



Medical care & clinical practice



european standards of
care for newborn health

EFGNI european foundation for
the care of newborn infants



Topic Expert Group
Medical care and clinical practice

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Topic Expert Group: Medical care and clinical practice

Overview

Preterm and ill infants, treated in the neonatal intensive care unit have multiple medical clinical conditions, resulting in an extremely vulnerable patient group. (1–4) Enormous improvements in neonatal care during the last years have also made care increasingly complex.

The most important neonatal event is the postnatal adaptation to extrauterine life during which air breathing is established and circulatory changes take place. Difficulties may occur with transition in situations such as preterm birth and following perinatal asphyxia, accounting for much of the associated neonatal mortality and morbidity. (5–8) Other conditions that are of great relevance for preterm and other ill infants are bronchopulmonary dysplasia, respiratory distress syndrome, suspected early onset neonatal sepsis, hypoglycaemia, hypoxic ischaemic encephalopathy, persistent pulmonary hypertension of the newborn infant, neonatal jaundice, Retinopathy of Prematurity, and vitamin K deficiency bleeding.

Additionally, infants requiring neonatal intensive care constitute a high-risk population for developing brain injury, particularly full term and preterm infants exposed to hypoxia-ischaemia, CNS infections, or with congenital anomalies. Therefore, early recognition of disturbed brain function or structural brain injury is important in the institution of preventive or treatment strategies, and appropriate follow-up. Early identification of impaired function will improve clinical management and long-term functional outcomes. (9–14)

The Topic Expert Group on Medical care and clinical practice develops standards on the prevention, diagnosis and management of the main medical conditions and challenges affecting preterm or ill babies. Additionally, standards on specific clinical procedures and techniques are developed.

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Hypoglycaemia in at risk term infants

Mitanchez D, Hellström-Westas L, Zimmermann L, Buonocore G, Beardsall K, Boardman J, Tin W

Target group

Term newborn infants and parents

User group

Healthcare professionals, neonatal units, hospitals, and health services

Statement of standard

Measures are taken to identify, prevent, and manage hypoglycaemia in newborn infants who are at risk for impaired metabolic adaptation, including those with growth restriction, maternal diabetes, asphyxia, maternal beta-blocker medication.

Rationale

The goal is to prevent the adverse effect of hypoglycaemia while minimising unnecessary separation of mother and the newborn infant.

Hypoglycemia in newborn infants is associated with risk for brain damage and neurodevelopmental sequelae. (1) At birth, the discontinuation of nutrients from the mother results in a decline in plasma glucose level during the first two hours of postnatal life to as low as 1.1-1.4 mmol/L (20-25 mg/dL) that is considered to be part of normal adaptation to postnatal life. (2,3) Many newborn infants tolerate these initially low blood glucose levels even though glucose is the major oxidative fuel of the brain, because the neonatal brain also has the capacity to oxidise ketone bodies and lactate. After the first two postnatal hours, glucose concentration rises to more stable concentrations. During this period, endogenous production of glucose is promoted by glycogenolysis and gluconeogenesis. Enhancement of fat oxidative metabolism also contributes to the production of ketone bodies. Metabolic neonatal transition is integrated under the influence of a postnatal hormonal surge and timely production of key regulatory enzymes. (4)

In addition to the risk categories listed above, perturbations of adaptive responses can occur in preterm infants and those with, sepsis, haemolytic disease and specific inborn errors of metabolism. They can also occur in term infants with congenital disorders that prevent infants from mounting an adequate counter-regulatory metabolic and endocrine response, such as hyperinsulinism. (5)

Benefits

Short-term benefits

- Reduced exposure to potentially harmful hypoglycemia in at risk infants (6)
- Reduced unnecessary investigations and interventions (7)
- Minimised separation of mother and infant (consensus)
- Increased rate of diagnoses of infants with hypoglycemic disorders before discharge (8)

Long-term benefits

- Improved neurologic outcome (consensus)



Components of the standard

Component	Grading of evidence	Indicator of meeting the standard
For parents and family		
1. Parents are informed by healthcare professionals about the importance of early energy provision and blood glucose monitoring. (9)	A (Low quality) B (High quality)	Patient information sheet
For healthcare professionals		
2. A unit guideline on identification, prevention, and management of hypoglycaemia is adhered to by all healthcare professionals.	B (High quality)	Guideline
3. Training on identification, prevention, and management of hypoglycaemia is attended by all responsible healthcare professionals.	B (High quality)	Training documentation
4. Risk factors for hypoglycaemia are identified at birth. (10)	A (Moderate quality)	Clinical records, guideline
5. An early feed, within one hour, is provided. (11,12)	A (High quality)	Clinical records, guideline
6. Thermal care, ideally given by skin-to-skin positioning, is provided. (13)	A (Moderate quality)	Clinical records, guideline
7. Blood glucose is measured at predetermined times. (6)	A (Moderate quality)	Clinical records, guideline
8. Observation of well-being and feeding documentation is conducted. (14)	B (High quality)	Clinical records, guideline
9. Interventions are administered according to operational thresholds approach. (15)	B (High quality)	Clinical records, guideline
For neonatal unit		
10. A unit guideline based on an operational threshold approach using values advocated by professional bodies is available and regularly updated in all maternity and neonatal units. (16)	A (Low quality) B (High quality)	Guideline
For hospital		
11. Training on identification, prevention, and management of hypoglycaemia is ensured.	A (High quality) B (High quality)	Training documentation



12. Equipment suitable for immediate and reliable blood glucose measurements is provided. (17)	A (High quality) B (High quality)	Audit report
13. Training in awareness of the limitations of the devices used for blood glucose monitoring is ensured. (17)	A (High quality) B (High quality)	Training documentation

For health service

14. A national guideline based on an operational threshold approach using values advocated by professional bodies is available and regularly updated.	B (High quality)	Guideline
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Where to go – further development of care

Further development	Grading of evidence
For parents and family N/A	
For healthcare professionals N/A	
For neonatal unit N/A	
For hospital N/A	
For health service	
<ul style="list-style-type: none">• Prioritise scientific studies investigating impaired metabolic adaptation, and the long term consequences of hypoglycaemia with or without clinical symptoms.	B (Moderate quality)

Getting started

Initial steps
For parents and family
<ul style="list-style-type: none">• Parents are verbally informed by healthcare professionals about the importance of early energy provision and blood glucose monitoring.
For healthcare professionals
<ul style="list-style-type: none">• Attend training on identification, prevention, and management of hypoglycaemia.• Promote early skin-to-skin contact and breastfeeding as standard care.
For neonatal unit
<ul style="list-style-type: none">• Develop and implement a unit guideline on identification, prevention, and management of hypoglycaemia, based on an operational threshold approach using values advocated by professional bodies.• Develop information material about the importance of early energy provision and blood glucose monitoring for parents.



For hospital

- Support healthcare professionals to participate in training on identification, prevention, and management of hypoglycaemia.

For health service

- Develop and implement a national guideline on prevention, diagnosis and management of hypoglycaemia, based on an operational threshold approach using values advocated by professional bodies.

Description

Glucose thresholds for intervention

- It is currently unknown at which glucose concentrations and after what duration neurologic injuries occur in newborn infants.
- Blood glucose levels below 1.0 mmol/L (18 mg/dL) that are associated with acute neurological dysfunction present the greatest risk of cerebral injury. (18–21)
- The tolerance to low glucose levels probably varies due to the newborn infant's ability to produce alternative substrates. (22)

→ Need to implement practices that prevent harm that results from unrecognised or untreated hypoglycemia whilst minimising unnecessary interventions and admission in neonatal unit.

- Measures to prevent and detect hypoglycaemia should be undertaken after birth in infants at risk, including: thermal care with skin-to-skin; support of breastfeeding; early energy provision and monitoring of blood glucose starting within the first hours of life.
- Feeding should be observed and abnormal feeding (not waking for feeds, not latching at the breast, not sucking effectively, appearing unsettled) should be recorded by the healthcare team.
- Glucose monitoring should be initiated before the second feed and no later than four hours after birth in asymptomatic infants, or at any time if there are abnormal clinical signs.
- Blood glucose concentration should be measured with validated devices. Local guidelines should be based on the operational threshold approach, using values advocated by professional bodies in their own country.

The lack of a clear evidence base for defining cerebral energy sufficiency is reflected in the contrast of recommendations between different organisations. (23)

1. Cornblath Operational Thresholds (2000), updated on review of the literature subsequently (14), and used by the British Association of Perinatal Medicine (2017). The suggested operational threshold concentrations at which clinicians should consider intervention are (15):

- Blood glucose level <2 mmol/L (36 mg/dL) in an asymptomatic baby, that remains below the same value at next measurement.
- A single measurement <2.5 mmol/L (45 mg/dL) in a newborn with abnormal clinical signs.



- A very low concentration of blood glucose <1.0 mmol/L (<18 mg/dL) indicates the need for intravenous glucose infusion aimed at raising plasma glucose concentration above 2.5 mmol/L. (45 mg/dL)

In symptomatic newborn infants with documented profound recurrent or persistent hyperinsulinic hypoglycaemia, therapeutic levels of 3.5 mmol/L (60 mg/dL) are recommended. (15) Infants with hypoxic ischemic encephalopathy have abnormal clinical signs by definition and the threshold of 2.5 mmol/L (45 mg/dL) should be used. (24)

2. The American Academy of Pediatrics (AAP) (2011)
The American Academy of Pediatrics (AAP) proposed an algorithm with suggested thresholds for intervention in at risk newborn infants at ≥ 34 weeks' gestation depending upon postnatal age: 1.4-2.2 mmol/L (25-40 mg/dL) in the first 4 hours, 1.9-2.5 mmol/L (35-45mg/dL) from 4-24 hours and 2.5 mmol/L (45 mg/dL) after 24 hours. (11)
3. The Paediatric Endocrine Society (2015)
Recently, the Paediatric Endocrine Society (PES) recommended higher plasma glucose levels to be considered safe in newborn infants: plasma glucose should be kept above 2.8 mmol/L (50 mg/dL) during the first 48 hours and above 3.3 mmol/L (60 mg/dL) for infants older than 48 hours. (8)

Measurement of glucose levels

- Accurate measurement of blood glucose level is essential for diagnosis and management of neonatal hypoglycaemia.
- The ward-based blood gas biosensor should be considered the reference standard for measuring blood glucose based on accuracy and speed of result availability.
- Blood gas analysers will produce glucose results as a calculated 'plasma glucose equivalent' concentration that should agree with laboratory plasma glucose results in the majority of cases.
- Most handheld glucometers also report results as 'plasma glucose equivalents', some devices are available that measure true whole blood glucose by rupturing the blood cells and measuring combined plasma and cellular glucose.
- This true whole blood glucose may be 10-15% lower than the corresponding plasma glucose. Practitioners should be aware that all current cot side technologies are prone to some inaccuracy, particularly in the range 0-2.0 mmol/l.
- If handheld glucometers are being used to screen for low blood glucose, only those devices conforming to the ISO 15197:2013 standard should be used and their limitations should be understood: possible error of ± 0.8 mmol/l (14.4 mg/dL) for values <5.5 mmol/l (<99 mg/dL).
- If a handheld glucometer is used, low values should be confirmed using an accurate method. (17)

Other considerations

- Oral dextrose gel may be considered as an adjunct to a feeding plan in newborn infants at risk of hypoglycaemia.
- Newborn infants presenting with clinical signs of hypoglycaemia or with very low glucose levels should be treated with intravenous dextrose (an



intravenous bolus of 2.5 ml/kg 10% glucose) as soon as possible, followed by constant rate infusion of glucose.

- Newborn infants with risk factors should not be discharged until at least two adequate-level consecutive pre-feed blood glucose measurements have been made, and effective feeding has been established over several fast-feed cycles.
- Hypoglycemia that persists beyond 72 hours after birth might have a different etiology than “transitional neonatal hypoglycemia” and requires specific investigations. (8)

Source

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Management of persistent pulmonary hypertension of the newborn infant (PPHN)

Reiss I, Zimmermann L, Hellström-Westas L, Buonocore G, Greenough A, Rabe H, Villamor E

Target group

Term and near-term infants >34 weeks of gestational age and parents

User group

Healthcare professionals, perinatal and neonatal units, hospitals, and health services

Statement of standard

Management of newborn infants with persistent pulmonary hypertension (PPHN) in a specialised centre improves mortality and morbidity.

Rationale

Persistent pulmonary hypertension of the newborn (PPHN) is characterised by sustained elevation of pulmonary vascular resistance (PVR) after birth resulting in extrapulmonary shunting from right to left via the fetal circulatory pathways (patent ductus arteriosus and patent foramen ovale). (1) PHN leads to severe hypoxaemia that may not respond to conventional respiratory support and to avoid severe cardiorespiratory failure. (2) The management of delivery and neonatal care should be transferred to a specialised centre to ensure optimal outcomes. (3,4)

Benefits

Short-term benefits

- Reduced mortality and morbidity (2,4,5)
- Reduced need for extra-corporeal membrane oxygenation (ECMO) (6)

Long-term benefits

- Reduced long-term morbidity (neurodevelopmental and cardiopulmonary outcome) (7)

Components of the standard

Component	Grading of evidence	Indicator of meeting the standard
For parents and family		
1. Parents are informed by healthcare professionals about persistent pulmonary hypertension (PPHN) in the newborn infant, treatment strategies as well as short- and long-term consequences.	B (High quality)	Patient information sheet
For healthcare professionals		
2. A unit guideline on indications of pre- or postnatal transfer to a specialised	A (High quality) B (High quality)	Guideline



centre, which may include facilities for ECMO, is adhered to by all healthcare professionals. (4,5) (see TEG Birth & transfer)

- | | | |
|--|------------------|------------------------|
| 3. Training on the management of PPHN is attended by all responsible healthcare professionals. | B (High quality) | Training documentation |
|--|------------------|------------------------|

For perinatal and neonatal unit

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|--|--------------------------------------|-----------|
| 4. A unit guideline on indications of pre- or postnatal transfer to a specialised centre, which may include facilities for ECMO is available and regularly updated, to include: (4,5) <ul style="list-style-type: none">• Resuscitation and early management are focused on optimal lung recruitment and ventilation, and based on neonatal resuscitation guidelines. (2)• Diagnosis is confirmed by detection of pre- and post-ductal saturation difference of 5-10%.• 2D echocardiography is performed to rule out the presence of cardiac anomalies and assess right heart function; the degree of pulmonary hypertension is classified relative to systemic blood pressure. (5)• Inotropic drugs are used to support organ perfusion. (5)• In case of poor organ perfusion, treatment with inhaled nitric oxide (iNO) is started. (5,7,8)• If there is insufficient response to iNO despite optimal lung recruitment, i.v. drugs such as phosphodiesterase inhibitors (sildenafil, milrinone) or prostaglandin are considered. (3)• ECMO is considered according the extracorporeal life support organisation (ELSO) guidelines (OI>20). (4)• Local protocols are updated in regular intervals to ensure individualised therapy. | A (High quality)
B (High quality) | Guideline |
|--|--------------------------------------|-----------|

For hospital

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|---|------------------|------------------------|
| 5. Training on the management of PPHN is ensured. | B (High quality) | Training documentation |
|---|------------------|------------------------|



6. Access to 24/7 echocardiography, radiology, and laboratory support is ensured.	B (High quality)	Guideline
7. ECMO is only provided in designated centres.	B (High quality)	Guideline

For health service

8. A national guideline on indications of pre- or postnatal transfer to a specialised centre, which may include facilities for ECMO, is available and regularly updated. (see TEG Birth & transfer)	B (High quality)	Guideline
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Where to go – further development of care

Further development	Grading of evidence
For parents and family N/A	
For healthcare professionals N/A	
For perinatal and neonatal unit N/A	
For hospital N/A	
For health service	
• Develop research into optimal saturation targets, use of inodilators and additional drugs to treat persistent pulmonary hypertension (PPHN).	A (Low quality)
• Provide long-term multidisciplinary standardised follow-up after discharge. (7)	A (Moderate quality)
• Set up an European-wide database for newborn infants with PPHN.	A (Low quality)

Getting started

Initial steps
For parents and family
• Parents and family are verbally informed by healthcare professionals about persistent pulmonary hypertension (PPHN), treatment strategies as well as short- and long-term consequences.
For healthcare professionals
• Attend training on management of PPHN.
• Raise awareness to diagnose PPHN.



For perinatal and neonatal unit

- Develop and implement a unit guideline on indications of pre- or postnatal transfer to a specialised centre, which may include facilities for ECMO.
- Develop information material about PPHN, treatment strategies as well as short- and long-term consequences for parents.

For hospital

- Support healthcare professionals to participate in training on management of PPHN and the use of licensed drugs.
- Ensure facilities and devices for optimal care and follow-up care.

For health service

- Develop and implement a national guideline on indications of pre- or postnatal transfer to a specialised centre, which may include facilities for ECMO.

Source

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Lifecycle

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Management of Respiratory Distress Syndrome

Sweet DG, Zimmermann L, Hellström-Westas L, Buonocore G, Bohlin K, Herting E

Target group

Newborn infants at risk of Respiratory Distress Syndrome (RDS) and parents

User group

Healthcare professionals, neonatal units, hospitals, and health services

Statement of standard

Newborn infants at risk of Respiratory Distress Syndrome (RDS) receive appropriate perinatal care including place of delivery, antenatal corticosteroids, guidance around optimal strategies for delivery room stabilisation, and ongoing respiratory support.

Rationale

The goal is to promote optimum survival without complications for newborn infants at risk of Respiratory Distress Syndrome (RDS), whilst minimising potential risks of adverse effects such as pulmonary air leak and bronchopulmonary dysplasia. Many available therapies for the management of RDS involve balancing benefits of treatment with potential risks. With modern practice it is essential that anyone involved in the care of newborn infants is able to comply within their setting to standards of care expected to achieve best outcomes. (1) Treatment of newborn infants with RDS requires access to specialist skills and equipment that are not readily available outside of the neonatal environment. The overall aim is to treat with early surfactant if it is needed, whilst at the same time trying to avoid unnecessary intubation and mechanical ventilation by maximising the use of non-invasive respiratory support and less invasive surfactant administration. (1–3) There are regularly updated European consensus guidelines which form the basis of this standard, and provide more detail where required. (1)

Benefits

Short-term benefits

- Reduced mortality (3)
- Reduced pulmonary air leaks (pulmonary interstitial emphysema and pneumothorax) (4)
- Reduced need for invasive ventilation (1)

Long-term benefits

- Improved long-term neurodevelopment (5)
- Reduced healthcare costs (6)
- Reduced bronchopulmonary dysplasia (BPD) diagnoses (2)



Components of the standard

Component	Grading of evidence	Indicator of meeting the standard
For parents and family		
1. Parents are informed by healthcare professionals about Respiratory Distress Syndrome (RDS), survival rates/morbidity, treatment, and short- and long-term care. (7)	A (Low quality) B (High quality)	Patient information sheet
For healthcare professionals		
2. A unit guideline on management of RDS is adhered to by all healthcare professionals.	B (High quality)	Guideline
3. Training on detection and treatment of RDS in the neonatal intensive care unit (NICU) is attended by all healthcare professionals. (8)	A (Low quality) B (High quality)	Training documentation
4. A unit guideline to determine which pregnant women have to be transferred for care to a perinatal centre is adhered to by all healthcare professionals. (9) (see TEG Birth & transfer)	A (Moderate quality)	Guideline, audit report
For neonatal unit		
5. A unit guideline to ensure a standardised approach to initial stabilisation after birth for newborn infants at risk of RDS is available and regularly updated, including <ul style="list-style-type: none"> • access to blended oxygen (10) • access to CPAP from birth (2) • access to manual ventilation with devices that control pressures (11) • access to pulse oximetry from birth (12) 	B (High quality) A (High quality) A (High quality) A (Moderate quality) A (Low quality)	Guideline
6. A unit guideline is available and regularly updated including surfactant administration, criteria for intubation, and ventilation strategies with optimal lung protection. (1,13–16)	A (High quality) B (High quality)	Guideline
For hospital		
7. Training on management of RDS is ensured.	B (High quality)	Training documentation



8. Access to radiology, biochemistry, and blood gas analysis is provided throughout the 24 hours.	B (High quality)	Audit report
9. A unit guideline and evidence of quality improvement initiatives are available within the obstetric service to optimise the use of prenatal corticosteroid therapy. (5) (see TEG Birth & transfer)	A (High quality) B (High quality)	Guideline, audit report

For health service

10. Women at risk for very preterm birth are referred in a timely fashion for expert care during pregnancy and delivery. (17) (see TEG Birth & transfer)	A (High quality)	Audit report
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Where to go – further development of care

Further development	Grading of evidence
For parents and family N/A	
For healthcare professionals N/A	
For neonatal unit	
<ul style="list-style-type: none"> Update guidelines using the current European consensus guideline. 	B (High quality)
For hospital N/A	
For health service N/A	

Getting started

Initial steps

For parents and family

- Parents are verbally informed by healthcare professionals about Respiratory Distress Syndrome (RDS), survival rates/morbidity treatment, and short- and long-term care.

For healthcare professionals

- Attend training on management of RDS.
- Appraise healthcare professional knowledge in the detection and treatment of RDS and identify gaps in knowledge and training.

For neonatal unit

- Develop and implement a unit guideline on management of RDS based on the European consensus guidelines.
- Develop information material on RDS for parents.
- Develop quality improvement plan for the management of RDS.



For hospital

- Support healthcare professionals to participate in training on management of RDS.

For health service

N/A

Source

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Lifecycle

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Management of suspected early-onset neonatal sepsis (EONS)

Stocker M, Buonocore G, Zimmermann L, Hellström-Westas L, Klingenberg C, Kornelisse R, Maier RF, Metsvaht T

Target group

Infants with suspected infection within the first 72 hours after birth and parents

User group

Healthcare professionals, neonatal units, hospitals, and health services

Statement of standard

Newborn infants with suspected early-onset infection receive prompt diagnosis and effective treatment of sepsis while avoiding overuse of antibiotics.

Rationale

The goal is to reduce morbidity and mortality from early-onset sepsis and adverse effects of overuse of antibiotics. Early diagnosis and treatment of early-onset neonatal sepsis (EONS) are critical in preventing severe and life threatening complications and mortality. Diagnosis of EONS is difficult due to the often subtle, nonspecific clinical presentation and low predictive values of biomarkers. (1–4) Uncertainty about the presence of neonatal infection may result in unnecessary and prolonged antibiotic treatment. (5,6) A population-based study in Norway reported a rate of 2.3% of all term infants started on antibiotic therapy due to suspected EONS, whereas the incidence of culture-proven EONS was 0.05%. (7) In other European countries and the United States of America even higher proportions of all term infants are started on antibiotic therapy. (8,9)

Antibiotics may have several effects: life-saving for the individual with a severe infection; beneficial for the community hindering spreads of bacteria; problematic for the community regarding development of resistance and for the individual via collateral damage of the microbiome. (10) In early life, antibiotic mediated alteration of the microbiome may have potential consequences for future health. (11–13) In addition, prolonged duration of antibiotic exposure in preterm infants is associated with higher mortality and morbidity, such as chronic lung disease, retinopathy of prematurity, periventricular leucomalacia, and necrotising enterocolitis. (14) Therefore, reduction of unnecessary or prolonged antibiotic therapy is one of the key steps of antimicrobial stewardship to improve future health of the individual and to impede the emergence of multidrug resistant bacteria. (11–16)

Benefits

Short-term benefits

- Reduced mortality (17–20) and morbidity (21,22)
- Reduced unnecessary and prolonged antibiotic therapy for suspected infection (7–9)

Long-term benefits

- Reduced development of multidrug resistance (MDR) (15)
- Reduced alteration of the infant microbiome, with implication for later health (10–13)



Components of the standard

Component	Grading of evidence	Indicator of meeting the standard
For parents and family		
1. Parents (at the hospital and at home) are informed by healthcare professionals about signs, treatment and consequences of early-onset neonatal infection. (17,23–26) (see TEG “Infant- & family-centred developmental care”)	A (Low quality) B (High quality)	Patient information sheet
For healthcare professionals		
2. A unit guideline on management of newborn infants with suspected early-onset neonatal sepsis (EONS) is adhered to by all healthcare professionals.	B (High quality)	Guideline
3. Training on management of newborn infants with suspected EONS is attended by all healthcare professionals.	B (High quality)	Training documentation
4. In infants with only one risk factor for EONS, vital signs are observed and monitored for 12-24 hours (17,23–26), and do not receive antibiotics unless symptomatic. (17,24,25)	A (Moderate quality)	Guideline
5. Always consider to start parenteral antibiotic therapy if newborn infants have two or more risk factors or clinical signs possibly related to sepsis. (17,23–26)	A (Moderate quality)	Guideline
6. Blood cultures are drawn before start of antibiotic therapy. (17,23–26)	A (Moderate quality)	Guideline
7. The need for antibiotic therapy is re-evaluated after 36-48 hours. (17,23–26)	A (Moderate quality)	Guideline
8. Antibiotic therapy is streamlined as soon as blood culture results are available. (17,23–26)	A (Moderate quality)	Guideline
9. ≥3 rd generation cephalosporins or carbapenems are not routinely used for empiric therapy. (17,23–26)	A (Moderate quality)	Guideline



For neonatal unit

- | | | |
|---|--|--------------|
| 10. A unit guideline on management of newborn infants with suspected EONS is available and regularly updated in conjunction with obstetric guidance on intrapartum prophylaxis. (17,27) | A (Moderate quality)
B (High quality) | Guideline |
| 11. A unit-based antibiotic stewardship programme is established: minimum for use of $\geq 3^{\text{rd}}$ generation cephalosporins or carbapenems. (28–30) | A (Moderate quality) | Audit report |

For hospital

- | | | |
|---|----------------------|------------------------|
| 12. Training on management of newborn infants with suspected EONS is ensured. | B (High quality) | Training documentation |
| 13. Analysis of blood cultures including determination of antibiotic resistance patterns with daily report of results is conducted. (15,16,31,32) | A (High quality) | Audit report |
| 14. Hospital-based antibiotic stewardship programme is established: minimum recording of multidrug resistance (MDR). (28–30) | A (Moderate quality) | Audit report |

For health service

- | | | |
|--|----------------------|--------------|
| 15. A national guideline on management of newborn infants with suspected EONS is available and regularly updated in conjunction with obstetric guidance on intrapartum prophylaxis. (27,31–33) | A (Moderate quality) | Guideline |
| 16. Regional/national surveillance and reports of antibiotic resistance patterns of positive blood cultures are available. (15,16,31,32) | A (Moderate quality) | Audit report |



Where to go – further development of care

Further development	Grading of evidence
For parents and family N/A	
For healthcare professionals N/A	
For neonatal unit	
<ul style="list-style-type: none">Develop an algorithm with biomarker guidance for duration of antibiotic therapy. (34–36)	A (Moderate quality)
For hospital	
<ul style="list-style-type: none">Consolidate an antibiotic stewardship programme. (28–30)	A (Moderate quality)
For health service N/A	

Getting started

Initial steps

For parents and family

- Parents are verbally informed by healthcare professionals about signs, treatment and consequences of early-onset neonatal infection.

For healthcare professionals

- Attend training on management of newborn infants with suspected early-onset neonatal sepsis (EONS).
- Reduce the use of unnecessary antibiotic therapy.

For neonatal unit

- Develop and implement a unit guideline on management of newborn infants with suspected EONS in conjunction with obstetric guidance on intrapartum prophylaxis.
- Develop information material on signs, treatment and consequences of early-onset neonatal infection for parents.
- Use published guidelines regarding management of newborn infants with suspected EONS.

For hospital

- Support healthcare professional to participate in training on management of newborn infants with suspected EONS.
- Ensure facilities for rapid detection of bloodstream infection.
- Start with an antibiotic stewardship programme.

For health service

- Use published guidelines regarding management of newborn infants with suspected EONS.
- Develop and implement a national guideline on management of newborn infants with suspected EONS in conjunction with obstetric guidance on intrapartum prophylaxis.



Description

Different national guidelines for the management of suspected EONS are published in Europe and may serve as examples: Guidelines from the United Kingdom (NICE) (17), from Belgium (24), and Switzerland (26). These guidelines are not uniform and differ in some points. (27) The diversity of the guidelines reflects the diversity of their national healthcare system. It is also a consequence of a different translation of available data to clinical practice such as the approach of maternal risk factors for EONS. Guidelines for the management of EONS have to be adapted to the specific healthcare practices such as screening for maternal colonisation with Group B streptococci, and possibilities for observation of newborns at increased risk for EONS.

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Neonatal jaundice

Borszewska-Kornacka M, Buonocore G, Zimmermann L, Hellström-Westas L, Marlow N, Özek E, Perrone S, Tołłoczko J

Target group

Newborn infants and parents

User group

Healthcare professionals, neonatal units, hospital, and health service

Statement of standard

All newborn infants are assessed for neonatal jaundice with the aim of implementing effective prevention of severe hyperbilirubinaemia.

Rationale

Hyperbilirubinaemia is common in newborn infants. Physiological jaundice appears after the first 24 hours of life and usually resolves spontaneously within the first week. However, neonatal hyperbilirubinaemia may also become more severe and require treatment to prevent or treat bilirubin encephalopathy and risk of later cerebral palsy and hearing deficiencies. Monitoring of bilirubin levels in all newborn infants, and awareness of risk factors, are vital for adequate management. Risk factors for severe neonatal hyperbilirubinaemia include: prematurity, haemolytic disorders, early jaundice (<24 hours), bruising and haematoma after delivery, infections, excessive weight loss, family history of jaundice – including conditions such as spherocytosis, conjugation disorders, and haemoglobinopathies, for example sickle cell anaemia and glucose-6-phosphate dehydrogenase deficiency (G6PD), which are more prevalent in Mediterranean, African and Asian populations. (1–3)

Phototherapy is effective in reducing bilirubin concentrations. Initiation of phototherapy should take into account the gestational age, postnatal age and risk factors. Phototherapy usually may be implemented without separating mother and infant. Severe hyperbilirubinaemia may be treated effectively by blood exchange transfusion and the use of gammaglobulin may reduce the need for exchange transfusion in the presence of ongoing haemolysis. (4,5)

In most European countries, national professional societies and health services have developed comprehensive guidelines and charts for the management of hyperbilirubinaemia in their populations, which should be followed. (6–12) It is also critical to monitor for prolonged jaundice (greater than 14 days) in newborn infants and investigation should detect the presence of conjugated hyperbilirubinaemia in such infants. (4,13,14)

Benefits

Short-term benefits

- Reduced occurrence of severe neonatal jaundice (4,15,16)
- Reduced length of hospital/NICU stay (5)
- Early detection of cholestasis (17)



Long-term benefits

- Reduced neurological complications (16)
- Reduced occurrence of hearing loss (16)
- Reduced hospital readmission (17)

Components of the standard

Component	Grading of evidence	Indicator of meeting the standard
For parents and family		
1. Parents are informed by healthcare professionals about identification, prevention, and management of hyperbilirubinaemia. (2,14,15)	A (Moderate quality) B (High quality)	Patient information sheet
2. Parents are informed by healthcare professionals about the role of breastfeeding and adequate nutrition in the prevention of hyperbilirubinaemia. (4) (see TEG Nutrition, see TEG Care procedures)	A (High quality) B (High quality)	Patient information sheet
For healthcare professionals		
3. A unit guideline on hyperbilirubinaemia including management after discharge is adhered to by all healthcare professionals.	B (High quality)	Guideline
4. Transcutaneous bilirubinometers is used to screen newborn infants for hyperbilirubinaemia. (3,18–23)	A (High quality)	Guideline
5. Training in the management of hyperbilirubinaemia is attended by all healthcare professionals. (4,16)	A (High quality) B (High quality)	Training documentation
For neonatal unit		
6. A unit guideline on hyperbilirubinaemia including management after discharge is available and regularly updated.	B (High quality)	Guideline
For hospital		
7. Training in the management of hyperbilirubinaemia is ensured.	B (High quality)	Training documentation
8. Equipment for the diagnosis and management of hyperbilirubinaemia, including transcutaneous bilirubinometers, is provided.	B (High quality)	Audit report



For health service

9. A national guideline on management of hyperbilirubinaemia including management after discharge is available and regularly updated.	B (High quality)	Guideline
10. Systems for the identification of prolonged jaundice are available and audited. (4)	A (High quality)	Audit report, guideline

Where to go – further development of care

Further development	Grading of evidence
For parents and family N/A	
For healthcare professionals N/A	
For neonatal unit N/A	
For hospital N/A	
For health service <ul style="list-style-type: none"> Support research in new therapeutic modalities, cost effectiveness, and improvement in technology. (24) 	A (Moderate quality)

Getting started

Initial steps
For parents and family <ul style="list-style-type: none"> Parents are verbally informed by healthcare professionals about identification, prevention, and management of hyperbilirubinaemia.
For healthcare professionals <ul style="list-style-type: none"> Attend training in the management of hyperbilirubinaemia.
For neonatal unit <ul style="list-style-type: none"> Use published guidelines regarding management of hyperbilirubinaemia including management after discharge. (17) Develop and implement a unit guideline on hyperbilirubinaemia including management after discharge. Develop information material about identification, prevention, and management of hyperbilirubinaemia for parents.
For hospital <ul style="list-style-type: none"> Support healthcare professionals to participate in training in the management of hyperbilirubinaemia. Provide equipment for non-invasive measurement of bilirubin.
For health service <ul style="list-style-type: none"> Develop and implement a national guideline on hyperbilirubinaemia including management after discharge.



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Neurological monitoring of the high-risk infant: EEG and aEEG

Hellström-Westas L, Zimmermann L, Buonocore G, Dudink J, Gressens P, Pellicer A

Target group

- Term and preterm infants at risk for brain injury:
 - Infants with hypoxic-ischaemic encephalopathy (HIE)
 - Infants with encephalopathy for other causes (e.g. metabolic)
 - Infants with suspected or verified seizures
 - Infants requiring intensive care and/or surgery
 - Infants with suspected/confirmed congenital central nervous system (CNS) anomalies
- Parents

User group

Healthcare professionals, neonatal units, hospitals, and health services

Statement of standard

In order to improve evaluation and outcomes of newborn infants at risk of brain injury, management includes neurological monitoring using a structured, age-appropriate neurological assessment and a range of devices to evaluate brain haemodynamics, oxygen transport, brain function, and imaging, as required.

Rationale

Newborn infants comprise a high-risk population for developing brain injury, during the first days after birth due to respiratory, haemodynamic, infectious, or metabolic instability. Full term and preterm infants with hypoxia-ischaemia, CNS infections, or congenital anomalies are at particular risk of brain injury. Early recognition of on-going disturbances of brain function or structural damage is important in implementing preventive or treatment strategies, and appropriate follow-up. Early detection of cerebral compromise, such as encephalopathy and seizures, is associated with better management of these conditions. High-risk infants should be identified as early as possible, the patient history together with a structured clinical examination and repeated clinical observations form the basis of the evaluation. The electroencephalogram (EEG) provides sensitive detection of abnormal brain function. (1,2) Continuous monitoring with a full montage EEG or the limited-channel amplitude-integrated EEG (aEEG) has been increasingly used in neonatal units and is excellent in the detection and grading of the severity of cerebral compromise in both term and preterm infants, and can be used for early evaluation before interventions such as therapeutic hypothermia. (3–11) Modern aEEG monitors also display the raw EEG (aEEG/EEG), which improves seizure detection. (12,13) The use of continuous EEG or aEEG/EEG monitoring is associated with earlier seizure diagnosis and better seizure management. (14,15) Studies in asphyxiated newborn infants have shown that aEEG combined with near-infrared spectroscopy is useful. (16,17)



Benefits

Short-term benefits

- Improved evaluation of clinical symptoms, including seizures, and early detection of cerebral compromise (2,6,14,18,19)
- Refined clinical management of neonatal seizures, including more efficient treatment and less use of antiepileptic drugs (14,15,18–20)
- Early prediction of outcome may assist medical decisions such as interventions and redirection of care (5,9,10,21)

Long-term benefits

- Improved long-term outcomes (22–25)
- Improved cost-effectiveness (26,27)
- Reduced exposure to antiepileptic drugs (15,20)

Components of the standard

Component	Grading of evidence	Indicator of meeting the standard
For parents and family		
1. Parents are informed by healthcare professionals about the role of EEG and aEEG/EEG monitoring.	B (High quality)	Patient information sheet
For healthcare professionals		
2. A unit guideline on neurological monitoring including EEG and aEEG/EEG monitoring is adhered to by all healthcare professionals, to include <ul style="list-style-type: none"> • asphyxiated newborn infants, including undergoing therapeutic hypothermia (3–5,5,6,16,23,26) • infants at risk of and undergoing treatment for seizures. (6,12–15,18–20,22,23,28) 	A (High quality) B (High quality)	Audit report, guideline
3. Specific training on the use of EEG and aEEG/EEG monitoring is attended by all responsible healthcare professionals. (5,11,14,27,29)	A (Moderate quality) B (High quality)	Training documentation
4. Teams with a focus of interest on EEG and aEEG/EEG monitoring (e.g. neonatologists, neurologists, neurophysiologists, nurses, radiologists, radiographers, and physicists) are established. (29,30)	A (High quality) B (High quality)	Guideline
For neonatal unit		
5. A unit guideline on the implications of EEG and aEEG/EEG monitoring is available and regularly updated.	B (High quality)	Guideline



For hospital		
6. Training on the use of EEG and aEEG/EEG monitoring is ensured. (5,11,14,27,29)	A (Moderate quality) B (High quality)	Guideline
7. An interdisciplinary team for neurological evaluation (including EEG and aEEG/EEG) of high-risk infants in the NICU is supported. (14,15)	A (Moderate quality)	Audit report
8. Facilities for EEG and aEEG/EEG monitoring and interpretation are provided.	B (High quality)	Audit report
For health service		
9. High-risk infants are transferred to NICUs with appropriate neuro-monitoring systems and expertise. (31)	A (High quality)	Audit report, guideline

Where to go – further development of care

Further development	Grading of evidence
For parents and family N/A	
For healthcare professionals N/A	
For neonatal unit	
<ul style="list-style-type: none"> Develop a full neonatal neuro-critical care concept, including guidelines and close collaboration with neurologists. (13,19,24) 	A (Moderate quality)
For hospital	
<ul style="list-style-type: none"> Use monitoring systems that allow for expert evaluation of aEEG/EEG or EEG 24/7 also from outside the hospital. 	A (Low quality)
For health service	
<ul style="list-style-type: none"> Monitor incidence, treatment and long-term outcomes after neonatal seizures. (15,24,25) Develop multi-centre expertise by sharing EEG databases. 	A (High quality) B (Moderate quality)

Getting started

Initial steps
For parents and family
<ul style="list-style-type: none"> Parents are verbally informed by healthcare professionals about the implications of EEG monitoring.
For healthcare professionals
<ul style="list-style-type: none"> Attend training on the use of EEG and aEEG/EEG monitoring.



- Identify leading staff with a focus of interest on neonatal neurological evaluation and monitoring.

For neonatal unit

- Develop and implement a unit guideline on the use of EEG and aEEG/EEG monitoring.
- Develop parental information material about EEG and aEEG/EEG monitoring, also including parental perspectives.
- Provide resources for specific training on EEG and aEEG/EEG monitoring tools.

For hospital

- Support healthcare professionals to participate in training on the use of aEEG/EEG and EEG monitoring.
- Provide technology for EEG or aEEG/EEG monitoring.

For health service

- Create systems to effectively transfer high-risk infants to NICUs with appropriate neuromonitoring systems and expertise.

Description

Electroencephalography (EEG) and amplitude-integrated EEG (aEEG) for evaluation of brain function in high risk infants

A majority of adverse events affecting brain function in term and preterm infants occur during delivery or the first week after birth. Such events include perinatal asphyxia, cerebral haemorrhages, ischaemia, metabolic and infectious conditions. Cerebral symptoms may be vague or entirely absent but may also include encephalopathy and seizures. Evaluation of brain function with conventional EEG or continuous monitoring with the aEEG/EEG gives diagnostic and prognostic information in high-risk term and preterm infants. Continuous video-EEG monitoring can be considered to be the gold standard, but this method is not available in all neonatal intensive care units (NICU) and not feasible for routine monitoring of large numbers of high-risk infants. During the last two decades EEG and aEEG/EEG monitoring have been increasingly used worldwide in compromised newborn infants.

Newborn infants with compromised brain function or at risk for developing severe cerebral complications should be monitored closely by clinical observation and continuously with aEEG/EEG. Conventional EEG should be performed in newborn infants monitored by aEEG/EEG.

Regular knowledge updates and training of healthcare professionals in basic management and evaluation of aEEG/EEG and EEG is of utmost importance. Several studies have reported that insufficient training in aEEG/EEG is associated with poorer and unreliable performance of the monitoring. For this reason, aEEG/EEG monitoring should be conducted in collaboration with clinical neurophysiologists or neurologists, and for most monitored newborn infants at least one standard EEG should be recorded. (13,28–30,32–35)

Several studies have demonstrated that the electrocortical activity is one of the most sensitive measures for early evaluation of brain function and early prediction of outcome in asphyxiated newborn infants. Consequently, it is recommended to record the aEEG/EEG for evaluation of asphyxiated newborn infants before hypothermia treatment. (5,21) In asphyxiated term infants, simultaneous monitoring with aEEG/EEG and NIRS is associated with more precise outcome prediction. (16,17)



Clinical identification of suspected seizures is not reliable since a majority of neonatal seizures have only subtle clinical symptoms or are entirely subclinical. Brain monitoring with aEEG/EEG and EEG in asphyxiated newborn infants allows earlier recognition of seizures in newborn infants with HIE, and with more precise treatment of seizures and the use of fewer antiepileptic drugs. (14,15,18,19,22–25,36)

The compressed aEEG trend alone is not sensitive enough for detection of seizures since especially brief seizures may be missed in the compressed trend. However, if both aEEG and raw-EEG is inspected around 80-90% of all seizures that can be identified in a standard EEG may be detected. (13,37) Development of efficient automated seizure detection alarms is urgently needed in the busy NICU setting.

Many studies have also shown that aEEG and EEG may be sensitive early predictors of outcome in preterm infants (1,7,9,10), but clinical experience of aEEG in very preterm infants is still limited. The early predictive accuracy of aEEG and EEG can be expected to be lower in preterm infants than in term infants since the long-term outcome of especially very preterm infants may be affected by later complications during the clinical course.

The neonatal neurocritical care concept is an emerging strategy which includes a care concept based on specially trained NICU healthcare professionals and interdisciplinary teams that include neurologists, guidelines and protocols for consistent management of newborn infants at risk of neurological injury, aEEG/EEG and EEG monitoring of high-risk infants, and long-term follow up. (31) The first reports from NICUs practicing neurocritical care show very promising results. (15,24,25,27)

Source

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Neurological monitoring in the high-risk infant: Near-infrared spectroscopy (NIRS)

Pellicer A, Hellström-Westas L, Zimmermann L, Buonocore G, Dudink J, Gressens P

Target group

- Term and preterm infants at risk for brain injury:
 - Infants with hypoxic-ischaemic encephalopathy (HIE)
 - Infants with encephalopathy for other causes (e.g. metabolic)
 - Infants with suspected or verified seizures
 - Infants requiring intensive care and/or surgery
 - Infants with suspected/confirmed congenital central nervous system (CNS) anomalies
- Parents

User group

Healthcare professionals, neonatal units, hospitals, and health services

Statement of standard

In order to improve evaluation and outcomes of newborn infants at risk of brain injury, management includes neurological monitoring using a structured, age-appropriate neurological assessment and a range of devices to evaluate brain haemodynamics, oxygen transport, brain function, and imaging, as required.

Rationale

Infants requiring neonatal intensive care constitute a high-risk population for developing brain injury, particularly full term and preterm infants exposed to hypoxia-ischaemia, CNS infections, or with congenital anomalies.

In the first hours after birth, there is imbalance between blood flow and oxygen supply to the brain due to haemodynamic adaptation during transitional circulation, particularly in the very preterm infant. (1) Low and fluctuating cerebral blood flow are associated with adverse outcomes. (2,3) Experimental models and observational studies confirm that both hyper- and hypoxaemia may cause irreversible brain injury. (4–6) The vulnerability of this population, the severity of underlying clinical conditions, and the complexity of care make continuous, cot-side, and non-invasive monitoring tools valuable. Near-infrared spectroscopy (NIRS) derived regional tissue oxygen saturation of haemoglobin (rStO₂) is an absolute value, which corresponds to mixed blood saturation, used in the clinical setting as a surrogate measure for venous oxygen saturation (SvO₂). (7) Indirect assessment of cerebral blood flow has been shown to correlate with rStO₂. (8) This non-invasive, continuous monitoring system may help to adjust interventions that have effects on blood and oxygen supply to the brain. (9) Bilateral brain monitoring may detect differential perfusion between hemispheres.



Benefits

Short-term benefits

- Reduced burden of cerebral hypo- and hyperoxia in preterm infants in the first 72 h after birth (10,11)
- Improved neuroprotection after asphyxia using combined NIRS and MRI measurements of brain perfusion (12)
- Improved maintenance of theoretically safe cerebral oxygenation levels in infants with congenital heart defects (13)

Long-term benefits

- Reduced all-cause mortality in extremely preterm infants (10)
- Improved long-term outcomes in extremely preterm infants (14)

Components of the standard

Component	Grading of evidence	Indicator of meeting the standard
For parents and family		
1. Parents are informed by healthcare professionals about the role of near-infrared spectroscopy (NIRS) monitoring.	B (High quality)	Patient information sheet
For healthcare professionals		
2. A unit guideline on neurological monitoring including NIRS is adhered to by all healthcare professionals, to include <ul style="list-style-type: none"> • Newborn infants during resuscitation at birth (≤ 15 min) (11,15,16) • Extremely preterm infants in the first 72 h after birth (9,10,17) • Asphyxiated newborn infants undergoing therapeutic hypothermia (18,19) • Infants undergoing surgery with cardio-pulmonary bypass (13,20–22) 	A (High quality) B (High quality)	Guideline
3. Training on NIRS monitoring is attended by all responsible healthcare professionals. (9,17,20,21,23)	A (High quality) B (High quality)	Training documentation
4. Teams with a focus of interest on neuro-critical care, including neonatologists, neurologists, neuro-physiologists, nurses, radiologists, radiographers, and physicists are established.	B (High quality)	Guideline



For neonatal unit		
5. A unit guideline on neurological monitoring including NIRS is available and regularly updated including standardised operational procedures. (7,9,17,23)	A (High quality) B (High quality)	Guideline
For hospital		
6. Training on NIRS monitoring is ensured. (7,17,20,21,23)	A (High quality) B (High quality)	Training documentation
7. Facilities for NIRS monitoring are provided.	B (High quality)	Audit report
8. An interdisciplinary team for neuro-critical care of high-risk infants in the NICU is supported.	B (Moderate quality)	Audit report
For health service		
9. High-risk infants are transferred to NICUs with appropriate neuro-monitoring systems and expertise. (24–26)	A (High quality)	Audit report, guideline

Where to go – further development of care

Further development	Grading of evidence
For parents and family N/A	
For healthcare professionals	
<ul style="list-style-type: none"> Monitor perioperative NIRS in infants with non-cardiac complex neonatal surgery. (27,28) 	A (Low quality)
For neonatal unit N/A	
For hospital N/A	
For health service N/A	

Getting started

Initial steps
For parents and family
<ul style="list-style-type: none"> Parents are verbally informed by healthcare professionals about the role of NIRS.
For healthcare professionals
<ul style="list-style-type: none"> Attend training on NIRS monitoring.



- Identify leading healthcare professionals with a focus of interest on neonatal neurological monitoring.

For neonatal unit

- Develop and implement a unit guideline on neurological monitoring including NIRS.
- Develop parental information material about NIRS monitoring also including parent perspectives.
- Provide resources for specific training on NIRS monitoring.

For hospital

- Support healthcare professionals to participate in training on NIRS monitoring.

For health service

- Create systems to effectively transfer high-risk infants to NICUs with appropriate neuro-monitoring systems and expertise.

Description

The NIRS sensor is placed at the forehead avoiding cavities, superior sagittal sinus, intra or extra-cranial huge blood collections, or vascular malformations, if known. Scalp oedema will also influence the quality of the NIRS signal. In the smallest newborn infants and those with poor perfusion states sensor position is rotated to avoid tissue injury related to compression or heat. (7,17)

Commercial NIRS devices incorporate similar technology but different wavelengths and computational algorithms translating changes in light absorption into rStO₂ absolute values. (7) Systematic approach has evidenced huge differences in rStO₂ according to device or probe (23,29), so that device-specific reference ranges or limits have to be used.

Neonatal resuscitation after birth: Clinical assessment of the newborn infant carries high inter-observer variability particularly when scoring preterm or term infants in need of resuscitation. (30) Oxygen saturation targeting and the use of supplemental oxygen during transition remain controversial topics. (31) The use of pulse oximetry or heart rate monitoring during resuscitation has not led to improvements on the short or long-term outcomes. (32) rStO₂ and fractional oxygen extraction reference ranges and percentile charts for the interpretation of cerebral oxygenation during immediate transition to avoid hypo- and hyperoxia of the brain during resuscitation appears promising. (11,15,16) Yet, routine interventions based on rStO₂ during resuscitation need development and evaluation.

Extremely low gestational age newborn infants: Recent studies have shown an association of cerebral rStO₂ levels and clinical outcomes. (33) Low rStO₂ on the first day of life associates surrogated measures of compromised systemic blood flow and risk of intraventricular haemorrhage. (34) Impaired cerebral blood flow autoregulation assessed by NIRS and arterial blood pressure monitoring associates abnormal systemic (and cerebral) blood flow distribution, death and severe brain injury. (35,36) Cerebral oxygenation can be stabilised in the preterm infant during the first 72 hours from birth by the combined use of rStO₂-NIRS monitoring and a pathophysiological, brain oriented treatment guideline with no record of severe adverse events. (9,10) The quality of evidence supporting some of the listed statements in the intervention algorithm is generally low, however, are all routinely used in clinical care of these patients. (9) Although important early surrogate outcomes, such as aEEG at day 3 of postnatal life or neuroimaging, did not significantly differ between the study groups (37,38), post hoc analyses showed that early burden of cerebral hypoxia was



significantly associated with low brain electrical activity and severity of intracranial haemorrhage. (14) So far, definitive evidence of benefit for improvement of long-term clinical outcomes is needed as the technology is not cheap, requires manipulation and additional staff time, and may have unwanted effects. (10)

HIE: Cerebral hypoperfusion during the first hours after birth is followed by hyperperfusion, even during treatment with moderate hypothermia. Potential differences according to the severity of brain injury (moderate vs severe) have been identified. (12,18) NIRS measurements of oxygenation and MRI measurements of brain perfusion show good correlation. (12) However, the predictive capacity of NIRS changes lacks consistency. (18,19) As yet, widespread recommendation of NIRS monitoring to guide important clinical decisions in asphyxiated newborn infants cannot be made.

Congenital heart disease (CHD): NIRS may be a useful adjunct particularly during cardiopulmonary bypass to optimise perfusion. NIRS-derived measures of systemic oxygen balance correlate with global circulatory measures and biochemical indicators of shock. (20) Algorithms have been developed to guide interventions based on rStO₂ values during the perioperative period. (21) However, the current literature on the use of NIRS alone does not demonstrate improvement in neurologic outcome. (22) Prospective data evaluating NIRS findings and relevant outcomes in this population difficult to compare, because of the variable disease physiology, variable baseline values, and small sample sizes. These issues prevent extrapolation to wider CHD population.

Other complex surgical procedures conducted during the neonatal period, such as congenital diaphragmatic hernia or esophageal atresia (27,28), might be additional scenarios where NIRS may play a role to guide surgeons and anesthetists during the intervention procedures.

Source

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Neurological monitoring in the high-risk infant: ultrasound and MRI scanning

Dudink J, Hellström-Westas L, Zimmermann L, Buonocore G, Gressens P, Pellicer A

Target group

- Term and preterm infants at risk for brain injury:
 - Infants with hypoxic-ischaemic encephalopathy (HIE)
 - Infants with encephalopathy for other causes (e.g. metabolic)
 - Infants with suspected or verified seizures
 - Infants requiring intensive care and/or surgery
 - Infants with suspected/confirmed congenital central nervous system (CNS) anomalies
- Parents

User group

Healthcare professionals, neonatal units, hospitals, and health services

Statement of standard

In order to improve evaluation and outcomes of newborn infants at risk of brain injury, management includes neurological monitoring using a structured, age-appropriate neurological assessment and a range of devices to evaluate brain haemodynamics, oxygen transport, brain function, and imaging, as required.

Rationale

Infants requiring neonatal intensive care constitute a high-risk population for developing brain injury, especially during the first days after birth due to respiratory, haemodynamic, infectious, or metabolic instability. Full term and preterm infants exposed to hypoxia-ischaemia or infections, or carrying conditions such as congenital malformations, antenatal (maternal) risk factors, neonatal diseases potentially involving CNS, or late prematurity, among others, are exposed to increased risk of brain injury. Early recognition of on-going disturbances of brain function or structural damage is important in implementing preventive or treatment strategies, and appropriate follow-up. Early detection of cerebral compromise, such as encephalopathy or seizures, is associated with better management of these conditions. High-risk infants should be identified as early as possible, the patient history together with a structured clinical examination and repeated clinical observations form the basis of the evaluation. The vulnerability of this population, the severity of underlying clinical conditions, and the complexity of care deserve preferably continuous, cot-side, and non-invasive monitoring tools. This can be accomplished from four perspectives: haemodynamics and oxygen transport, connectivity and function, structure, and clinical expression. The ultimate goal is to prevent or reduce risk for brain injury by early identification of high-risk infants and improved clinical management.



Benefits

Short-term benefits

- Reduced mortality and morbidity (i.e., detect sinovenous thrombosis, severe haemorrhages or post-haemorrhagic ventricular dilatation) (1–11)
- Direct feedback on neuroprotective interventions (i.e., low molecular weight heparin treatment for cerebral vein thrombosis, ventricular reservoir taps, ventriculo-peritoneal shunt treatment) (1–8)
- Improved assessment of severity of brain damage which might redirect care (i.e., in patients with hypoxic ischaemic encephalopathy (HIE), arterial stroke, venous infarction) (1–12)
- Provides proxy biomarker for outcome for evaluation in neuroprotective intervention trials (11–16)
- Informs prognosis for physicians and parents (11–16)

Long-term benefits

- More focused follow-up programmes (5,16–20)
- Improved understanding of brain injury pathophysiology (5,12,14,17–19)
- Improved assessment of neonatal brain development to guide future prevention and intervention strategies (5,16–19)

Components of the standard

Component	Grading of evidence	Indicator of meeting the standard
For parents and family		
1. Parents are informed by healthcare professionals about the role of brain imaging. (21)	A (Moderate quality) B (High quality)	Patient information sheet
For healthcare professionals		
2. A unit guideline on neurological monitoring including brain imaging is adhered to by all healthcare professionals, to include <ul style="list-style-type: none"> • term infants with suspected brain injury (1–5,9–13,15,16) • very preterm infants (1–5,12) 	A (High quality) B (High quality)	Audit report, guideline
3. Training on ultrasound and MRI procedures is attended by all responsible healthcare professionals.	B (High quality)	Training documentation
4. Teams with a focus of interest on neuroimaging (e.g. nurses, neonatologists, neurologists, neuro-physiologists, radiologists, radiographers, and physicists) are established. (18)	B (High quality)	Guideline



For neonatal unit		
5. A unit guideline on neurological monitoring including brain imaging is available and regularly updated, to include standardised operational procedures for cranial ultrasound (CUS) (22–24) and magnetic resonance imaging (MRI). (20,21,25–27)	A (High quality) B (High quality)	Guideline
For hospital		
6. Training on ultrasound and MRI procedures is ensured. (20,21,25–27)	A (High quality) B (High quality)	Training documentation
7. An interdisciplinary team for neurological evaluation of high-risk infants in the NICU is supported.	B (Moderate quality)	Audit report
8. Facilities for brain imaging (CUS and MRI) are provided.	B (High quality)	Audit report
For health service		
9. High-risk infants are transferred to NICUs with appropriate neuro-monitoring systems and expertise. (17,28)	A (High quality)	Audit report, guideline

Where to go – further development of care

Further development	Grading of evidence
For parents and family N/A	
For healthcare professionals N/A	
For neonatal unit	
<ul style="list-style-type: none"> Develop a full neonatal neuro-critical care concept, including guidelines and close collaboration with neurologists. 	B (Moderate quality)
For hospital N/A	
For health service	
<ul style="list-style-type: none"> Monitor incidence, treatment and long-term outcomes after neonatal brain injury such as intra-ventricular haemorrhage. (18) Develop multi-centre expertise by sharing imaging databases. 	A (High quality) B (Moderate quality)



Getting started

Initial steps

For parents and family

- Parents are verbally informed by healthcare professionals about the role of brain imaging.

For healthcare professionals

- Attend training on ultrasound and magnetic resonance imaging (MRI) procedures.
- Identify leading healthcare professionals with a focus of interest on neonatal neurological monitoring.

For neonatal unit

- Develop and implement a unit guideline on neurological monitoring including brain imaging.
- Develop parental information material about brain imaging, also including parental perspectives.
- Provide resources for specific training on brain imaging tools.

For hospital

- Support healthcare professionals to participate in training on ultrasound and MRI procedures.

For health service

- Create systems to effectively transfer high-risk infants to NICUs with appropriate neuro-monitoring systems and expertise.

Description

Despite several major advances in fetal and neonatal care, the frequency of neurodevelopmental disability among the survivors of neonatal intensive care remains high. Although mortality for both, preterm infants and severely compromised term infants has decreased, the population of newborn infants at risk for neurological disability is still increasing. (29,30) Neuroimaging is a critical investigation in the provision of adequate diagnostic or prognostic information for parents. (1–5)

Neuroimaging in newborn infants at risk of brain damage is oriented to:

- a. Diagnosing brain injury to provide the most appropriate medical management.
- b. Early detection of lesions associated with long-term neurodevelopmental disabilities.

Early diagnosis of structural brain damage can steer neuroprotective and/or neurorehabilitation treatment strategies, and guide appropriate follow up. It can also give us an understanding of the pathophysiology. (1–5)

Neonatal neuroimaging techniques such as CUS, MRI and CT scanning have been used for many decades and have proven to be extremely helpful assessing brain maturation and injury. However, there are still several challenges associated with neonatal neuroimaging, which will be highlighted below. (5,11,13,25)

Proper assessment of neonatal brain images requires extensive knowledge about neonatal brain injury (aetiology, pathophysiology, prognosis), developmental neuro-anatomy (neuro-embryology), the advantages and disadvantages of the different imaging techniques, pitfalls and optimal timing. (5,11,13,25) Furthermore, the transport and sedation of critically ill neonates for both MRI and CT scanning often



represents a major challenge. (25–27) Proper scanning requires a dedicated team. The most common used neonatal neuroimaging modalities are: CUS and MRI. The use of CT is very limited and because of radiation should be avoided. All these factors have to be taken into account when choosing timing and modality to image the neonatal brain.

There are advantages and disadvantages for each of the modalities: (5,11,13,25–27)

<i>Cerebral Ultrasound</i>	
Advantages	Disadvantages
<ul style="list-style-type: none"> • Bedside, patient friendly, save • Reliable for detection of severe haemorrhagic lesions (e.g. peri-intraventricular haemorrhage-P/IVH- in preterms) and severe white matter damage • Doppler technique (detection of thrombosis) • Specific lesions: germinolytic cysts, calcifications, lenticulo-strriate vasculopathy -LSV • Repeated assessments (i.e., measurements such as the Levene index in posthaemorrhagic ventricle dilatation –PHVD patients) 	<ul style="list-style-type: none"> • Difficult to detect cortical abnormalities • Difficult to detect posterior fossa abnormalities (the use of posterior fontanel and mastoid fontanel can be of help) • Less reliable in detecting small lesions and subtle white matter damage • Difficult to assess myelinisation
<i>MRI</i>	
Advantages	Disadvantages
<ul style="list-style-type: none"> • Relatively safe (no radiation) • Good assessment of whole brain (including cortex and posterior fossa) • Detailed information about brain development (including myelination) • Reliable information about localisation and extent of brain damage • Reliable for detection of small lesions and subtle white matter damage • Special sequences for different purposes: e.g., diffusion-weighted imaging (DWI) (cytotoxic oedema), diffusion tensor imaging (DTI) (quantitative white matter tract analysis), magnetic resonance venography (MRV) (venous 	<ul style="list-style-type: none"> • More burden/distress for (often unstable) infants and medical team: transport issues, sedation, time consuming • High costs (depending on hospital) • Some lesions more difficult to assess (LSV, calcifications, germinolytic cysts)



system), susceptibility weighted imaging (SWI) (haemorrhages), contrast (tumour, abscess), magnetic resonance angiography (MRA) (arterial vessels)	
<i>CT</i>	
Advantages	Disadvantages
<ul style="list-style-type: none"> • Good visualisation of bone structures • Often wider availability than MRI 	<ul style="list-style-type: none"> • Relatively unsafe (radiation) • Poor tissue contrast (low resolution) • To detect haemorrhages beyond one week can be difficult

Disease states and recommended neuroimaging technique:*

*Based on several factors, including local availability, expertise, and protocols.

Cerebral Ultrasound (examples)

- High-risk neonatal conditions: e.g. preterms (gestational age (GA) less than 32 weeks), intrauterine growth restriction, congenital abnormalities (syndromes), post-resuscitation, HIE, meningitis/encephalitis, metabolic diseases, symptomatic hypoglycaemia, hyperbilirubinemia (above exchange transfusion threshold), sudden severe anaemia, congenital heart defects, post-surgery, pre-extracorporeal membrane oxygenation (ECMO), post-ECMO, sudden clinical deterioration.
- Newborn infants with neurological symptoms/signs: e.g. seizures, hyper- or hypotonia, abnormal movements, abnormal consciousness, unexplained central apneas, unexplained irritability and restlessness, micro- or macrocephaly.

MRI (examples)

- Neurological symptoms not explained by other diagnoses
- Convulsions
- Symptomatic hypoglycaemia
- Severe hyperbilirubinemia and neurological symptoms or abnormal ultrasound
- HIE grade II or III
- P/IVH with PHVD or periventricular haemorrhagic infarction (PVHI)
- (Suspected) congenital CNS abnormalities
- (Suspected) sinovenous thrombosis
- Abnormalities in posterior fossa
- Parenchymal injury (periventricular leukomalacia -PVL>II, intraparenchymal haemorrhage, stroke, inhomogeneous periventricular echogenicity -PVE)
- Symptomatic extra-cerebral haemorrhage

Suggested timing of neuroimaging:

Cerebral Ultrasound

Term infants:

- Neurological symptoms suggesting brain injury: as soon as possible (to exclude acute conditions that need intervention)



- Suspected congenital CNS abnormalities: 1st day after birth
- Preterm infants:
- GA >28 weeks: scan on day 1-3-7-14,21,28, at 6 weeks and at term equivalent age (TEA)
 - GA < 28 weeks: scan on day 1-3-7-14-21-28- than every two weeks until 34 weeks GA and at term equivalent age (TEA)
 - Intensify CUS in case of abnormalities or after episode of clinical deterioration (e.g. unexplained anaemia, neurological symptoms, P/IVH, PHVD, inhomogeneous PVE, cerebellar haemorrhage, surgery, HIE, CNS infection, metabolic disease, etc.)

MRI

Term infants (examples):

- Neurological symptoms of unknown origin: as soon as possible
- Hypoxic Ischemic Encephalopathy: between day 4-7
- Suspected parenchymal damage (e.g. stroke): between 3-7 days after insult

Preterm infants (examples):

- Neurological symptoms of unknown origin: as soon as possible
- Routine neuroimaging in extreme preterm infants: preferred timing around TEA

Source

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Neurological monitoring in the high-risk infant: clinical neurological evaluation

Gressens P, Hellström-Westas L, Zimmermann L, Buonocore G, Dudink J, Pellicer A

Target group

- Term and preterm infants at risk for brain injury:
 - Infants with hypoxic-ischaemic encephalopathy (HIE)
 - Infants with encephalopathy for other causes (e.g. metabolic)
 - Infants with suspected or verified seizures
 - Infants requiring intensive care and/or surgery
 - Infants with suspected/confirmed congenital central nervous system (CNS) anomalies
- Parents

User group

Healthcare professionals, neonatal units, hospitals, follow-up teams, and health services

Statement of standard

In order to improve evaluation and outcomes of newborn infants at risk of brain injury, management includes neurological monitoring using a structured, age-appropriate neurological assessment and a range of devices to evaluate brain haemodynamics, oxygen transport, brain function, and imaging, as well as long-term follow-up of neuro-motor function as required.

Rationale

Infants requiring neonatal intensive care constitute a high-risk population for developing brain injury, particularly full term and preterm infants exposed to hypoxia-ischaemia, CNS infections, or with congenital anomalies.

Early recognition of disturbed brain function or structural brain injury is important in the institution of preventive or treatment strategies, and appropriate follow-up. Early detection of neurological compromise, such as encephalopathy or seizures, is associated with better management of these conditions. (1–4)

The patient history, a structured neurological examination and repeated clinical observations form the basis of evaluation. After discharge, standardised follow-up and assessment of neurological, motor, cognitive and behavioural function are the mainstay of monitoring, to identify sequelae of perinatal brain injury (see TEG Follow-up & continuing care). Early identification of impaired function will improve clinical management and long-term functional outcomes. (5–10) Parental questionnaires can be combined with formal motor assessment in high-risk populations. (11) Motor assessment tests should be validated in their specific cultural settings. (12)

Benefits

Short-term benefits

- Early identification of neuromotor impairments (5–8)

Long-term benefits

- Improved long-term neuromotor outcomes (8)



Components of the standard

Component	Grading of evidence	Indicator of meeting the standard
For parents and family		
1. Parents are informed by healthcare professionals about the role of clinical neurological evaluation and the importance of neurological follow-up.	B (High quality)	Patient information sheet
For healthcare professionals		
2. A unit guideline on comprehensive clinical neurological evaluation and the use of technological investigation is adhered to by all healthcare professionals. (see TEG Medical care & clinical practice) (5–9)	A (High quality) B (High quality)	Guideline
3. Specific training on clinical neurological evaluation of high-risk infants is attended by all responsible healthcare professionals. (5–7,9)	A (High quality) B (High quality)	Training documentation
4. Teams with a focus of interest on neuro-critical care, including neonatologists, neurologists, neuro-physiologists, nurses, radiologists, radiographers, and physicists are established.	B (High quality)	Guideline
For neonatal unit		
5. A unit guideline on comprehensive clinical neurological evaluation and the use of technological investigation is available and regularly updated. (5–9)	A (High quality) B (High quality)	Guideline
For hospital and follow-up team		
6. Specific training on clinical neurological evaluation of high-risk infants is attended is ensured. (5–7,9)	A (High quality) B (High quality)	Training documentation
7. Facilities for clinical neurological evaluation of high-risk infants are provided.	B (High quality)	Audit report
8. An interdisciplinary team for neuro-critical care of high-risk infants in the NICU is supported.	B (Moderate quality)	Audit report
9. An organised follow-up programme for high-risk infants including neurological,	B (High quality)	Guideline



motor and behavioural assessments is established.

For health service

10. Pregnant women with fetuses with identified neurological problems and high-risk newborn infants are transferred to centres with appropriate clinical neurological evaluation systems and expertise. (see TEG Birth & transfer) (13)	A (High quality)	Audit report, guideline
11. Follow-up programme for high-risk newborn infants, including neurological, motor and behavioural assessments, as well as parental questionnaires is ensured.	B (High quality)	Guideline
12. Benchmarking of long-term neurological outcomes of high-risk infants is established. (11,14)	A (High quality) B (High quality)	Audit report

Where to go – further development of care

Further development	Grading of evidence
For parents and family N/A	
For healthcare professionals N/A	
For neonatal unit N/A	
For hospital N/A	
For health service N/A	

Getting started

Initial steps

For parents and family

- Parents are verbally informed about the role of clinical neurological evaluation and the importance of neurological follow-up.

For healthcare professionals

- Attend training on clinical neurological evaluation of high-risk infants.
- Identify leading healthcare professionals with a focus of interest on neonatal neurological evaluation.



For neonatal unit

- Develop and implement a unit guideline comprehensive clinical neurological evaluation and the use of technological investigation.
- Develop parental information material on clinical neurological evaluation and the importance of follow-up also including parent perspectives.
- Provide resources for specific training on the various neonatal neurological examination tools.

For hospital

- Support healthcare professionals to participate in training on clinical neurological evaluation of high-risk infants.

For health service

- Create systems to effectively transfer high-risk infants to NICUs with appropriate neuro-monitoring systems and expertise.
- Establish a follow-up programme for high-risk newborn infants including neurological, motor and behavioural assessments as well as parental questionnaires.

Description

The standardised clinical neurological examination constitutes the basis of the evaluation of high-risk infants and should be performed repeatedly in the acute phase and later on in infants at risk for neurodevelopmental sequels.

In the neonatal intensive care unit (NICU)

- Neurological assessment should be performed repeatedly in term and preterm infants with overt or suspected clinical signs from the central and/or peripheral nervous system, including seizures. Several validated methods are available for term (1,5,6) and preterm infants (7–9), including for example the Dubowitz Neurological Assessment of the Preterm and Full-term Infant (5,7), the neurological assessment by Amiel-Tison (6), the Assessment of Preterm Infants' Behaviour (APIB) (15), Neonatal Intensive Care Unit Network Neurobehavioural Scale (NNNS) (16), Precht's Assessment of General Movements (GMs) (17), and other. (8,9,18)
- Moderately preterm and term infants with hypoxic-ischaemic encephalopathy (HIE), including infants subjected to therapeutic hypothermia, should be repeatedly assessed during the first days of life to produce gradings of encephalopathy using Sarnat criteria or Thompson scores. (1–3)
- Neonatal pain/comfort assessments are used for repeated assessments of infant behaviour during, intensive care and pain should always be excluded as a potential cause of abnormal behaviour in infants. (19)

Long-term outcomes

First two years after birth

Several neurodevelopmental and neuropsychological tests have been developed for postnatal evaluation of high-risk infants in different countries and hence in different languages. Some of them have been translated and validated in different (but not all) languages, making in some way, general recommendations very difficult.

Accordingly, the following description is based on relatively largely adopted tests but might require some adaptations, depending on the considered part of the world. It is important to remember that a translated test must be validated prior to its generalised use.



- The follow-up should aim at early diagnosis and categorisation of neurodevelopmental problems, including cerebral palsy, motor function, hearing and vision impairments, alongside medical problems such as feeding problems, growth and respiratory function.
- Systematic neuro-motor evaluation can be valuable using well validated tests, such as the Alberta Infant Motor Scale (AIMS) (20), and the Peabody Developmental Motor Scales. (21)
- The clinical neurodevelopmental evaluation should be combined with other assessment methods as required and which may include cerebral ultrasound and MRI, NIRS, aEEG/EEG, EEG, hearing tests, ophthalmological and genetic testing, as appropriate.

Evaluation around 2 and 5-5½ years of age

Long-term follow-up should be offered to infants with a significant risk of developing long-term neurodevelopmental sequels, and who could benefit in their function and quality of life from early detection and special intervention/training for these sequels. High-risk groups include: extremely preterm infants (gestational age <28 weeks), severely growth restricted infants, infants with morphological brain injury (intraventricular haemorrhage grade 3-4, periventricular leukomalacia, stroke, posthaemorrhagic ventricular dilatation, malformations), infants with moderate-severe HIE including infants who needed hypothermia treatment, infants with severe encephalopathies of other causes (e.g. kernicterus, seizures due to hypoglycaemia, metabolic diseases), central nervous system infection and severe neonatal morbidities (e.g. major surgery, sepsis, necrotising enterocolitis, need for nitric oxide or extracorporeal membrane oxygenation). (11,14)

There seems to be some international agreement that 2 and 5-5½ years of (corrected for prematurity, when relevant) age are suitable for evaluation of high-risk infants. These age levels have been chosen since children with adverse development, including cerebral palsy, benefit from early diagnosis and training by physiotherapists. The standardised age-groups also allow for better international comparisons of outcomes.

The present standard has a focus on neurological and motor assessment which should be combined with evaluation of cognitive, behavioural and psychiatric outcomes (see TEG Follow-up & continuing care). Several methods are available, e.g. the Bayley Scales of Infant and Toddler Development (BSID) (22) and the Brunet-Lezine assessment in the younger children. (23) Neurological examination should be performed in a standardised way (24), and e.g. the Movement Assessment Battery for Children (Movement ABC) (25) and other motor assessment tests can be used for evaluation of motor function, including developmental coordination disorders (DCD). Cognitive testing is often done with the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) or the Wechsler Intelligence Scale for Children (WISC).

Categorisation of motor outcome should preferably be done according to the Gross Motor Function Classification System (GMFCS) (26), which also facilitates international comparisons of outcomes. Hand function in children with cerebral palsy can easily be classified with the Manual Ability Classification System (MACS) (27), also in children younger than 4 years.

Follow-up at 2 years should include:

Neurological and neurodevelopmental testing, including cognition and language (e.g. BSID, Brunet-Lezine or equivalent). Assessment of motor function (e.g. Peabody,



Movement ABC). Behavioural and autism screening as required (see TEG Follow-up & continuing care).

Follow up at 5-5½ years should include:

Neurological testing (standardised) and motor function (e.g. Movement-ABC) cognitive function (WPPSI IV or WISC), behavioural tests. Reading and writing evaluation at school age (see TEG Follow-up & continuing care).

For infants at risk of developing motor deficits it is recommended to have a dedicated paediatric physiotherapist present during follow up visits for motor assessments (preferably using standardised test). Hand function should preferably be assessed in conjunction with motor assessment in children with suspected or deviant motor function. (28)

A high proportion of children with morphological brain injury develop cerebral visual impairments, including preterm infants with white matter injury, term infants with stroke or other perinatal brain injury. In order to optimise long-term outcomes by early support of visual functioning in compromised children, it is recommended to screen children with known perinatal brain injury for cerebral visual impairments. (29)

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Postnatal management of newborn infants with hypoxic ischaemic encephalopathy (HIE)

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Target group

Term and near term infants with hypoxic ischaemic encephalopathy (HIE) and parents

User group

Healthcare professionals, neonatal units, hospitals, and health services

Statement of standard

Newborn infants who have suffered from severe hypoxic-ischaemia receive early evaluation and appropriate postnatal management including therapeutic hypothermia and monitoring.

Rationale

The goal is to reduce long-term effects of hypoxic ischaemic brain injury. Moderate to severe perinatal asphyxia in term and near term infants is one of the most important causes of neonatal death and adverse motor and cognitive outcome, with an incidence of 2-20 per 1000 live born infants, depending in which part of the world they are born. (1) Until recently, therapy was limited to stabilisation of the newborn infant and treatment of hypoxic ischaemic encephalopathy (HIE) induced seizures. Reduction of the body temperature to 33.5°C is the only established therapy which has shown a decrease in adverse outcomes after perinatal asphyxia (death or substantial disability at 18 months of age) from about 66% for non-cooled infants to 50% in cooled infants. (2,3) Intensive research is ongoing to explore (pharmacological) neuroprotective interventions which could be used in addition to hypothermia to improve outcome. (4–7)

Benefits

Short-term benefits

- Reduced brain injury due to excitatory neurotransmitters and reactive oxygen species (8,9)
- Improved prognosis using stratified hypoxic ischaemic encephalopathy (HIE) severity, e.g. using neurophysiological monitoring (a-EEG (10–12) or EEG) (13) (see TEG Medical care & clinical practice)
- Reduced brain injury by early treatment of seizures (13,14)
- Reduced mortality (3)

Long-term benefits

- Improved neurocognitive outcome, increasing the rate of disability free outcome at 5 years (3,15) reduced health and societal costs (16), reduced occurrence of epilepsy at 2 years (7), less severe cerebral palsy in survivors (15)



Components of the standard

Component	Grading of evidence	Indicator of meeting the standard
For parents and family		
1. Parents are informed by healthcare professionals about the management and outcome of hypoxic ischaemic encephalopathy (HIE). (17–20)	A (Low quality) B (High quality) C (Moderate quality)	Patient information sheet
2. Parents receive counselling regarding the expected short- and long-term outcome and prognosis related to HIE prior to discharge by healthcare professionals. (20)	B (High quality) C (Moderate quality)	Clinical records
For healthcare professionals		
3. A unit guideline on management of HIE including criteria for hypothermia treatment is adhered to by all healthcare professionals.	B (High quality)	Guideline
4. Training in assessment and management of encephalopathic infants is attended by all responsible healthcare professionals. (21,22)	A (Moderate quality) B (High quality)	Training documentation
5. Moderate hypothermia treatment is started within 6 hours and continued for 72 hours after birth of eligible infants. (2,23)	A (High quality)	Audit report
For neonatal unit		
6. A unit guideline on management of HIE (22) including monitoring blood glucose, a-EEG, seizures (14), heart rate (24), oxygen saturation (25), PCO ₂ (14,25), and blood pressure is available and regularly updated.	A (Moderate quality) B (High quality)	Guideline
7. Infants who require hypothermia treatment are managed in centres with documented expertise and experience including necessary transfer. (see TEG Birth & transfer)	B (Moderate quality)	Guideline
For hospital		
8. Training in assessment and management of encephalopathic infants is ensured.	B (High quality)	Training documentation



9. At designated units, cooling devices and monitoring equipment are available.	B (High quality)	Audit report
For health service		
10. A national guideline on management of HIE including criteria for hypothermia treatment is available and regularly updated.	B (High quality)	Guideline
11. Hypothermia treatment including documented follow-up at 2 years (e.g. Bayley III or similar) and necessary education is coordinated and organised.	B (High quality)	Audit report
12. Support services for families with infants with HIE are available.	B (High quality)	Audit report

Where to go – further development of care

Further development	Grading of evidence
For parents and family	
<ul style="list-style-type: none"> Use routine health service and education data for long-term follow-up programmes. 	B (Moderate quality)
For healthcare professionals	
N/A	
For neonatal unit	
<ul style="list-style-type: none"> Develop regional training programmes on early assessment and management of hypoxic ischaemic encephalopathy (HIE). Research on improved interventions, monitoring care and outcome predictors. 	B (High quality) B (Moderate quality)
For hospital	
N/A	
For health service	
<ul style="list-style-type: none"> Develop asphyxia registry service including outcome at 2 years. (14,18) 	B (Moderate quality)

Getting started

Initial steps
For parents and family
<ul style="list-style-type: none"> Parents are verbally informed by healthcare professionals about the management and outcome of hypoxic ischaemic encephalopathy (HIE) by healthcare professionals.
For healthcare professionals
<ul style="list-style-type: none"> Attend training in assessment and management of encephalopathic infants. Join post-graduate education with respect to hypothermia and a-EEG or EEG monitoring and interpretation technique/knowledge. Develop appropriate neurodevelopmental follow-up expertise.



For neonatal unit

- Develop and implement a unit guideline on management of HIE including criteria for hypothermia treatment.
- Develop information material on management and outcome of HIE for parents.
- Provide appropriate devices and knowledge how to use device(s). (22)

For hospital

- Support healthcare professionals to participate in training assessment and management of encephalopathic infants.
- Provide appropriate budget and technical support for training and equipment.

For health service

- Develop and implement a national guideline on management of HIE including criteria for hypothermia treatment and follow-up.
- Recognise that therapies discussed in this statement are mandatory.

Description

Apart from the supportive therapies such as stabilisation of haemodynamics, support of respiration, monitoring of physiological parameters and metabolism (e.g. glucose metabolism, electrolytes, etc.) and treatment of seizures, moderate hypothermia (target; 33-34°C) should be initiated as soon as possible and not later than six hours after birth (within the so-called therapeutic window) and continued for 72 hours, with appropriate sedation and pain management. (2,23) It is important to anticipate the possible side effects of induced hypothermia; including thrombocytopenia; hypotension; arrhythmia/bradycardia and hearing loss. (3,26) If sepsis or infection is suspected, antibiotic treatment should be considered. Although beyond the scope of this topic, appropriate (brain) monitoring is mandatory. Depression of background amplitude on early amplitude-integrated EEG (a-EEG) or abnormal multi-channel EEG activity is an excellent indicator of severity, and can be used to stratify babies for therapeutic hypothermia. Continuous a-EEG/EEG monitoring is essential to detect electrographic seizures and the effect of anticonvulsant treatment. In addition, the use of near infrared spectroscopy-monitored cerebral oxygenation (rScO₂) can be useful to estimate severity. Proper documentation of brain injury, including serial neurological examination (cranial ultrasound; MRI, preferably with diffusion sequences) as well as biochemical markers in blood/serum or plasma is important to determine the prognosis in the first week of life. Be aware of the effect of hypothermia per se on biochemical markers (27–29) and physiological variables. (21) Systematic neurobehavioural testing and documentation at two years follow-up in survivors (e.g. Bayley III (30) or Griffiths (31) as well as at early school age for long term, e.g. 5-8 years (see TEG Follow-up & continuing care). (18)

1. General measures (hemodynamic/respiratory stabilisation; treatment of convulsions; metabolic/electrolyte surveillance)
2. Moderate whole body hypothermia (33.5±0.5°C)
3. Add-on therapies when such are proven effective in trials (e.g. pharmacology/noble gasses/repair with umbilical cord stem cells)

1 and 2 are established therapies and are standard clinical practice, 3 are experimental and are currently under clinical investigation.



Several phase II and III studies are underway for assessment as add-on therapies to be used with hypothermia, mostly pharmacological therapy (rhEPO; melatonin; allopurinol) and ventilation with noble gases (Xenon); Repair with stem cells (e.g. mesenchymal stem cells, autologous (UMBC cells) and allogeneic transplantation are being investigated). (4,13,32–34)

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Prevention, detection, documentation, and treatment of retinopathy of prematurity (ROP)

Hellström A, Hellström-Westas L, Zimmermann L, Buonocore, G, Hård AL, Stahl A

Target group

Preterm infants at risk of severe retinopathy of prematurity (ROP) defined by national guidelines and parents

User group

Healthcare professionals, neonatal units, hospitals, and health services

Statement of standard

Screening programmes for detection, documentation, and treatment of sight threatening retinopathy of prematurity (ROP) in all units caring for very preterm infants, as well as preventive measures such as control of oxygen supplementation and promotion of optimal nutrition are established.

Rationale

The goal is to prevent visual impairment and blindness due to retinopathy of prematurity (ROP), which is a major cause of childhood blindness and mainly affects extremely preterm infants. (1,2) Uncontrolled oxygen supplementation and poor neonatal monitoring are important factors contributing to increased ROP risk, even in more mature infants. (3)

Hospitals caring for very preterm infants need programmes promoting adherence to oxygen saturation targets and avoidance of hyperoxia, through implementation of appropriate alarm levels, education of healthcare professionals, oxygen titration guidelines, and sufficient number of skilled attendants. Automated oxygen control can improve SpO₂ targeting and may be an alternative. (4) Prevention and management of ROP require close inter-disciplinary collaboration.

Hospitals caring for very preterm infants should adhere to screening and treatment programmes for ROP, based on existing evidence.

These programmes define:

- screening inclusion criteria,
- timing of eye examination:
 - first examination generally at 4-6 weeks of age but not before a postmenstrual age of 31 weeks
 - follow-up screening examinations biweekly to twice a week depending on findings
- choice of dilating drops and information on how to avoid systemic absorption
- any topical anaesthesia
- indication for treatment
- follow-up of treated infants following appropriate protocols based on the type of treatment

Currently, most hospitals adhere to the US recommendations for screening (5) and for treatment, the recommendations of the Early Treatment for Retinopathy of Prematurity Group (6) are followed in many countries.



Benefits

Short-term benefits

- Reduced occurrence of severe retinopathy of prematurity (ROP) needing treatment (7–9)
- Improved identification of infants needing treatment for ROP (5,10)
- Increased number of infants treated timely (5,10)
- Reduced stress for parents (11)

Long-term benefits

- Reduced occurrence of visual impairment and blindness caused by ROP (7–9)

Components of the standard

Component	Grading of evidence	Indicator of meeting the standard
For parents and family		
1. Parents are informed by healthcare professionals about retinopathy of prematurity (ROP), screening, treatment, and outcomes including the importance of breastfeeding for the prevention of ROP. (see TEG Care procedures) (11,12)	A (Low quality) B (High quality)	Patient information sheet
For healthcare professionals		
2. A unit guideline on prevention and management of ROP is adhered to by all healthcare professionals.	B (High quality)	Guideline
3. Training on oxygen saturation targets is attended by all responsible healthcare professionals. (13)	A (High quality) B (High quality)	Training documentation
For neonatal unit		
4. A unit guideline on prevention and management of ROP is available and regularly updated. (5,6,14)	A (High quality) B (High quality)	Guideline
5. A unit guideline for control of oxygen supplementation is available and regularly updated. (15)	A (Moderate quality) B (High quality)	Audit report, guideline
For hospital		
6. Training on prevention and management of ROP is ensured.	B (High quality)	Training documentation
7. Availability of expert personnel for fail-safe system of ophthalmological screening and treatment is ensured. (5)	A (Moderate quality) B (High quality)	Audit report



For health service

8. A national guideline on prevention and management of ROP is available and regularly updated.	B (High quality)	Guideline
9. Rate of blindness and impaired vision due to ROP is monitored nationally.	B (High quality)	Audit report

Where to go – further development of care

Further development	Grading of evidence
For parents and family N/A	
For healthcare professionals	
<ul style="list-style-type: none"> Initiate seamless information transfer systems between clinics and hospitals and measures to improve patient adherence to ophthalmological follow-up during screening and after treatment. (16–18) (see TEG Follow-up & continuing care) 	B (Moderate quality)
For neonatal unit N/A	
For hospital N/A	
For health service	
<ul style="list-style-type: none"> Consider telemedicine support for screening for retinopathy of prematurity (ROP). (10,19) Support research into causes and treatment of ROP. (20) 	<p>A (Moderate quality)</p> <p>B (Moderate quality)</p>

Getting started

Initial steps
For parents and family
<ul style="list-style-type: none"> Parents are verbally informed by healthcare professionals about retinopathy of prematurity (ROP), screening, treatment and outcomes including the importance of breastfeeding for the prevention of ROP.
For healthcare professionals
<ul style="list-style-type: none"> Attend training on prevention and management of ROP.
For neonatal unit
<ul style="list-style-type: none"> Develop and implement a unit guideline on prevention and management of ROP. Develop information material on ROP for parents. Develop fail-safe systems for the identification of infants at risk of ROP. Ensure fail-safe systems for referral and continuous cover by ophthalmologist. Develop formalised programmes for education in oxygen saturation targets. Develop formalised programmes for promotion of mother's own milk feeding.



For hospital

- Support healthcare professionals to participate in training on prevention and management of ROP.
- Identify pathways for infants with progressive ROP to receive expert assessment and treatment.

For health service

- Develop and implement a national guideline on prevention and management of ROP.

Description

Despite the success of retinopathy of prematurity (ROP) screening and treatment much is unknown about the progression and response to treatment.

There is controversy over the precise oxygen saturation targets but current evidence suggests that, whereas ROP is less frequent when saturations are targeted at 85-89%, mortality is increased. Thus, most units maintain targets of 91-95%. (21) However, recent European consensus guidelines recommend a target range of 90-94% with alarm limits set at 89% and 95%. (22) It is important to avoid higher saturations and research is ongoing into whether these targets can be refined further. Most importantly better adherence to saturation targets is associated with lower rates of ROP. (15)

Furthermore, early breastfeeding is associated with a reduced risk of ROP. (23,24)

If treated at the appropriate stage, vision of infants with severe ROP can be preserved by laser therapy or anti-VEGF therapy where indicated. (20) The long-term safety of anti-VEGF treatment needs further research. (25) If left untreated, severe ROP may lead to irreversible blindness – often in both eyes. (26) Importantly, even less severe ROP affects vision (27) and infants treated for ROP have an increased risk of retinal detachment, myopia, and other complications throughout life. (28,29)

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Prevention of Bronchopulmonary Dysplasia (BPD)

Poets C, Zimmermann L, Hellström-Westas L, Buonocore G, Hallman M, Lista G, van Kaam A, Kramer B

Target group

Very preterm and particularly extremely preterm infants, small for gestational age infants, and parents

User group

Healthcare professionals, neonatal units, hospitals, and health services

Statement of standard

Bronchopulmonary Dysplasia (BPD) is prevented using evidence-based strategies including avoiding mechanical ventilation, minimally invasive administration of exogenous surfactant, volume targeted ventilation and early caffeine, and administration of systemic steroids in infants still requiring ventilation during their 2nd postnatal week.

Rationale

Bronchopulmonary Dysplasia BPD results from the effects of non-physiologic stimuli (e.g. inflammation, ventilator induced lung injury, high supplemental oxygen levels) in an infant with underdeveloped lungs and defence mechanisms (e.g. anti-oxidant capacity). (1) Interventions that reduce inflammation (e.g. steroids) or any of these non-physiologic stimuli (e.g. mechanical ventilation) are likely to reduce BPD rates. Some of these interventions may additionally promote the survival of the target group; none decreases the chances of survival. (2)

BPD, defined as supplemental oxygen requirement at 36 weeks post-menstrual age, is a risk factor for later respiratory hospitalisation in infancy, compromised lung function in childhood, neurodevelopmental impairment, and a potential risk factor for chronic obstructive pulmonary disease in later life. (1,3)

Benefits

Short-term benefits

- Reduced risk of BPD by avoiding invasive mechanical ventilation (risk ratio (RR), 0.91; 95% Confidence Interval 0.84-0.99) (2)
- Reduced risk of BPD by use of minimally invasive surfactant administration (RR 0.75; 0.59-0.94) (4,5)
- Reduced risk of BPD by use of volume targeted ventilation (as opposed to pressure targeting) (RR 0.61; 0.46-0.82) (6)
- Reduced risk of BPD by starting caffeine on postnatal day one or two instead of later (RR 0.51; 0.40-0.64) (7,8)
- Reduced risk of BPD by administration of vitamin A intramuscularly for the first four postnatal weeks (RR 0.87; 0.77-0.98) (9)
- Reduced rate of death or BPD by administration of systemic steroids in ventilated infants (RR 0.72; 0.63-0.82) without increasing the risks of cerebral palsy (10)

Long-term benefits

- Reduced adverse neurodevelopmental outcome if BPD can be prevented (3)



Components of the standard

Component	Grading of evidence	Indicator of meeting the standard
For parents and family		
1. Parents are informed by healthcare professionals about Bronchopulmonary Dysplasia (BPD) and strategies to minimise its risk. (1)	A (High quality)	Patient information sheet
For healthcare professionals		
2. A unit guideline on the management and prevention BPD is adhered to by all healthcare professionals, and includes the following advice: <ul style="list-style-type: none">• Surfactant is administered via a thin intra-tracheal catheter if FiO_2 is >0.30 or using INSURE (intubate surfactant extubate). (11)• Volume targeted ventilation (at 5-7 ml/kg) is used plus adequate PEEP level, if intubation cannot be avoided. (6)• Infants on n-CPAP are switched to synchronised nasal ventilation if respiratory distress visible while on CPAP. (12)• Caffeine is administered from day 1-2 after birth (10 mg/kg loading, 5 mg/kg/d maintenance for caffeine base). (7,8)• Vitamin A is considered (5000 IE i.m. three times/week for week 1-4 after birth). (9)• If mechanical ventilation is still necessary during postnatal week 2, postnatal steroid use is considered (dexamethasone at the lowest effective dose possible. (13,14))• Efforts to reduce rates of nosocomial infection, as a risk factor for BPD, are made. (15)	A (High quality)	Guideline



3. Training on the management and prevention of BPD is attended by all responsible healthcare professionals.	B (High quality)	Training documentation
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For neonatal unit

4. A unit guideline on prevention and management of BPD is available and regularly updated.	B (High quality)	Guideline
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For hospital

5. Training on management and prevention of BPD is ensured.	B (High quality)	Training documentation
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6. Institutional BPD rates are monitored together with length of hospital stay and use of supplemental oxygen.	B (High quality)	Audit report
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For health service

7. A national guideline on management and prevention of BPD is available and regularly updated.	B (High quality)	Guideline
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Where to go – further development of care

Further development	Grading of evidence
For parents and family	
N/A	
For healthcare professionals	
<ul style="list-style-type: none"> • Investigate in larger numbers whether using synchronised nasal ventilation rather than CPAP is the preferred mode of nasal respiratory support. (6) • Evaluate alternative anti-inflammatory strategies, e.g. hydrocortisone, inhaled budesonide, or tracheal instillation of budesonide together with exogenous surfactant to generate more data on their long-term effectiveness and safety. (10,16,17) • Investigate the role of eradicating <i>Ureaplasma urealyticum</i> shortly after birth. (18) • Investigate oral Vitamin A administration as well as the role of other nutrients. (9,19) • Find the optimal drug and dose for postnatal steroid application. (9) • Investigate the potential of mesenchymal stem cells in repairing the injured immature lung. (20,21) • Investigate the effect of various delivery-room practices (e.g. sustained inflations) and of early enteral feeding on the prevention of BPD. (22) 	<p>A (Moderate quality)</p> <p>A (High quality)</p> <p>A (Moderate quality)</p> <p>A (High quality)</p> <p>A (Moderate quality)</p> <p>A (High quality)</p> <p>A (Moderate quality)</p>
For neonatal unit	
N/A	



For hospital

N/A

For health service

N/A

Getting started

Initial steps

For parents and family

- Parents are verbally informed by healthcare professionals about BPD and strategies to minimise its risk. (1)

For healthcare professionals

- Attend training on management and prevention of BPD.
- Apply exogenous surfactant via less/minimally invasive administration via a thin catheter, i.e. without using an endotracheal tube, or via the INSURE method (intubate, surfactant, extubate).
- Use nasal continuous positive airway pressure (n-CPAP) instead of intubation and mechanical ventilation. (22)
- Start caffeine on postnatal day 1 or 2 instead of later.

For neonatal unit

- Develop and implement a unit guideline on management and prevention of BPD.
- Develop information material about BPD for parents.

For hospital

- Support healthcare professionals to participate in training on management and prevention BPD.

For health service

- Develop and implement a national guideline on management and prevention of BPD.

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Prevention of vitamin K deficiency bleeding (VKDB) at birth

Koletzko B, Buonocore G, Zimmermann L, Hellström-Westas L, Fewtrell M, Perrone S, Verkade H

Target group

Newborn infants and parents

User group

Healthcare professionals, neonatal units, hospitals, and health services

Statement of standard

Prophylactic supplementation with vitamin K for all infants is given to prevent vitamin K deficiency bleeding (VKDB).

Rationale

Vitamin K deficiency bleeding (VKDB) in infants is prevented by vitamin K supplementation. Healthy newborn infants have low hepatic stores of vitamin K (1) and are at risk of developing serious bleeding, including intracranial hemorrhage, due to low hepatic synthesis of vitamin K–dependent clotting factors. (2,3) Preterm infants appear to be at even higher risk. (4) Postnatal supplementation of vitamin K can markedly reduce the incidence of VKDB, associated morbidity, including devastating brain injury, neurodevelopmental impairment and mortality. (5–7)

Healthy infants should either receive 1 mg of vitamin K intramuscular at birth, or three doses of 2 mg vitamin K orally at birth, at four to six days and at four to six weeks; or 2 mg vitamin K orally at birth followed by weekly doses of 1 mg orally for three months for breastfed infants. (3) Intramuscular application has the best preventive efficiency. (3) The administration of low daily oral doses (e.g. 25-150 µg/d) is less effective than either of the earlier mentioned alternatives and is thus not recommended. (8) Vitamin K should be administered parenterally to newborn infants who are unwell, those who have cholestasis or impaired intestinal absorption, or who are unable to take oral vitamin K, those whose mothers have taken medications that interfere with vitamin K metabolism, and to preterm infants. (9)

Preterm infants may require reduced doses of vitamin K prophylaxis such as 0.5 mg intramuscular for infants >1000 g or 0.2 mg intramuscular/intravenous for infants <1000 g. (8) Vitamin K supplementation protocols should be developed and implemented in all obstetric and neonatal units. (3,10)

Benefits

Short-term benefits

- Reduced risk of Vitamin K deficiency bleeding and related infant mortality and morbidity (11–13)

Long-term benefits

- Reduced long-term damage and neurodevelopmental handicap (12)
- Reduced healthcare costs arising from chronic morbidity (consensus)



Components of the standard

Component	Grading of evidence	Indicator of meeting the standard
For parents and family		
1. Parents are informed before and after birth by healthcare professionals about the importance of vitamin K supplementation and its benefits. (10)	A (High quality) B (High quality)	Patient information sheet
For healthcare professionals		
2. A unit guideline on Vitamin K supplementation in all infants is adhered to by all healthcare professionals. (3)	A (High quality) B (High quality)	Guideline
3. Training on prevention of vitamin K deficiency bleeding (VKDB) is attended by all healthcare professionals.	A (Low quality) B (High quality)	Training documentation
4. Parental refusal of vitamin K prophylaxis is clearly documented.	B (High quality)	Clinical records
For neonatal unit		
5. A unit guideline on vitamin K supplementation in all infants is available and regularly updated. (3)	A (High quality) B (High quality)	Guideline
6. Administration of vitamin K supplementation is monitored.	A (Low quality) B (High quality)	Audit report
For hospital		
7. Training on prevention of VKDB is ensured.	A (Low quality) B (High quality)	Training documentation
For health service		
8. A national guideline on vitamin K supplementation in all infants is available and regularly updated. (3)	A (High quality) B (High quality)	Guideline
9. Rate of vitamin K deficiency related haemorrhage in infants is monitored.	A (Low quality)	Audit report



Where to go – further development of care

Further development	Grading of evidence
For parents and family N/A	
For healthcare professionals N/A	
For neonatal unit N/A	
For hospital	
<ul style="list-style-type: none">Participate in and implement communication strategies to promote acceptance of universal vitamin K supplementation.	A (Low quality)
For health service	
<ul style="list-style-type: none">Develop and implement communication strategies to promote acceptance of universal vitamin K supplementation.Monitor the proportion of infants who receive vitamin K supplementation according to established standards across the population.	A (Low quality) B (High quality)

Getting started

Initial steps

For parents and family

- Parents are verbally informed by healthcare professionals before and after birth about the importance of vitamin K supplementation and its benefits.

For healthcare professionals

- Attend training on prevention of vitamin K deficiency bleeding (VKDB).

For neonatal unit

- Develop a unit guideline on vitamin K supplementation in all infants.
- Develop information material on the importance of vitamin K supplementation and its benefits for parents.

For hospital

- Support healthcare professionals to participate in training on prevention of VKDB.

For health service

- Develop and implement a national guideline for vitamin K supplementation in all infants.
- Raise awareness of the importance of vitamin k supplementation to effectively address common concerns and disinformation.



Source

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