Hypoxic–ischaemic encephalopathy

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Abstract
Encephalopathy occurring soon after birth continues to be a major complication in near- and full-term newborn infants. Early neonatal encephalopathy is most likely to be due to perinatal hypoxia–ischaemia, but precise criteria supporting hypoxia–ischaemia should be applied when defining this syndrome. Careful clinical assessment together with specific investigations allows precise assessment of prognosis during the first few days after birth. MRI is the best method available for confirming the diagnosis and predicting specific patterns of outcome in babies with perinatal hypoxia–ischaemia. Management of infants with hypoxia–ischaemic encephalopathy is largely supportive, but current studies indicate that mild/moderate hypothermia may increase the chance of survival without disabilities up to 18 months of age.

Keywords neonatal encephalopathy; hypoxic–ischaemic encephalopathy; standardised neurological examination; amplitude integrated EEG; cranial ultrasound; cerebral blood flow velocity; magnetic resonance imaging; secondary energy failure; neuroprotection; hypothermia

Introduction
Encephalopathy occurring soon after birth continues to be a major complication in near- and full-term newborn infants, occurring in about 2.6 per 1000 births in wealthy countries. In developing countries, neonatal encephalopathy accounts for the largest number of deaths in infancy and childhood – approximately 1 million per year worldwide. Early neonatal encephalopathy is often assumed to be due to perinatal hypoxia–ischaemia. Ideally, precise criteria supporting hypoxia–ischaemia should be applied when defining this syndrome, but frequently they are not all fulfilled yet no other explanation for the infant’s symptoms is found. Alternative causes of neonatal encephalopathy, such as metabolic or developmental abnormalities or evidence of long-standing brain injury, occur infrequently, but it is not uncommon to identify coexisting conditions such as fetal growth restriction or evidence of prior low-grade infection.

A significant reduction of the incidence of hypoxic–ischaemic encephalopathy (HIE) requires improvements in obstetric care, especially maternal care, fetal monitoring and safe delivery practices. However, HIE sometimes occurs despite best current obstetric practice. Until recently, the only available management was standard intensive care, but studies now completed suggest that treatment with cooling very soon after birth in infants with HIE improves the chances of recovery without disability.

In this paper, we discuss the assessment of infants following HIE, the pathophysiological processes leading to cerebral injury, and current attempts at neuroprotection.

Clinical assessment
The clinical picture of an infant with HIE is generally divided into magnetic resonance imaging (MRI) three stages.

- Stage 1 encephalopathy, with transient irritability, hypertonia and poor feeding is usually associated with a good outcome, though there are reports that some children in this category developed cerebral palsy, and there are concerns about learning and memory difficulties even in infants who appear to do well.
- Stage 2 encephalopathy is associated with a poor outcome in approximately 25% of infants; the prognosis is worse if there are prolonged or frequent seizures, the Apgar score is less than 3 at 10 minutes, or there is delayed onset of feeding or visual attention.
- Stage 3 encephalopathy almost invariably leads to death or a severely abnormal outcome.

Prognosis is difficult from the clinical features alone, and distinguishing the different stages is complicated by anticonvulsant therapies, paralytic agents and co-morbidities.

A standardised neurological examination at 2–3 weeks is a simple and good prognostic tool and correlates with MRI findings. Infants with widespread lesions affecting the central grey matter have a severely abnormal neurological examination and a poor outcome in all developmental domains. More focal basal ganglia lesions are associated with briefer neonatal seizures, early feeding and visual responsiveness, but often also persisting central hypotonia, jitteriness and hyperreflexia, and later an athetoid type of cerebral palsy with good head growth and cognitive and visual function. Infants with significant white matter injury but normal central grey matter normalise neurologically more quickly than infants with basal ganglia lesions and tend to have relatively good motor outcome and feeding, but later cognitive deficits, squints, behavioural problems and sometimes seizures are apparent. Such children may appear normal in their early years, but have deficits later. A standardised neurological examination is easy to perform, quick and cheap, and of good predictive value. have described affected infants’ general movements. The presence or absence of normal writhing movements in the early post-natal weeks or fidgety movements at 9–16 post-term with or without weeks are good predictors of normal or abnormal motor outcome, respectively. Specific movement abnormalities are seen in infants who develop athetoid cerebral palsy.

Clinical assessment during infancy
We have shown that, using a standardised neurological examination suitable for infants from 9–18 months, sitting and walking abilities at 2 and 4 years can be predicted, and the neurological
findings correlate with the severity of MRI findings. A recent study has shown that the pattern of neurological abnormality persisting in the first months after neonatal HIE relates to the sites of damage seen on MRI.

Head growth is a useful measure after HIE, and it is important that a relative decline of occipitofrontal circumference on the centile lines even within the normal range is recognised. The major contributor to head growth is the volume of the white matter. In a study of head growth following HIE, over 50% of infants had suboptimal head growth at 1 year (defined by a decrease of two or more standard deviations, with or without microcephaly) associated with severe white matter with or without severe basal ganglia and thalamic lesions. Infants with focal basal ganglia lesions but preserved white matter maintain normal head growth but may have significant motor problems, while infants with suboptimal head growth with abnormal white matter but normal basal ganglia are likely to have cognitive deficits.

Investigations assessing outcome following HIE

Amplitude integrated EEG using a cerebral function monitor (aEEG/CFM) and Doppler measurement of cerebral blood flow velocity (CBFV) allow prediction of severely abnormal or normal outcome in the first few days after birth. Brain imaging provides more specific information about the outcome, becomes more accurate after the first few days, and is helpful in distinguishing certain developmental and metabolic disorders that give rise to neonatal encephalopathy. Magnetic resonance spectroscopy (MRS) can also be helpful both early and later.

Neurophysiology

aEEG/CFM patterns correlate well with both standard EEG and MRI findings and developmental outcome. CFM is available at the bedside and is easy and quick to apply, and the patterns are relatively easy to analyse, showing good inter-observer agreement. Electographic data is most useful for prognosis the earlier it is obtained, but care must be taken as in a few cases abnormal traces normalise in 6–12 hours after birth. Brief seizures may be missed on CFM, but it is the background activity that has the greatest prognostic value in HIE. A full EEG should be undertaken, especially if there are any doubts about the diagnosis. Early continuous two-channel EEG is an accurate prognostic tool, but it is expensive and requires more time and expertise to interpret, and is less practical than CFM for assessing the severity of HIE. Most modern CFM equipment can show one or two channels of raw EEG (Figure 1) and some can be used for more extensive EEG monitoring. Visual and somatosensory evoked potentials have also been used to predict outcome in HIE; though accurate, the technique is more difficult than CFM and does not give continuous data.

Cranial ultrasonography

Cranial ultrasonography is another readily available bedside tool. Modern machines give high-quality images that can be stored on disc and provide very good detail of many aspects of both normal brain development and pathology (Figure 2). Cranial ultrasonography has some limitations in HIE, but has a valuable role in defining the major anatomical structures on the admission of the infant to the neonatal intensive care unit (HIE is rarely associated with structural abnormality and any anatomical variants suggest metabolic or other diagnoses), detecting calcification and cysts suggestive of viral infection and detecting atrophy suggestive of long-standing damage. It also identifies cerebral haemorrhage. Sequential observation of the evolution of injury following a recent hypoxic-ischaemic insult at birth is helpful for both defining the pattern of the lesion and timing its onset. This has important medico-legal implications.

Generalised swelling may be seen after the first hours but is not a universal feature in infants with HIE, being more common in those with a longer or more sub-acute insult and less often seen with insults affecting only the grey matter. Widespread basal ganglia and thalamic abnormalities and increased echogenicity in the white matter are significant findings. Typically after a recent acute hypoxic–ischaemic insult, the central grey matter becomes echogenic within 3–4 days (Figure 2b and c), though more subtle abnormalities may be poorly defined and focal echogenicity may be seen later at 2–3 weeks, associated with dilatation of the third ventricle secondary to poor growth of the adjacent central grey matter. The appearance of a hypoechogetic line running through the central grey matter is often associated with a poor outcome and appears to relate to abnormality in the internal capsule as also seen on MRI (see below; Figure 2b and c). Awareness of these more subtle features is important for outcome in babies with stage 1 or 2 HIE, especially when recovery from the acute perinatal events seems good. The role of ultrasonography is perhaps greater in following the time course and pattern of lesions and excluding other diagnoses, though it is not so specific in predicting detailed outcome. However, persisting normality of the brain parenchyma (Figure 2a) over 3–4 weeks with good brain and head growth are positive prognostic signs.

Doppler ultrasound measurement of CBFV and calculation of the pulsatility index (PI; peak systolic velocity – end-diastolic velocity/peak systolic velocity) is valuable in predicting outcome in HIE. A normal PI is 0.65–0.9; values of less than 0.55 are associated with death or a severe outcome, while normal PIs are highly predictive of a normal outcome at 18 months (Figure 3). PI measurements should be made 2–4 days after birth if the insult is acutely perinatal. If the PI is already abnormal on day 1, the outcome is usually very poor and suggests an insult before delivery.

MRI and MRS

MRI is the best method available for predicting specific patterns of outcome in babies with HIE. It is clearly superior to CT, which has little place in defining outcome in HIE and involves ionising radiation. Correlation between images obtained in the neonatal period and images after 1 year of age is good, as is the correlation between patterns of injury on early MRI and neurodevelopmental outcome. With MRI-compatible ventilators and monitoring equipment, it is now possible to perform MRI in very sick infants, but medical and nursing staff skilled in caring for such infants while in the scanner are needed. Care has to be taken in interpreting very early images, and more widespread experience in image interpretation is needed. MRI also gives information about the timing of injury, and specific patterns of abnormality may suggest diagnoses other than HIE such as metabolic disorders and developmental disorders of the brain. MRI has shown that there is a low prevalence of established brain lesions
acquired before birth in HIE and also a low prevalence of associated congenital abnormality.\textsuperscript{4} Post-mortem data does suggest that injury predating the onset of labour is common. However, this is based on small numbers and it is unclear whether the injuries described, which are mostly in the white matter, were the primary injuries leading to death.\textsuperscript{25}

**Figure 1** CFM/EEG patterns. (a) Normal CFM, showing normal amplitude, sleep–wake cycling and continuous EEG. The interval between arrowheads is 10 minutes on the CFM window and 1 sec on the EEG window; (b) Moderately abnormal CFM, with abnormally wide amplitude and moderately discontinuous EEG; (c) Severely abnormal CFM, with suppressed amplitude and extremely discontinuous EEG. Seizures are also present towards end of record, indicated by arrow.
The optimal timing for MRI for prognostic purposes is from postnatal week 1 to 4 in term-born infants. Very early scans, within 1–2 days after birth, when lesions are still evolving and there is swelling, can be difficult to interpret, but established injury at this time supports a prenatal timing. Diffusion-weighted imaging can be used in the first days after birth, and with the use of improved sequences, measurements of diffusion coefficients, fractional anisotropy and eigenvector values it is likely that the specificity and sensitivity of very early scans for predicting outcome will improve.

When MRI is normal (Figure 4) or mildly abnormal (mild cortical highlighting, Figure 5, with or without mild or moderate white matter changes), the outcome is almost invariably normal. Extensive cortical or white matter involvement (Figure 6) is associated with significant motor and cognitive deficits. Some of these infants may seem relatively normal in the first year, though most have tone abnormalities and relative microcephaly. Moderate basal ganglia and thalamic injury in the posterolateral lentiform and ventrolateral nuclei of the thalami is associated with athetoid cerebral palsy, with relatively good cognition and social and visual interaction and a low incidence of seizures (Figure 7a). Severe bilateral basal ganglia and thalamic lesions are always associated with spastic quadriplegia, microcephaly, and feeding and often visual and other communication
difficulties. Seizures, which occur frequently, are often difficult to control (Figure 7b).

The presence of abnormal signal in the posterior limb of the internal capsule is highly predictive of an abnormal motor outcome; a normal appearance is usually associated with a normal motor though not necessarily a normal cognitive outcome.\(^{22,27}\) In infants with normal scans, the outcome is very good, but it is important to be aware that assessment of, for example, subtle change in the hippocampus is difficult in the neonatal period, and longer-term follow-up is warranted in this vulnerable group of infants.\(^8,28\)

Proton and phosphorous MRS have been used to predict outcome in infants with HIE (Figure 8). Abnormal lactate/creatinine ratios (> 1.0) within 18 hours of birth predict an adverse outcome (death during the neonatal period or abnormal neurodevelopmental outcome at 1 year of age).\(^{29}\) Persistently raised tissue lactate weeks after HIE is also associated with severely abnormal neurodevelopment at 1 year of age, suggesting an ongoing pathological process in these infants.\(^{30}\) The best predictor of outcome from MRS in asphyxia is probably the plasma creatinine:inorganic phosphate ratio and pH shift in the brain issue, but this requires a phosphorus-tuned coil, which is rarely available on standard scanners.\(^{31}\)
HIE in preterm infants

HIE is more poorly defined in preterm infants. Of 63 preterm infants who fulfilled criteria for HIE and who had been referred to us for evaluation, basal ganglia lesions were seen in three-quarters and were severe in one-half of the cases, with a high prevalence of brainstem lesions (unpublished observations). Unsurprisingly in this preterm group, white matter abnormality was very common, but it was severe in only one-quarter. Cortical injury was more often seen in the more mature preterm infants. The pattern of injury seen on MRI was similar to that in term-born infants, but with a higher rate of brainstem and severe basal ganglia injury and consequently a poor prognosis in this selected population. MRI was accurate for predicting outcome.

Pathophysiology following HIE

Following asphyxia, clinical and physiological abnormalities often worsen over the subsequent several hours. Although the

Figure 6 (a) Axial T1-weighted MR image showing extensive cortical highlighting (thin black arrows); (b) Axial T2-weighted MR image showing widespread infarction in the white matter (short black arrows). Both these features, in the absence of any abnormality in the basal ganglia are associated with some mild–moderate motor but significant cognitive deficits.

Figure 7 Axial T1-weighted images at the level of the basal ganglia showing (a) moderate abnormality as regions of high signal intensity in the lentiform nucleus and some mild change in the thalami and; (b) severe abnormality with regions of very high and low signal intensity throughout the basal ganglia and thalami. In both cases the internal capsule (arrows) is abnormal (compare to Figure 4). Case (a) will be associated with a milder athetoid pattern of quadriplegia and relatively good preservation of other developmental domains but case (b) will have a very severe spastic dystonic quadriplegia with the need for tube feeding, microcephaly and seizures.
The severity of HIE staging may improve in the first few hours after resuscitation, there often follows a deterioration over the next 48–72 hours. This clinical deterioration is associated with progressive changes in cerebrovascular and metabolic parameters.

CBFV is often normal during the first 6–24 hours after birth asphyxia, but then increases progressively in infants who subsequently have a poor outcome compared with infants who recover. Using near-infrared spectroscopy, regional cerebral tissue saturation was shown to increase and fractional oxygen tissue extraction to decrease 24 hours after asphyxia, followed by a poor neurological outcome.

Perhaps the most dramatic evidence for the progression of cerebral abnormalities following asphyxia comes from studies of cerebral metabolism using MRS. These have shown that cerebral energy metabolism recovers promptly with resuscitation but, subsequently, after a variable delay often lasting several hours, progressive and prolonged impairment in cerebral metabolism is observed in infants who later have a poor neurodevelopmental outcome.

Several adverse biological events ensue after restoration of oxygen supply and reperfusion of cerebral tissues, including the accumulation of excitatory neurotransmitters, generation of reactive oxygen radicals, intracellular calcium accumulation and mitochondrial dysfunction, and these culminate in necrotic cell death. While necrotic cell death is prominent in the immediate and acute phases of severe cerebral insults, apoptosis may be more important with less severe insults and may occur over a longer period of time.

An inflammatory response also occurs following an acute cerebral insult. Disruption of the blood–brain barrier allows entry of leucocytes and macrophages that may phagocyte cells. Inflammation induced by lipopolysaccharide, a bacterial product, and pro-inflammatory cytokines such as interleukin-1 may play an important role in acute neuronal injury by increasing the damaging effects of ischaemia and the excitotoxicity due to accumulation of glutamate.

**Neuroprotection in infants with HIE**

A better understanding of the pathophysiological processes that contribute to delayed secondary injury, and evidence suggesting that there may be a therapeutic window lasting several hours following cerebral injury, have promoted the development of novel pharmaceutical products that may have neuroprotective properties. These products include calcium channel blockers, free radical scavengers, glutamate receptor blockers, anti-inflammatory and anti-apoptotic agents, and growth factors to promote repair. Although many of these agents have shown benefit in experimental studies, the results of clinical studies of pharmacological interventions have been disappointing. Therapies that target multiple pathophysiological mechanisms are more likely to be effective. A reduction of body temperature by about 3°C (mild/moderate hypothermia) alters the biological response to hypoxia–ischaemia. Mild hypothermia reduces blood–brain barrier damage, the release of excitatory neurotransmitters and free radical production, which protects cells and cellular organelles from oxidative damage during reperfusion. In addition, mild hypothermia may have protective anti-inflammatory effects, and reduces apoptosis by limiting caspase activity and cytochrome c translocation.

Mild hypothermia also preserves high-energy phosphates following hypoxia–ischaemia, and reduces cerebral lactic alkaloysis. The cytotoxic oedema and loss of cerebral cortical activity that accompany secondary energy failure are prevented.

The multiple beneficial biological effects of mild hypothermia observed in experimental studies are associated with a long-lasting reduction in cerebral tissue injury and improved cerebral function. Although some of these benefits may diminish over time, long-term protection with hypothermia has also been demonstrated.
Preliminary clinical studies of cooling following asphyxia

Two techniques of applied hypothermia have been investigated. To reduce the risk of potential complications associated with systemic hypothermia, Gunn et al. introduced head cooling using a cap of cooled tubing filled with cooled fluid wrapped around the head. Excessive systemic cooling was prevented by use of an overhead heater and by shielding of the head. Using this technique, the rectal temperature was maintained at about 34.5 °C, but the brain temperature achieved is uncertain because it was not measured. An alternative method involves whole-body cooling to a target rectal temperature of 33.5 °C using cooled air or a fluid-filled mattress. Rectal or oesophageal temperature is usually used as a surrogate for brain temperature in these studies, because they are thought to correlate closely with deep brain temperature.

Safety of treatment with induced prolonged mild hypothermia

Cooling is associated with physiological changes in cardiovascular parameters; blood pressure rises and heart rate decreases linearly with cooling, but these changes are not usually clinically significant. However, cardiovascular instability may occur with rapid changes in body temperature. The Q–T interval on ECG increases with cooling, but this has not been associated with arrhythmia in newborn infants treated with cooling. Arrhythmia has been observed in adults when the rectal temperature falls below 33 °C.

Hypothermia may also alter clotting and biochemical and metabolic measurements. One study of cooling to 33 °C found that thrombocytopenia and abnormal coagulation were more common in cooled infants, but this was not confirmed in larger controlled trials. Cooling is associated with higher blood glucose and lower blood potassium levels, but these were not clinically significant and did not require correction. Although an increased incidence of sepsis (primarily pneumonia) has been observed in adults treated with cooling, this has not been noted in clinical studies of newborns.

Controlled trials of cooling after birth asphyxia

After preliminary studies had indicated that prolonged treatment with mild hypothermia very soon after birth was feasible and could be applied safely, multi-centre randomised studies commenced. Studies of head cooling combined with mild body cooling (rectal temperature 34.5 °C) and of whole-body cooling to 33–33.5 °C have been completed, and others are on going (Table 1).

The first study to report its findings was Selective Head Cooling with Mild Systemic Hypothermia to Improve Neurodevelopmental Outcome: the CoolCap Study, in which 234 infants with moderate-to-severe encephalopathy and abnormal aEEG were randomised to head cooling for 72 hours starting within 6 hours of birth, with rectal temperature maintained at 34.5 °C, or to conventional care. Cooling resulted in a significant improvement in survival without major disability at 18 months, when the analysis was adjusted for severity of encephalopathy, as judged by pre-randomisation aEEG and clinical markers (odds ratio (OR) 0.52, 95% CI 0.28–0.70, p = 0.04). There was no effect of hypothermia in the 46 infants with the most severe aEEG abnormalities, but in the remaining 172 infants death or severe disability at 18 months were reduced from 65.9% in controls to 47.6% in cooled infants (OR 0.42, 95% CI 0.22–0.8, p = 0.01). In this less severe group, deaths were reduced from 38.6% to 28.6% and severe disability from 27.8% to 11.7%. There were no clinically important complications associated with cooling.

A similarly sized study of whole-body cooling to 33.5 °C for 72 hours in infants selected by clinical assessment without EEG has also been completed. In the cooled group, 45 of 102 infants died or were disabled at 18 months, compared with 64 of 106 control infants. The relative risk reduction was 0.77 (95% CI 0.6–0.98) after adjustment by centre and severity of encephalopathy. A borderline significant reduction in deaths was observed in the cooled group (24/102 vs 38/106, relative risk 0.66, 95% CI 0.43–1.01) but not in disability.

A further, smaller study of whole-body cooling in 65 asphyxiated newborns has also been reported. Although, the authors reported a significant reduction in the primary outcome measure (death or severely abnormal scores up to 12 months of age) in the cooled infants, approximately 30% of the survivors were not followed-up, and thus the findings of this study may not be reliable. Other small studies examining the effect of hypothermia on biological markers or outcome in the neonatal period have been completed. Preliminary MRI studies suggest that the cerebral effects of hypothermia may differ with the severity of HIE and the mode of cooling.

Summary of currently reported randomised studies of moderate hypothermia following birth asphyxia

<table>
<thead>
<tr>
<th>Study author</th>
<th>Cooled:controls</th>
<th>Hypothermia method</th>
<th>Temperature (core) (°C)</th>
<th>Duration of hypothermia (hours)</th>
<th>Primary outcome</th>
<th>Follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akisu</td>
<td>11:10</td>
<td>Selective</td>
<td>36.5</td>
<td>72</td>
<td>Cerebrospinal fluid platelet-activating factor, CT, EEG</td>
<td>4–10 days</td>
</tr>
<tr>
<td>Eicher</td>
<td>32:33</td>
<td>Selective</td>
<td>33</td>
<td>48</td>
<td>Death+severe disabilities</td>
<td>12 months</td>
</tr>
<tr>
<td>Gluckman</td>
<td>116:118</td>
<td>Systemic</td>
<td>34–35</td>
<td>72</td>
<td>Death+severe disabilities</td>
<td>18 months</td>
</tr>
<tr>
<td>Shankaran</td>
<td>102:106</td>
<td>Selective</td>
<td>33.5</td>
<td>72</td>
<td>Death+moderate+severe disabilities</td>
<td>18 months</td>
</tr>
<tr>
<td>Lin</td>
<td>32:30</td>
<td>Selective</td>
<td>34–35</td>
<td>72</td>
<td>CT, Brazelton scale</td>
<td>7–10 days</td>
</tr>
<tr>
<td>Zhou</td>
<td>22:27</td>
<td>Selective</td>
<td>34.5</td>
<td>72</td>
<td>Cardiac function</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 1
Current studies suggest that moderate cooling improves neurological outcomes up to 18 months of age. Despite significant differences in their design, analysis of these studies suggests that moderate cooling has a modest beneficial effect in reducing both mortality and disability following HIE (Figure 9). However, at present, the relatively small numbers of infants included in the analysis prevents the drawing of conclusions. Data from the ongoing studies (expected to be available in 2008) will allow more precise assessment of the therapeutic efficacy of induced hypothermia following asphyxia.

**Conclusion**

Neonatal encephalopathy, most commonly HIE, remains the most important perinatal complication affecting near- and full-term newborns worldwide. Careful clinical assessment together with specific investigations allows precise assessment of prognosis during the first few days after birth. Management of infants with HIE is largely supportive, but current studies indicate that cooling may improve short-term (to 18 months of age) outcome following birth asphyxia. This improvement is more likely to occur in infants with moderate but not severe perinatal asphyxia. Long-term follow-up of study cohorts is essential to determine whether these short-term benefits are maintained. Studies are needed to determine the optimal temperature and timing of hypothermia and to explore combination treatment with pharmacological agents.

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**Practice points**

- Understanding the genetic, pregnancy and intrapartum antecedents of HIE is of primary importance in its prevention
- Causes other than apparent hypoxia–ischaemia are uncommon but must be sought
- Very early prediction of neurological outcome following HIE is best assessed by CFM or EEG
- Early cranial ultrasonography shows suggestive of diagnoses other than HIE, cerebral injury established before birth and the evolution of acute cerebral damage
- The most accurate means of understanding the pattern and timing of injury is brain MRI in the first 1–4 weeks after birth
- A standardised neurological examination 2–3 weeks after birth and observations of the quality of general movements are good bedside predictors of outcome
- Hypothermia within 6 hours of birth has shown modest improvements in outcome in moderately affected babies
- Future therapeutic studies will assess the effects of combining hypothermia with other neuroprotective agents in contemporaneous and/or sequential protocols based on our understanding of the pathophysiological processes of this condition
- Early brain imaging by both cranial ultrasonography and MRI is important from a medico-legal perspective