to 80.9)	4.1% (0.7 to 20.8)	48.02 (4.78 to 482.59)
72 hours	2 (41)	60.3% (45.8 to 73.3)	8% (1.6 to 28)	19.59 (2.99 to 128.37)	2 (53)	64.4% (43.4 to 80.9)	4.1% (0.7 to 20.8)	48.02 (4.78 to 482.59)

Table 3. Included studies, pre- and posttest probabilities and diagnostic ORs of the aEEG for CP, broken down by hours of life

	No Hypothermia				Hypothermia			
	Pre- Prob. 31.28%				Pre- Prob. 19.37%			
	Studies (Newborn)	Positive post Prob. (95% CI)	Negative post Prob. (95% CI)	Diagnostic OR (95% CI)	Studies (Newborn)	Positive post Prob. (95% CI)	Negative post Prob. (95% CI)	Diagnostic OR (95% CI)
6 hours	3 (113)	56.9% (46.5 to 66.7)	13.1% (2.2 to 49.9)	15.40 (2.58 to 92.02)	2 (34)	21.6% (17 to 27.3)	11.1% (1.7 to 48)	2.26 (0.23 to 22.39)
24 hours	1 (27)	33.4% (22.3 to 82.8)	22.6% (1.8 to 82.8)	1.71 (0.06 to 50.42)	2 (34)	33.4% (22.3 to 46.5)	22.6% (1.8 to 82.8	6.81 (0.72 to 64.30)
36 hours	0	•	•	•	1 (22)	43.5% (25.4 to 63.4)	3.5% (0.2 to 34.3)	20.80 (0.92 to 469.01)
48 hours	0	•	•	•	1 (22)	61.9% (28.1 to 87.1)	7.5% (2.1 to 22.9)	24 (1.62 to 356.65)
72 hours	0	•	•	•	1 (22)	35.1% (5.9 to 82.1)	16.8% (9.2 to 28.9)	2.67 (0.18 to 39.63)

Table 4. Included studies, pre- and posttest probabilities and diagnostic ORs of the aEEG for CP, broken down by hours of life

	No Hypothermia				Hypothermia			
	Pre- Prob. 38.69%				Pre- Prob. 22.76%			
	Studies (Newborn)	Positive post Prob. (95% CI)	Negative post Prob. (95% CI)	Diagnostic OR (95% CI)	Studies (Newborn)	Positive post Prob. (95% CI)	Negative post Prob. (95% CI)	Diagnostic OR (95% CI)
6 hours	6 (302)	43.7% (36 to 51.9)	39.6% (32.7 to 46.9)	1.23 (0.57 to 2.65)	1 (43)	47.9% (40.3 to 55.7)	10.2% (0.6 to 63.9)	7.91 (0.41 to 150.98)
24 hours	3 (220)	44.3% (20.6 to 70.8)	31.2% (10.2 to 64.5)	1.65 (0.19 to 14.22)	2 (34)	53.5% (42.0 to 64.4)	14.6% (2.5 to 52.2)	6.71 (0.73 to 61.49)
36 hours	2 (56)	72.7% (58.5 to 83.5)	8.6% (2.5 to 25.8)	29.69 (5.56 to 158.52)	1 (43)	59.6% (42.7 to 74.4)	20.6% (7 to 46.7)	5.68 (0.95 to 33.92)
48 hours	2 (47)	32.7% (19.3 to 48.6)	32.7% (19.3 to 48.6)	2.02 (0.51 to 7.97)	1 (43)	56.5% (36.2 to 74.9)	27.1% (13.2 to 48.3)	3.47 (0.66 to 18.33)
72 hours	2 (41)	48.6% (35.2 to 62.2)	32.7% (19.7 to 49.3)	1.99 (0.5 to 7.91)	1 (41)	47.6% (21.7 to 75)	34.4% (18.9 to 53.7)	1.73 (0.25 to 11.97)

Table 5: Newborns treated with hypothermia

	No Hypothermia				Hypothermia			
	Pre- Prob. 47.88%				Pre- Prob. 47.88%			
	Studies (N)	Positive post. (95% CI)	Negative post (95% CI)	Diagnostic OR (95% CI)	Studies (N)	Positive post. (95% CI)	Negative post (95% CI)	Diagnostic OR (95% CI)
1-30d	13 (543)	86% (80 to 90%)	23% (25 to 30%)	29.80 (17.09 to 51.95)	4 (181)	80% (74 to 86%)	14% (8 to 24%)	29.59 (12.12 to 72.25)
1-7d	6 (211)	88 (76 to 95%)	22 (9 to 42%)	31.05 (10.62 to 90.84)	2 (32)	86% (62 to 96%)	12% (1 to 78%)	48.34 (1.85 to 1246.90
8-30d	5 (149)	88% (68 to 96%)	20% (5 to 56%)	43.87 (6.94 to 281.31)	1 (36)	73.5 (43.3 to 90.3%)	28.3% (14.3 to 48.3%)	

Table 6. When predictive efficacy data were not provided

Main characteristics of the included studies						
Author and year	No. of patients	Moment of determination in hours	Negative outcome	Follow-up (months)	Type of evaluation	Quality
García-Alix, 1994	70 with HIE	12 (12.2 ± 4.2)	Death or severe disability (DP)	12	Neuro exam and Denver (DDST)	Moderate
Thornberg, 1995	9 controls, 22 with HIE	Between 2 and 32 hours	Death or severe damage	18	Neuro exam	Low
Ezgü, 2002	32 with HIE	First 72 hours	Iterada (7-14 d) Griffith < 85	12	MR and Griffith	Low
Tekgul, 2004	21 with HIE	24-72 hours	Death, neurological alteration and delay	14	Neuro exam (functional class.) and Denver (DDST) II	Moderate
Vasiljevic, 2012	90 with HIE	First 72 hours	Death, CP, epilepsy	12	Neuro exam and Denver (DDST)	Moderate

Table 7. Results for the adverse development outcome (death or severe disability)

Author	Favourable Outcome	Adverse Outcome	VP	FP	FN	VN	Cut-off point
García-Alix, 1994 (at 12 hours)	54	6	6	6	1	57	25 ng/Ml
Thornberg, 1995	14	6	6	1	0	13	50 ng/mL
Ezgü, 2002	9	10	9	1	1	8	6 µg/L
Tekgul, 2004	14	7	6	5	1	9	17.6 ng/mL
Vasiljevic, 2012	75	15	15	14	0	61	25.5 ng/mL

FP: false positive, FN: false negative; VP: true positive; VN: true negative

Table 8. Sensitivity, specificity, 95% CI, and the PLRs, NLRs and ORs for each study

Author	Se (CI)	Sp (CI)	PLR (CI)	NLR (CI)	OR (CI)
García-Alix, 1994 (at 12 hours)	0.857 (0.41-0.996)	0.905 (0,804-0,964)	9.00 (3.968-20.414)	0.158 (0.026-0.971)	57.00 (5.84-556.17)
Thornberg, 1995	1.0 (0.541-1.00)	0.929 (0.661-0.998)	9.286 (2.007-42.970)	0.079 (0.005-1.153)	117.00 (4.169-3283.8)
Ezgü, 2002	0.90 (0.555-0.997)	0.889 (0.518-0.997)	8.100 (1.262-52.001)	0.113 (0.017-0.733)	72.00 (3.841-1349.6)
Tekgul, 2004	0.857 (0.421-0.996)	0.643 (0.351-0.872	2.400 (1.117-5.158)	0.222 (0.035-1.422)	10.80 (0.997-117.00)
Vasiljevic, 2012	1.00 (0.782-1.00)	0.813 (0.707-0.894)	5.078 (3.169-8.135)	0.039 (0.003-0.592)	131.48 (7.427-2327.6)
Overall Heterogeneity	0.93386 4.06, p = 0.398	0.784-0.896) 6.96, p = 0.138	5.242 (3.159-8.697)	0.1 24 (0.049-0.314)	49.3 78 (14.89-163.68)

Table 9: Main results of Verdu, 2001; Tekgul, 2004; and Çeltic, 2004

Main results for the predictive capacity of the concentration of NSE in serum									
Reference	Moment	Cut-off point and age	Differences between normal and adverse outcome	Se	Sp	PPV:	NPV:	PLR	AUC
Verdu, 2003	24-72 hours	27.6 µg/L	Yes	100	79	60	100	4.76	Not reported
Tekgul, 2004	First 24 hours	9.5 µg/L	No	57	43	67	33	0.0	Not reported
Celtic, 2004	4-48 hours (20 ± 14)	45 µg/L	Yes	84	70	39	95	2.8	Not reported

Table 10. Main results of Nagdyman, 2003;[214] Thorngren-Jernek, 2004;[215] and Murabayasi, 2008[216]

Predictive value of S100B in the serum of neonates not treated with hypothermia									
Reference	Cut-off point and age	Moment	Differences between normal and adverse outcome	Se	Sp	PPV:	NPV:	PLR	AUC
Nagdyman, 2003	NR	2, 6, 12, 24 hours	No	NR	NR	NR	NR	NR	NR
Thorngren Jerneck, 2004	> 12 µg/L	1st day (1-19 hours) 2nd day (24-48 hours) 3rd day (48-96 hours)	Yes	73	74	50	89	2.80	NR
Murabayasi, 2008	> 10 µg/L	First 24 hours	Yes	100	90.9	60	100	11	NR

Table 11. Main results of the study by Gazzolo, 2003217

Predictive value of S100ß in urine for predicting adverse outcome (disability at one year or death)								
Reference	Cut-off point in µg/L	Moment	Differences between Normal and Adverse	Se	Sp	PPV:	NPV:	AUC
Gazzolo, 2003	0.28	First urination	Yes	100	87.3	46.2	100	0.978
	urination	Yes	100	87.3	46.2	100	0.978	0.999
	0.52	24 hours	Yes	100	95.5	70.6	100	0.997
	72 hours	72 hours	Yes	100	98.2	85.7	100	0.998

Table 12. The meta-estimate of the proportion of patients with said outcome according to the degree of perinatal HIE without treatment with hypothermia

Degree of neonatal HIE	Proportion of death or severe disability (95% CI)
Mild	0.01 (-0.08, 0.10)
Moderate	0.42 (0.34, 0.50)
Severe	0.95 (0.90, 1.00)

Table 13. Meta-estimate of the proportion of patients with said outcome depending on the degree of neonatal HIE according to our re-analysis of hypothermia RCTs

Degree of neonatal HIE	Proportion of death or severe disability (95% CI)
Moderate	0.52 (0.44, 0.60)
Severe	0.83 (0.72, 0.93)

Table 14. Meta-estimates of the proportions of patients with said outcome depending on the degree of neonatal HIE, both for the cases treated with hypothermia and for the controls

Degree of neonatal HIE	Proportion of death or severe disability (95% CI)	
	Hypothermia	Normothermia
Moderate	0.35 (0.28 to 0.41)	0.52 (0.44 to 0.60)
Severe	0.67 (0.58 to 0.76)	0.83 (0.72 to 0.93)

Table 15. Estimate of the risks of death or major disability for severe HIE versus moderate HIE in patients treated with hypothermia and patients managed in normothermia

	Hypothermia	Normothermia
OR (95% CI)	3.77 (2.62 to 5.41)	4.14 (2.40 to 7.13)

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