Hypoxic Ischemic Encephalopathy

Number: 0812

Policy
*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers total body cooling (TBC, also known as whole-body cooling) and/or selective head cooling (SHC) medically necessary for the treatment of neonates (28 days of age or younger) with moderate or severe hypoxic ischemic encephalopathy (HIE).

Aetna considers TBC and SHC experimental and investigational for other indications because their effectiveness for indications other than the one listed above has not been established.

Aetna considers the use of serum interleukin-6, as a biomarker for HIE experimental and investigational because the effectiveness of this approach has not been established.

Aetna considers the following adjunctive therapies experimental and investigational for the treatment of HIE because they have not been established as effective for the treatment of this condition (not an all-inclusive list):

- Acupuncture
- Adenosinergic agents
Allopurinol
Anti-tissue plasminogen activator
Apoptosis inhibitors (e.g., calyculin A, cyclosporin A, decylubiquinone, melatonin, and sodium phenylbutyrate)
Autologous cord blood cells
Cannabinoids
Erythropoietin
Growth factors (e.g., brain derived growth factor, insulin-like growth factor-1 (ILGF-1), and monosialo-gangliosides (GM1))
Magnesium
N-acetylcysteine
Nitric oxide synthase inhibitors (e.g., bromocriptine mesylate, camptothecin, chlorpromazine HCl, melatonin, and paroxetine HCl)
Platelet-activating factor antagonists
Stem cell therapy
Xenon (inhaled).

Notes: Therapeutic hypothermia (TH) should be administered to high-risk term neonates within 6 hrs of birth; TH may not be effective in asphyxiated newborns whose placentas show evidence of chorioamnionitis with fetal vasculitis and chorionic plate meconium.

Background
Peri-natal asphyxia and resulting hypoxic ischemic encephalopathy (HIE) occur in 1 to 3 per 1000 births in the United States. It is characterized by the need for resuscitation at birth, neurological depression, seizures as well as electroencephalographical abnormalities. Hypoxic-ischemic encephalopathy is the major cause of encephalopathy in the neonatal period and represents a major cause of mortality and long-term morbidity in affected infants. Until recently, management of a newborn with HIE has consisted mainly of supportive care to restore and maintain cerebral perfusion, provide adequate gas exchange and treat seizures with anti-convulsants. Recent randomized controlled trials (RCTs) have shown that mild therapeutic hypothermia (TH) initiated within 6 hrs of birth reduces death as well as
neurodevelopmental disabilities at 18 months of age in surviving infants. Cooling can be accomplished through total body cooling (TBC, also known as whole-body cooling) or selective head cooling (SHC). Meta-analysis of these trials suggested that for every 6 or 7 infants with moderate to severe HIE who are treated with mild hypothermia, there will be 1 fewer infant who dies or has significant neurodevelopmental disability. In response to this evidence, major policy makers and guideline developers have recommended that cooling therapy be offered to infants with moderate to severe HIE (Selway 2010; Pfister and Soll, 2010).

In a multi-center RCT, Gluckman and colleagues (2005) examined if delayed head cooling can improve neurodevelopmental outcome in babies with neonatal encephalopathy. A total of 234 term infants with moderate to severe neonatal encephalopathy and abnormal amplitude integrated electroencephalography (aEEG) were randomly assigned to either head cooling for 72 hrs, within 6 hrs of birth, with rectal temperature maintained at 34 to 35 degrees C (n = 116), or conventional care (n = 118). Primary outcome was death or severe disability at 18 months. Analysis was by intention-to-treat. These investigators examined in 2 pre-defined subgroup analyses the effect of hypothermia in babies with the most severe aEEG changes before randomization -- i.e., severe loss of background amplitude, and seizures -- and those with less severe changes. In 16 babies, follow-up data were not available. Thus, in 218 infants (93 %), 73/110 (66 %) allocated conventional care and 59/108 (55 %) assigned head cooling died or had severe disability at 18 months. Analysis was by intention-to-treat. These investigators examined in 2 pre-defined subgroup analyses the effect of hypothermia in babies with the most severe aEEG changes before randomization -- i.e., severe loss of background amplitude, and seizures -- and those with less severe changes. In 16 babies, follow-up data were not available. Thus, in 218 infants (93 %), 73/110 (66 %) allocated conventional care and 59/108 (55 %) assigned head cooling died or had severe disability at 18 months (odds ratio 0.61; 95 % confidence interval [CI]: 0.34 to 1.09, p = 0.1). After adjustment for the severity of aEEG changes with a logistic regression model, the odds ratio for hypothermia treatment was 0.57 (0.32 to 1.01, p = 0.05). No difference was noted in the frequency of clinically important complications. Pre-defined subgroup analysis suggested that head cooling had no effect in infants with the most severe aEEG changes (n = 46, 1.8; 0.49 to 6.4, p = 0.51), but was beneficial in infants with less severe aEEG changes (n = 172, 0.42; 0.22 to
These data suggested that although induced head cooling is not protective in a mixed population of infants with neonatal encephalopathy, it could safely improve survival without severe neurodevelopmental disability in infants with less severe aEEG changes.

Shankaran et al (2005) conducted a randomized trial of hypothermia in infants with a gestational age of at least 36 weeks who were admitted to the hospital at or before 6 hrs of age with either severe acidosis or peri-natal complications and resuscitation at birth and who had moderate or severe encephalopathy. Infants were randomly assigned to usual care (control group) or whole-body cooling to an esophageal temperature of 33.5 degrees C for 72 hrs, followed by slow rewarming (hypothermia group). Neurodevelopmental outcome was assessed at 18 to 22 months of age. The primary outcome was a combined end point of death or moderate or severe disability. Of 239 eligible infants, 102 were assigned to the hypothermia group and 106 to the control group. Adverse events were similar in the 2 groups during the 72 hrs of cooling. Primary outcome data were available for 205 infants. Death or moderate or severe disability occurred in 45 of 102 infants (44 %) in the hypothermia group and 64 of 103 infants (62 %) in the control group (risk ratio, 0.72; 95 % CI: 0.54 to 0.95; p = 0.01). Twenty-four infants (24 %) in the hypothermia group and 38 (37 %) in the control group died (risk ratio, 0.68; 95 % CI: 0.44 to 1.05; p = 0.08). There was no increase in major disability among survivors; the rate of cerebral palsy was 15 of 77 (19 %) in the hypothermia group as compared with 19 of 64 (30 %) in the control group (risk ratio, 0.68; 95 % CI: 0.38 to 1.22; p = 0.20). The authors concluded that whole-body hypothermia reduces the risk of death or disability in infants with moderate or severe HIE.

In the Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trial, Azzopardi and colleagues (2009) performed a randomized study of infants who were less than 6 hrs of age and had a gestational age of at least 36 weeks and peri-natal asphyxial encephalopathy. These researchers compared
intensive care plus cooling of the body to 33.5 degrees C for 72 hrs and intensive care alone. The primary outcome was death or severe disability at 18 months of age. Pre-specified secondary outcomes included 12 neurological outcomes and 14 other adverse outcomes. Of 325 infants enrolled, 163 underwent intensive care with cooling, and 162 underwent intensive care alone. In the cooled group, 42 (25.8%) infants died and 32 (19.6%) survived but had severe neurodevelopmental disability, whereas in the non-cooled group, 44 (27.1%) infants died and 42 (25.9%) had severe disability (relative risk [RR] for either outcome, 0.86; 95% CI: 0.68 to 1.07; p = 0.17). Infants in the cooled group had an increased rate of survival without neurological abnormality (RR, 1.57; 95% CI: 1.16 to 2.12; p = 0.003). Among survivors, cooling resulted in reduced risks of cerebral palsy (RR, 0.67; 95% CI: 0.47 to 0.96; p = 0.03) and improved scores on the Mental Developmental Index and Psychomotor Developmental Index of the Bayley Scales of Infant Development II (p = 0.03 for each) and the Gross Motor Function Classification System (p = 0.01). Improvements in other neurological outcomes in the cooled group were not significant. Adverse events were mostly minor and not associated with cooling. The authors concluded that induction of moderate hypothermia for 72 hrs in infants who had peri-natal asphyxia did not significantly reduce the combined rate of death or severe disability but resulted in improved neurological outcomes in survivors.

Rutherford et al (2010) ascertained the effect of TH on neonatal cerebral injury. These researchers assessed cerebral lesions on magnetic resonance imaging (MRI) scans of infants who participated in the Total TOBY trial. In the TOBY trial, HIE was graded clinically according to the changes seen on amplitude integrated EEG, and infants were randomly assigned to intensive care with or without cooling. The relation between allocation to hypothermia or normothermia and cerebral lesions was assessed by logistic regression with peri-natal factors as co-variates, and adjusted odds ratios (ORs) were calculated. A total of 325 infants were recruited in the TOBY trial. Images were available for analysis from 131 infants.
Therapeutic hypothermia was associated with a reduction in lesions in the basal ganglia or thalamus (OR 0.36, 95 % CI: 0.15 to 0.84; p = 0.02), white matter (0.30, 0.12 to 0.77; p = 0.01), and abnormal posterior limb of the internal capsule (0.38, 0.17 to 0.85; p = 0.02). Compared with non-cooled infants, cooled infants had fewer scans that were predictive of later neuromotor abnormalities (0.41, 0.18 to 0.91; p = 0.03) and were more likely to have normal scans (2.81, 1.13 to 6.93; p = 0.03). The accuracy of prediction by MRI of death or disability to 18 months of age was 0.84 (0.74 to 0.94) in the cooled group and 0.81 (0.71-0.91) in the non-cooled group. The authors concluded that TH decreases brain tissue injury in infants with HIE. The predictive value of MRI for subsequent neurological impairment is not affected by TH.

Lando et al (2010) studied the effects of induced hypothermia in infants born with HIE. This retrospective study comprised data from medical records of newborn children born with HIE during a period of 32 months. Relevant data for cooling were recorded. Structured neurological examinations were carried out on survivors when they were 10 and/or 18 months old. A total of 32 infants fulfilled the criteria for cooling, the incidence being 0.4/1000 births. Twenty infants were cooled for 72 hrs. Eleven infants had cooling discontinued before 72 hrs because of their grave prognosis. One infant had cooling discontinued because of pulmonary hypertension. Most infants were cooled before 6 hrs of age (median of 4 hrs). The mortality rate was 41 %. A total of 45 % were cooled without being placed in a ventilator. The side effects were of no major concern. Eight children had a neurological follow-up. One child had developed cerebral palsy and 2 children suffered delayed development. Total body cooling was carried out before 6 hrs of age in the vast majority of infants born with HIE. Side effects were of less concern. Respiratory support with a ventilator could be avoided in 45 % of the infants cooled for 72 hrs; the mortality rate was 41 %.

Simbruner et al (2010) noted that mild hypothermia after perinatal HIE reduces neurological sequelae without significant
adverse effects, but studies are needed to determine the most-efficacious methods. In the neo.nEURO.network trial, term neonates with clinical and electrophysiological evidence of HIE were assigned randomly to either a control group, with a rectal temperature of 37°C (range of 36.5 to 37.5°C), or a hypothermia group, cooled and maintained at a rectal temperature of 33.5°C (range of 33 to 34°C) with a cooling blanket for 72 hrs, followed by slow re-warming. All infants received morphine (0.1 mg/kg) every 4 hrs or an equivalent dose of fentanyl. Neurodevelopmental outcomes were assessed at the age of 18 to 21 months. The primary outcome was death or severe disability. A total of 129 newborn infants were enrolled, and 111 infants were evaluated at 18 to 21 months (53 in the hypothermia group and 58 in the normothermia group). The rates of death or severe disability were 51% in the hypothermia group and 83% in the normothermia group (p = 0.001; OR: 0.21 [95% CI: 0.09 to 0.54]; number needed to treat (NNT): 4 [95% CI: 3 to 9]). Hypothermia also had a statistically significant protective effect in the group with severe HIE (n = 77; p = 0.005; OR: 0.17 [95% CI: 0.05 to 0.57]). Rates of adverse events during the intervention were similar in the 2 groups except for fewer clinical seizures in the hypothermia group. The authors concluded that systemic hypothermia in the neo.nEURO.network trial showed a strong neuroprotective effect and was effective in the severe HIE group.

Sarkar et al (2009) compared the multi-organ dysfunction in infants receiving TH induced by either SHC or TBC. In 59 asphyxiated newborns who received TH by either SHC (n = 31) or TBC (n = 28), the severity of pulmonary, hepatic and renal dysfunction and coagulopathy and electrolyte disturbances were assessed before the start of cooling (baseline), and at specific time intervals (24, 48 and 72 hrs) throughout cooling. Enrollment criteria, clinical monitoring and treatment during cooling, whether SHC or TBC, were similar, as reported earlier. The presence of clinical respiratory distress, along with the need for ventilatory support for varying duration during cooling, was similar in both the TBC and SHC groups (100% versus 94%,
p = 0.49, OR 1.9, 95 % CI: 1.5 to 2.5). The use of fresh frozen plasma and platelet transfusion to treat coagulopathy and thrombocytopenia was similar (TBC 48 % versus SHC 58 %, p = 0.59, OR 0.7, 95 % CI: 0.2 to 1.9, and TBC 41 % versus SHC 32 %, p = 0.58, OR 1.4, 95 % CI: 0.5 to 4.2, respectively), and equivalent numbers of infants from both groups were treated with vasopressors for greater than 24 hrs (TBC 59 % versus SHC 55 %, p = 0.79, OR 1.2, 95 % CI: 0.4 to 3.4). The incidence of oliguria (urine output less than 0.5 ml/kg/hr for greater than 24 hrs after birth) and rising serum creatinine (with maximum serum creatinine greater than 0.9 mg/dl) was also similar (TBC 18 % versus SHC 39 %, p = 0.15, OR 0.4, 95 % CI: 0.1 to 1.3, and TBC 48 % versus SHC 58 %, p = 0.59, OR 0.7, 95 % CI: 0.2 to 1.9, respectively). Laboratory parameters to assess the differential effect of TBC versus SHC on multi-organ dysfunction during 72 hrs of cooling, which include serum transaminases (serum aspartate aminotransferase and alanine aminotransferase), prothrombin time, partial thromboplastin time, international normalized ratio (INR), platelet counts, serum creatinine, serum sodium, serum potassium and serum calcium, were similar between the groups at the initiation of cooling and did not differ with the method of cooling. The authors concluded that multi-organ system dysfunction in asphyxiated newborns during cooling remains similar for both cooling methods. Concerns regarding a differential effect of TBC versus SHC on multi-organ dysfunction, other than of the brain, should not be a consideration in selecting a method to produce therapeutic hypothermia.

In a multi-center RCT, Zhou et al (2010) examined the safety and the effectiveness of SHC with mild systemic hypothermia in HIE. Infants with HIE were randomly assigned to the SHC or control group. Selective head cooling was initiated within 6 hrs after birth to a nasopharyngeal temperature of 34 +/- 0.2 degrees C and rectal temperature of 34.5 to 35.0 degrees C for 72 hrs. Rectal temperature was maintained at 36.0 to 37.5 degrees C in the control group. Neurodevelopmental outcome was assessed at 18 months of age. The primary outcome was a combined end point of death and severe disability. A total of
194 infants were available for analysis (100 and 94 infants in the SHC and control group, respectively). For the SHC and control groups, respectively, the combined outcome of death and severe disability was 31 % and 49 % (OR: 0.47; 95 % CI: 0.26 to 0.84; p = 0.01), the mortality rate was 20 % and 29 % (OR:0.62; 95 % CI: 0.32 to 1.20; p = 0.16), and the severe disability rate was 14 % (11/80) and 28 % (19/67) (OR: 0.40; 95 % CI: 0.17 to 0.92; p = 0.01). The authors concluded that SHC combined with mild systemic hypothermia for 72 hrs may significantly decrease the combined outcome of severe disability and death, as well as severe disability.

Schulzke et al (2007) reviewed RCTs assessing TH as a treatment for term neonates with HIE. The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL databases, reference lists of identified studies, and proceedings of the Pediatric Academic Societies were searched in July 2006. Randomized trials assessing the effect of TH by either selective head cooling or whole-body cooling in term neonates were eligible for inclusion in the meta-analysis. The primary outcome was death or neurodevelopmental disability at greater than or equal to 18 months. A total of 5 trials involving 552 neonates were included in the analysis. Cooling techniques and the definition and severity of neurodevelopmental disability differed between studies. Overall, there is evidence of a significant effect of TH on the primary composite outcome of death or disability (RR: 0.78, 95 % CI: 0.66 to 0.92, NNT: 8, 95 % CI: 5 to 20) as well as on the single outcomes of mortality (RR: 0.75, 95 % CI: 0.59 to 0.96) and neurodevelopmental disability at 18 to 22 months (RR: 0.72, 95 % CI: 0.53 to 0.98). Adverse effects include benign sinus bradycardia (RR: 7.42, 95 % CI: 2.52 to 21.87) and thrombocytopenia (RR: 1.47, 95 % CI: 1.07 to 2.03, NNH: 8) without deleterious consequences. The authors concluded that in general, TH seems to have a beneficial effect on the outcome of term neonates with moderate to severe HIE. Despite the methodological differences between trials, wide confidence intervals, and the lack of follow-up data beyond the second year of life, the consistency of the results is encouraging.
In a Cochrane review, Jacobs et al (2007) examined the effect of TH in HIE newborn infants on mortality, long-term neurodevelopmental disability and clinically important side effects. Randomized controlled trials comparing the use of TH with standard care in encephalopathic newborn infants with evidence of peri-partum asphyxia and without recognizable major congenital anomalies were included. The primary outcome measure was death or long-term major neurodevelopmental disability. Other outcomes included adverse effects of cooling and "early" indicators of neurodevelopmental outcome. Three review authors independently selected, assessed the quality of and extracted data from the included studies. Authors were contacted for further information. Meta-analyses were performed using RR and risk difference (RD) for dichotomous data, and weighted mean difference for continuous data with 95 % CI. A total of 8 RCTs were included in this review, comprising 638 term infants with moderate/severe encephalopathy and evidence of intra-partum asphyxia. Therapeutic hypothermia resulted in a statistically significant and clinically important reduction in the combined outcome of mortality or major neurodevelopmental disability to 18 months of age [typical RR 0.76 (95 % CI: 0.65 to 0.89), typical RD -0.15 (95 % CI: -0.24 to -0.07), NNT 7 (95 % CI: 4 to 14)]. Cooling also resulted in statistically significant reductions in mortality [typical RR 0.74 (95 % CI: 0.58 to 0.94), typical RD -0.09 (95 % CI: -0.16 to -0.02), NNT 11 (95 % CI: 6 to 50)] and in neurodevelopmental disability in survivors [typical RR 0.68 (95 % CI: 0.5 to 0.92), typical RD -0.13 (95 % CI: -0.23 to -0.03), NNT 8 (95 % CI: 4 to 33)]. Some adverse effects of hypothermia included an increase in the need for inotrope support of borderline significance and a significant increase in thrombocytopaenia. The authors concluded that there is evidence from the 8 RCTs included in this systematic review (n = 638) that TH is beneficial to term newborns with HIE. Cooling reduces mortality without increasing major disability in survivors. The benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects. However, this review comprised an analysis based on less than
50 % of all infants currently known to be randomized into eligible trials of cooling. Incorporation of data from ongoing and completed randomised trials (n = 829) will be important to clarify the effectiveness of TH and to provide more information on the safety of TH, but could also alter these conclusions.

In a meta-analysis, Edwards et al (2010) examined if moderate hypothermia after HIE in neonates improves survival and neurological outcome at 18 months of age. Studies were identified from the Cochrane central register of controlled trials, the Oxford database of peri-natal trials, PubMed, previous reviews, and abstracts. Reports that compared TBC or SHC with normal care in neonates with HIE and that included data on death or disability and on specific neurological outcomes of interest to patients and clinicians were selected. These researchers found 3 trials, encompassing 767 infants, that included information on death and major neurodevelopmental disability after at least 18 months' follow-up. They also identified 7 other trials with mortality information but no appropriate neurodevelopmental data. Therapeutic hypothermia significantly reduced the combined rate of death and severe disability in the 3 trials with 18 month outcomes (RR 0.81, 95 % CI: 0.71 to 0.93, p = 0.002; RD -0.11, 95 % CI: -0.18 to -0.04), with a NNT of 9 (95 % CI: 5 to 25). Hypothermia increased survival with normal neurological function (RR 1.53, 95 % CI: 1.22 to 1.93, p < 0.001; RD 0.12, 95 % CI: 0.06 to 0.18), with a NNT of 8 (95 % CI: 5 to 17), and in survivors reduced the rates of severe disability (p = 0.006), cerebral palsy (p = 0.004), and mental and the psychomotor developmental index of less than 70 (p = 0.01 and p = 0.02, respectively). No significant interaction between severity of encephalopathy and treatment effect was detected. Mortality was significantly reduced when these investigators assessed all 10 trials (1320 infants; RR 0.78, 95 % CI: 0.66 to 0.93, p = 0.005; RD -0.07, 95 % CI: -0.12 to -0.02), with a NNT of 14 (95 % CI: 8 to 47). The authors concluded that in infants with HIE, moderate hypothermia is associated with a consistent reduction in death and neurological impairment at 18 months.
In a systematic review and meta-analysis, Shah (2010) analyzed 13 clinical trials published to date on TH for the treatment of HIE. Therapeutic hypothermia was associated with a highly reproducible reduction in the risk of the combined outcome of mortality or moderate-to-severe neurodevelopmental disability in childhood. This improvement was internally consistent, as shown by significant reductions in the individual risk for death, moderate-to-severe neurodevelopmental disability, severe cerebral palsy, cognitive delay, and psychomotor delay. Patients in the TH group had higher incidences of arrhythmia and thrombocytopenia; however, these were not clinically important. This analysis supports the use of TH in reducing the risk of the mortality or moderate-to-severe neurodevelopmental disability in infants with moderate HIE.

Perlman (2006) stated that recent evidence suggested a potential role for modest hypothermia administered to high-risk term infants within 6 hrs of birth. Either SHC or TBC reduces the incidence of death and/or moderate to severe disability at 18-month follow-up. Additional strategies -- including the use of oxygen free radical inhibitors and scavengers, excitatory amino acid antagonists, and growth factors; prevention of nitric oxide formation; and blockage of apoptotic pathways -- have been evaluated experimentally but have not been replicated in a systematic manner in the human neonate. Other avenues of potential neuroprotection that have been studied in immature animals include adenosinergic agents, erythropoietin, insulin-like growth factor-1, monosialoganglioside GM1, and platelet-activating factor antagonists.

In a randomized, prospective study, Zhu and colleagues (2009) assessed the safety and effectiveness of erythropoietin in neonatal HIE. A total of 167 term infants with moderate/severe HIE were assigned randomly to receive either erythropoietin (n = 83) or conventional treatment (n = 84). Recombinant human erythropoietin, at either 300 U/kg body weight (n = 52) or 500 U/kg (n = 31), was administered every other day for 2 weeks, starting less than 48 hrs after birth. The primary outcome was
death or disability. Neurodevelopmental outcomes were assessed at 18 months of age. Complete outcome data were available for 153 infants; 9 patients dropped out during treatment, and 5 patients were lost to follow-up monitoring. Death or moderate/severe disability occurred for 35 (43.8%) of 80 infants in the control group and 18 (24.6%) of 73 infants in the erythropoietin group (p = 0.017) at 18 months. The primary outcomes were not different between the 2 erythropoietin doses. Subgroup analyses indicated that erythropoietin improved long-term outcomes only for infants with moderate HIE (p = 0.001) and not those with severe HIE (p = 0.227). No negative hematopoietic side effects were observed. The authors concluded that repeated, low-dose, recombinant human erythropoietin treatment reduced the risk of disability for infants with moderate HIE, without apparent side effects. The findings of this preliminary study need to be validated by a larger clinical trial.

Cilio and Ferriero (2010) noted that with the advent of hypothermia as therapy for term HIE, there is hope for repair and protection of the brain after a profound neonatal insult. However, it is clear from the published clinical trials and animal studies that hypothermia alone will not provide complete protection or stimulate the repair that is necessary for normal neurodevelopmental outcome. This review critically discusses drugs used to treat seizures after hypoxia-ischemia in the neonate with attention to evidence of possible synergies for therapy. In addition, other agents such as cannabinoids, erythropoietin, melatonin, N-acetylcysteine, and xenon were discussed as future potential therapeutic agents that might augment protection from hypothermia.

Wintermark and colleagues (2010) described placental findings in asphyxiated term newborns meeting TH criteria and examined if histopathological correlation exists between these placental lesions and the severity of later brain injury. These investigators conducted a prospective cohort study of the placentas of asphyxiated newborns, in whom later brain injury was defined by magnetic resonance imaging. A total of 23
newborns were enrolled. Eighty-seven percent of their placentas had an abnormality on the fetal side of the placenta, including umbilical cord lesions (39 %), chorioamnionitis (35 %) with fetal vasculitis (22 %), chorionic plate meconium (30 %), and fetal thrombotic vasculopathy (26 %). A total of 48 % displayed placental growth restriction. Chorioamnionitis with fetal vasculitis and chorionic plate meconium were significantly associated with brain injury (p = 0.03). Placental growth restriction appears to significantly offer protection against the development of these injuries (p = 0.03). The authors concluded that TH may not be effective in asphyxiated newborns whose placentas show evidence of chorioamnionitis with fetal vasculitis and chorionic plate meconium.

Shankaran and colleagues (2011) examined the predictive validity of the amplitude-integrated electroencephalogram (aEEG) and stage of encephalopathy among infants with HIE eligible for therapeutic whole-body hypothermia. Neonates were eligible for this prospective study if moderate or severe HIE occurred at less than 6 hours and an aEEG was obtained at less than 9 hours of age. The primary outcome was death or moderate/severe disability at 18 months. There were 108 infants (71 with moderate HIE and 37 with severe HIE) enrolled in the study. Amplitude-integrated EEG findings were categorized as normal, with continuous normal voltage (n = 12) or discontinuous normal voltage (n = 12), or abnormal, with burst suppression (n = 22), continuous low voltage (n = 26), or flat tracing (n = 36). At 18 months, 53 infants (49 %) experienced death or disability. Severe HIE and an abnormal aEEG were related to the primary outcome with uni-variate analysis, whereas severe HIE alone was predictive of outcome with multi-variate analysis. Addition of aEEG pattern to HIE stage did not add to the predictive value of the model; the area under the curve changed from 0.72 to 0.75 (p = 0.19). The authors concluded that the aEEG background pattern did not significantly enhance the value of the stage of encephalopathy at study entry in predicting death and disability among infants with HIE.
Shankaran and colleagues (2012) previously reported early results of a randomized trial of whole-body hypothermia for neonatal HIE showing a significant reduction in the rate of death or moderate or severe disability at 18 to 22 months of age. These investigators reported long-term outcomes in this study. In the original trial, the authors assigned infants with moderate or severe encephalopathy to usual care (the control group) or whole-body cooling to an esophageal temperature of 33.5°C for 72 hours, followed by slow re-warming (the hypothermia group). They evaluated cognitive, attention and executive, and visuo-spatial function; neurologic outcomes; and physical and psychosocial health among participants at 6 to 7 years of age. The primary outcome of the present analyses was death or an IQ score below 70. Of the 208 trial participants, primary outcome data were available for 190. Of the 97 children in the hypothermia group and the 93 children in the control group, death or an IQ score below 70 occurred in 46 (47%) and 58 (62%), respectively (p = 0.06); death occurred in 27 (28%) and 41 (44%) (p = 0.04); and death or severe disability occurred in 38 (41%) and 53 (60%) (p = 0.03). Other outcome data were available for the 122 surviving children, 70 in the hypothermia group and 52 in the control group. Moderate or severe disability occurred in 24 of 69 children (35%) and 19 of 50 children (38%), respectively (p = 0.87). Attention-executive dysfunction occurred in 4% and 13%, respectively, of children receiving hypothermia and those receiving usual care (p = 0.19), and visuo-spatial dysfunction occurred in 4% and 3% (p = 0.80). The authors concluded that the rate of the combined end point of death or an IQ score of less than 70 at 6 to 7 years of age was lower among children undergoing whole-body hypothermia than among those undergoing usual care, but the differences were not significant. However, hypothermia resulted in lower death rates and did not increase the rates of a low IQ score or severe disability among survivors. These data extend the authors’ previous support for the use of hypothermia in term as well as near-term infants with HIE.

In a Cochrane review, Chaudhari and McGuire (2012) examined the effect of allopurinol, a xanthine-oxidase inhibitor, on
mortality and morbidity in newborn infants with HIE. These investigators used the standard search strategy of the Cochrane Neonatal Group. They searched the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, 2012, Issue 1), MEDLINE (1966 to March 2012), EMBASE (1980 to March 2012), CINAHL (1982 to March 2012), conference proceedings, and previous reviews. Randomized or quasi-RCTs that compared allopurinol administration versus placebo or no drug in newborn infants with HIE were selected for review. These researchers extracted data using the standard methods of the Cochrane Neonatal Review Group with separate evaluation of trial quality and data extraction by 2 review authors. They included 3 trials in which a total of 114 infants participated. In 1 trial, participants were exclusively infants with severe encephalopathy. The other trials also included infants with mild and moderately severe encephalopathy. These studies were generally of good methodological quality, but were too small to exclude clinically important effects of allopurinol on mortality and morbidity. Meta-analysis did not reveal a statistically significant difference in the risk of death (typical risk ratio 0.88; 95 % CI: 0.56 to 1.38; risk difference -0.04; 95 % CI: -0.18 to 0.10) or a composite of death or severe neurodevelopmental disability (typical risk ratio 0.78; 95 % CI: 0.56 to 1.08; risk difference -0.14; 95 % CI: -0.31 to 0.04). The authors concluded that the available data are insufficient to determine whether allopurinol has clinically important benefits for newborn infants with HIE. They stated that much larger trials are needed. Such trials could assess allopurinol as an adjunct to therapeutic hypothermia in infants with moderate and severe encephalopathy and should be designed to exclude important effects on mortality and adverse long-term neurodevelopmental outcomes.

In a Cochrane review, Wong et al (2013) examined the safety and effectiveness of acupuncture on mortality and morbidity in neonates with HIE. These investigators searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library), Cochrane Neonatal Specialized Register, MEDLINE, AMED, EMBASE, PubMed, CINAHL, PsycINFO, WHO
International Clinical Trials Registry Platform, and various Chinese medical databases in November 2012. They included RCTs or quasi-RCTs comparing needle acupuncture to a control group that used no treatment, placebo or sham treatment in neonates (less than 28 days old) with HIE. Co-interventions were allowed as long as both the intervention and the control group received the same co-interventions. They excluded trials that evaluated therapy that did not involve penetration of the skin with a needle or trials that compared different forms of acupuncture only. Two review authors independently reviewed trials for inclusion. If trials were identified, the review authors planned to assess trial quality and extract data independently. These researchers used the risk ratio (RR), risk difference (RD), and number needed to benefit (NNTB) or harm (NNTH) with 95% CI for dichotomous outcomes, and mean difference (MD) with 95% CI for continuous outcomes. No trial satisfied the pre-defined inclusion criteria. Existing trials only evaluated acupuncture in older infants who survived HIE. There are currently no RCTs evaluating the effectiveness of acupuncture for treatment of HIE in neonates. The safety of acupuncture for HIE in neonates is unknown. The authors concluded that the rationale for acupuncture in neonates with HIE is unclear and the evidence from RCT is lacking. Therefore, the authors do not recommend acupuncture for the treatment of HIE in neonates; they stated that high quality RCTs on acupuncture for HIE in neonates are needed.

Tagin and colleagues (2013) systematically reviewed the safety and effectiveness of post-natal magnesium therapy in newborns with HIE. MEDLINE, EMBASE, CINAHL and CCRCT were searched for studies of magnesium for HIE. Randomized controlled trials that compared magnesium to control in newborns with HIE were selected. The primary outcome was a composite outcome of death or moderate-to-severe neurodevelopmental disability at 18 months. When appropriate, meta-analyses were conducted using random effects model and risk ratios (RRs) and 95% CIs were calculated. A total of 5 studies with sufficient quality were included. There was no difference in the primary outcome
between the magnesium and the control groups (RR 0.81, 95 % CI: 0.36 to 1.84). There was significant reduction in the unfavorable short-term composite outcome (RR 0.48, 95 % CI: 1.30 to 0.77) but no difference in mortality (RR 1.39, 95 % CI: 0.85 to 2.27), seizures (RR 0.84, 95 % CI: 0.59 to 1.19) or hypotension (RR 1.28, 95 % CI: 0.69 to 2.38) between the magnesium and the control groups. The authors concluded that the improvement in short-term outcomes without significant increase in side effects indicated the need for further trials to determine if there are long-term benefits of magnesium and to confirm its safety. They noted that mortality was statistically insignificant between the magnesium and the control groups. However, the trend toward increase in mortality in the magnesium group is a major clinical concern and should be monitored closely in future trials.

Cotton and associates (2014) evaluated the feasibility and safety of providing autologous umbilical cord blood (UCB) cells to neonates with HIE. These investigators enrolled infants in the intensive care nursery who were cooled for HIE and had available UCB in an open-label study of non-cyropreserved autologous volume- and red blood cell-reduced UCB cells (up to 4 doses adjusted for volume and red blood cell content, 1-5 × 10^7 cells/dose). They recorded UCB collection and cell infusion characteristics, and pre- and post-infusion vital signs. As exploratory analyses, these researchers compared cell recipients' hospital outcomes (mortality, oral feeds at discharge) and 1-year survival with Bayley Scales of Infant and Toddler Development, 3rd edition scores greater than or equal to 85 in 3 domains (cognitive, language, and motor development) with cooled infants who did not have available cells. A total of 23 infants were cooled and received cells. Median collection and infusion volumes were 36 and 4.3 ml, respectively. Vital signs including oxygen saturation were similar before and after infusions in the first 48 post-natal hours. Cell recipients and concurrent cooled infants had similar hospital outcomes; 13 of 18 (74 %) cell recipients and 19 of 46 (41 %) concurrent cooled infants with known 1-year outcomes survived with scores greater than 85. The authors concluded
that collection, preparation, and infusion of fresh autologous UCB cells for use in infants with HIE is feasible. Moreover, they stated that a randomized, double-blind, study is needed.

Gonzales-Portillo et al (2014) noted that treatments for neonatal HIE have been limited. These researchers offered translational research guidance on stem cell therapy for neonatal HIE by examining clinically relevant animal models, practical stem cell sources, safety and effectiveness of endpoint assays, as well as a general understanding of modes of action of this cellular therapy. They discussed the clinical manifestations of HIE, highlighting its overlapping pathologies with stroke and providing insights on the potential of cell therapy currently investigated in stroke, for HIE. These investigators drew guidance from recommendations outlined in stem cell therapeutics as an emerging paradigm for stroke or STEPS, which have been recently modified to Baby STEPS to cater for the "neonatal" symptoms of HIE. These guidelines recognized that neonatal HIE exhibit distinct disease symptoms from adult stroke in need of an innovative translational approach that facilitates the entry of cell therapy in the clinic. The authors provided new information about recent clinical trials and insights into combination therapy with the vision that stem cell therapy may benefit from available treatments, such as hypothermia, already being tested in children diagnosed with HIE.

Yang and colleagues (2015) noted that in recent years, acupuncture has increasingly being integrated into pediatric health care. It was used on approximately 150,000 children (0.2%). These researchers updated the evidence for the safety and effectiveness of acupuncture for children and evaluate the methodological qualities of these studies to improve future research in this area. They included 24 systematic reviews, comprising 142 RCTs with 12,787 participants. Only 25 % (6/24) reviews were considered to be high quality (10.00 ± 0.63). High-quality systematic reviews and Cochrane systematic reviews tend to yield neutral or negative results (p = 0.052, 0.009, respectively). The effectiveness of acupuncture for 5
diseases (cerebral palsy, nocturnal enuresis, tic disorders, amblyopia, and pain reduction) is promising. It was unclear for HIE, attention deficit hyperactivity disorder, mumps, autism spectrum disorder, asthma, nausea/vomiting, and myopia. Acupuncture is not effective for epilepsy. Only 6 reviews reported adverse events (AEs) and no fatal side effects were reported. The authors concluded that the effectiveness of acupuncture for some diseases is promising and there have been no fatal side effects reported. They stated that further high-quality studies are needed, with 5 diseases in particular as research priorities.

Atici and colleagues (2015) examined which method was superior by applying SHC or TBC therapy in newborns diagnosed with moderate or severe HIE. Newborns above the 35th gestational age diagnosed with moderate or severe HIE were included in the study and SHC or TBC therapy was performed randomly. The newborns who were treated by both methods were compared in terms of AEs in the early stage and in terms of short-term results. A total of 53 babies diagnosed with HIE were studied: SHC was applied to 17 babies and TBC was applied to 12 babies. There was no significant difference in terms of AEs related to cooling therapy between the 2 groups. When the short-term results were examined, it was found that the hospitalization time was 34 (7 to 65) days in the SHC group and 18 (7 to 57) days in the TBC group and there was no significant difference between the 2 groups (p = 0.097). Four patients in the SHC and 2 patients in the TBC group were discharged with tracheostomy because of the need for prolonged mechanical ventilation and there was no difference between the groups in terms of discharge with tracheostomy (p = 0.528). Five patients in the SHC group and 3 patients in the TBC group were discharged with a gastrostomy tube because they could not be fed orally and there was no difference between the groups in terms of discharge with a gastrostomy tube (p = 0.586). One patient who was applied SHC and 1 patient who was applied TBC died during hospitalization and there was no difference between the groups in terms of mortality (p = 0.665). The authors concluded that there was no
difference between the methods of SHC and TBC in terms of adverse effects and short-term results.

Wu and colleagues (2015) stated that perinatal HIE occurs in 1 to 3 per 1000 term births. Hypoxic ischemic encephalopathy is not preventable in most cases, and therapies are limited. Hypothermia improves outcomes and is the current standard of care. Yet, clinical trials suggested that 44 to 53 % of infants who receive hypothermia will die or suffer moderate-to-severe neurological disability. These investigators reviewed the pre-clinical and clinical evidence for erythropoietin (EPO) as a potential novel neuro-protective agent for the treatment of HIE. Erythropoietin is a novel neuro-protective agent, with remarkable neuro-protective and neuro-regenerative effects in animals. Rodent and primate models of neonatal brain injury support the safety and effectiveness of multiple EPO doses for improving histological and functional outcomes after hypoxia-ischemia. Small clinical trials of EPO in neonates with HIE have also provided evidence supporting safety and preliminary effectiveness in humans. There is currently insufficient evidence to support the use of high-dose EPO in newborns with HIE. However, several on-going trials will provide much needed data regarding the safety and effectiveness of this potential new therapy when given in conjunction with hypothermia for HIE. Novel neuro-protective therapies are needed to further reduce the rate and severity of neurodevelopmental disabilities resulting from HIE. The authors concluded that high-dose EPO is a promising therapy that can be administered in conjunction with hypothermia. However, they stated that additional data are needed to determine the safety and effectiveness of this adjuvant therapy for HIE.

**Biomarkers:**

Celik and colleagues (2015) noted that TH has become standard care in newborns with moderate to severe HIE, and the 2 most commonly used methods are SHC and whole body cooling (WBC). In a pilot study, these investigators examined if the effects of the 2 methods on some neural and inflammatory
This pilot study included newborns delivered after greater than 36 weeks of gestation; SHC or WBC was administered randomly to newborns with moderate-to-severe HIE that were prescribed TH. The serum interleukin (IL)-1β, IL-6, neuron-specific enolase (NSE), brain-specific creatine kinase (CK-BB), tumor necrosis factor-alpha (TNF-α), and protein S100 levels, the urine S100B level, and the urine lactate/creatinine (L/C) ratio were evaluated 6 and 72 hours after birth. The Bayley Scales of Infant and Toddler Development-III was administered at month 12 for assessment of neurodevelopmental findings. The SHC group included 14 newborns, the WBC group included 10, the mild HIE group included 7, and the control group included 9. All the biomarker levels in the SHC and WBC groups at 6 and 72 hours were similar, and all the changes in the biomarker levels between 6 and 72 hours were similar in both groups. The serum IL-6 and protein S100 levels at 6 hours in the SHC and WBC groups were significantly higher than in the control group. The urine L/C ratio at 6 hours in the SHC and WBC groups was significantly higher than in the mild HIE and control groups. The IL-6 level and L/C ratio at 6 and 72 hours in the patients who had died or had disability at month 12 were significantly higher than in the patients without disability at month 12. The authors concluded that the effects of SHC and WBC on the biomarkers evaluated did not differ. They stated that the urine L/C ratio might be useful for differentiating newborns with moderate and severe HIE from those with mild HIE. Furthermore, the serum IL-6 level and the L/C ratio might be useful for predicting disability and mortality in newborns with HIE.

Anti-Epileptic Drugs for Hypoxic Ischemic Encephalopathy-Associated Seizures:

In an open-label, phase I/II clinical trial, Pressler et al (2015) examined dose and feasibility of intravenous bumetanide as an add-on to phenobarbital for treatment of neonatal seizures associated with HIE. These researchers recruited full-term infants younger than 48 hours who had HIE and electrographic seizures not responding to a loading-dose of phenobarbital.
from 8 neonatal intensive care units (ICUs) across Europe. Newborn babies were allocated to receive an additional dose of phenobarbital and 1 of 4 bumetanide dose levels by use of a bi-variate Bayesian sequential dose-escalation design to assess safety and effectiveness. They assessed AEs, pharmacokinetics, and seizure burden during 48 hours continuous EEG monitoring. The primary effectiveness end-point was a reduction in electrographic seizure burden of more than 80% without the need for rescue anti-epileptic drugs in more than 50% of infants. Between September 1, 2011 and September 28, 2013, these investigators screened 30 infants who had electrographic seizures due to HIE; 14 of these infants (10 boys) were included in the study (dose allocation: 0.05 mg/kg, n = 4; 0.1 mg/kg, n = 3; 0.2 mg/kg, n = 6; 0.3 mg/kg, n = 1). All babies received at least 1 dose of bumetanide with the 2nd dose of phenobarbital; 3 were withdrawn for reasons unrelated to bumetanide, and 1 because of dehydration. All but 1 infant also received aminoglycosides. Five infants met EEG criteria for seizure reduction (1 on 0.05 mg/kg, 1 on 0.1 mg/kg and 3 on 0.2 mg/kg), and only 2 did not need rescue anti-epileptic drugs (i.e., met rescue criteria; 1 on 0.05 mg/kg and 1 on 0.3 mg/kg). These researchers recorded no short-term dose-limiting toxic effects, but 3 of 11 surviving infants had hearing impairment confirmed on auditory testing between 17 and 108 days of age. The most common non-serious AEs were moderate dehydration in 1, mild hypotension in 7, and mild-to-moderate electrolyte disturbances in 12 infants. The trial was stopped early because of serious AEs and limited evidence for seizure reduction. The authors concluded that these findings suggested that bumetanide as an add-on to phenobarbital did not improve seizure control in newborn infants who have HIE and might increase the risk of hearing loss, highlighting the risks associated with the off-label use of drugs in newborn infants before safety assessment in controlled trials.

Shetty (2015) stated that the risk of seizures is at its highest during the neonatal period, and the most common cause of neonatal seizures is HIE. This enhanced vulnerability is caused by an imbalance in the expression of receptors for excitatory
and inhibitory neurotransmission, which is age-dependent. There has been progress in detecting the electrophysiological abnormalities associated with seizures using aEEG. Data from animal studies indicated a variety of risk factors for seizures, but there are limited clinical data looking at the long-term neurodevelopmental consequences of seizures alone. Neonatal seizures are also associated with increased risk of further epileptic seizures; however, it is less clear whether or not this results from an underlying pathology, and whether or not seizures confer additional risk. Phenobarbital and phenytoin are still the first-line anti-epileptic drugs (AEDs) used to treat neonatal seizures, although they are effective in only 1/3 of affected infants. Furthermore, based on findings from animal studies, there are concerns regarding the risks associated with using these AEDs. Clinicians face a difficult challenge because, although seizures can be easily identified using aEEG, treatment options are limited, and there are uncertainties regarding treatment outcomes. The authors concluded that there is a need to obtain long-term follow-up data, comparing groups of infants treated with or without current therapies. If these analyses indicated a definite benefit of treating neonatal seizures, then novel therapeutic approaches should be developed.

Anti-Tissue Plasminogen Activator for the Treatment of Hypoxic Ischemic Encephalopathy:

Yang and Kuan (2015) noted that hypoxic-ischemic brain injury is an important cause of neurodevelopmental deficits in neonates. Intra-uterine infection and the ensuing fetal inflammatory responses augment hypoxic-ischemic brain injury and attenuate the effectiveness of therapeutic hypothermia. These investigators reviewed evidences from pre-clinical studies suggesting that the induction of brain parenchymal tissue-type plasminogen activator (tPA) plays an important pathogenic role in these conditions. Moreover, administration of a stable-mutant form of plasminogen activator inhibitor-1 called CPAI confers potent protection against hypoxic-ischemic injury with and without inflammation via different mechanisms. Besides
intra-cerebro-ventricular injection, CPAI can also be administered into the brain using a non-invasive intra-nasal delivery strategy, adding to its applicability in clinical use. The authors conclude that the therapeutic potential of CPAI in neonatal care merits further investigation with large-animal models of hypoxia-ischemia and cerebral palsy.

Other Experimental Agents:

An UpToDate review on “Clinical features, diagnosis, and treatment of neonatal encephalopathy” (Wu, 2015) states that “A variety of potential neuro-protective treatments are being studied to prevent the cascade of injurious effects after hypoxia-ischemia. As an example, erythropoietin has neuro-protective properties in animal models of hypoxic-ischemic brain injury and neonatal stroke. A preliminary randomized trial of 167 neonates with hypoxic-ischemic encephalopathy found that treatment with recombinant human erythropoietin for 2 weeks, starting within 48 hours of birth, was associated with improved neurologic outcome at 18 months. Confirmation of benefit in larger trials is needed. Additional strategies that may be useful as adjuncts to hypothermia include …. Administration of growth factors (monosialo-gangliosides, brain derived growth factor), nitric oxide synthase inhibitors, and blockers of apoptosis”.

Erythropoietin:

In a phase II, double-blinded, placebo-controlled trial, Wu and colleagues (2016) examined if multiple doses of erythropoietin (Epo) administered with hypothermia improve neuro-radiographical and short-term outcomes of newborns with HIE. These researchers randomized newborns to receive Epo (1,000 U/kg intravenously; n = 24) or placebo (n = 26) at 1, 2, 3, 5, and 7 days of age. All infants had moderate/severe encephalopathy; perinatal depression (10 minute Apgar less than 5, pH less than 7.00 or base deficit greater than or equal to 15, or resuscitation at 10 minutes); and received hypothermia. Primary outcome was neurodevelopment at 12
months assessed by the Alberta Infant Motor Scale and Warner Initial Developmental Evaluation. Two independent observers rated MRI brain injury severity by using an established scoring system. The mean age at 1st study drug was 16.5 hours (SD, 5.9). Neonatal deaths did not significantly differ between Epo and placebo groups (8 % versus 19 %, p = 0.42). Brain MRI at mean 5.1 days (SD, 2.3) showed a lower global brain injury score in Epo-treated infants (median of 2 versus 11, p = 0.01). Moderate/severe brain injury (4 % versus 44 %, p = 0.002), subcortical (30 % versus 68 %, p = 0.02), and cerebellar injury (0 % versus 20 %, p = 0.05) were less frequent in the Epo than placebo group. At mean age 12.7 months (SD, 0.9), motor performance in Epo-treated (n = 21) versus placebo-treated (n = 20) infants were as follows: Alberta Infant Motor Scale (53.2 versus 42.8, p = 0.03); Warner Initial Developmental Evaluation (28.6 versus 23.8, p = 0.05). The authors concluded that high-doses of Epo given with hypothermia for HIE may result in less MRI brain injury and improved 1-year motor function.

**Xenon:**

Azzopardi and associates (2015) examined if the addition of xenon (Xe) gas, a promising novel therapy, after the initiation of hypothermia for birth asphyxia would result in further improvement. Total body hypothermia plus Xe (TOBY-Xe) was a proof-of-concept, randomized, open-label, parallel-group trial done at 4 neonatal ICUs in the UK. Eligible infants were 36 to 43 weeks of gestational age, had signs of moderate-to-severe encephalopathy and moderately or severely abnormal background activity for at least 30 minutes or seizures as shown by aEEG, and had 1 of the following: Apgar score of 5 or less 10 minutes after birth, continued need for resuscitation 10 minutes after birth, or acidosis within 1 hour of birth. Participants were allocated in a 1:1 ratio by use of a secure web-based computer-generated randomization sequence within 12 hours of birth to cooling to a rectal temperature of 33.5°C for 72 hours (standard treatment) or to cooling in combination with 30 % inhaled Xe for 24 hours started immediately after randomization. The primary outcomes were
reduction in lactate to N-acetyl aspartate ratio in the thalamus and in preserved fractional anisotropy in the posterior limb of the internal capsule, measured with magnetic resonance spectroscopy (MRS) and MRI, respectively, within 15 days of birth. The investigator assessing these outcomes was masked to allocation. Analysis was by intention-to-treat. The study was done from January 31, 2012 to September 30, 2014. These researchers enrolled 92 infants, 46 of whom were randomly assigned to cooling only and 46 to Xe plus cooling; 37 infants in the cooling only group and 41 in the cooling plus Xe group underwent magnetic resonance assessments and were included in the analysis of the primary outcomes. These investigators noted no significant differences in lactate to N-acetyl aspartate ratio in the thalamus (geometric mean ratio 1.09, 95 % CI: 0.90 to 1.32) or fractional anisotropy (mean difference of -0.01, 95 % CI: -0.03 to 0.02) in the posterior limb of the internal capsule between the 2 groups; 9 infants died in the cooling group and 11 in the Xe group; 2 adverse events were reported in the Xe group: subcutaneous fat necrosis and transient desaturation during the MRI. No serious adverse events were recorded. The authors concluded that administration of Xe within the delayed time-frame used in this trial was feasible and apparently safe, but is unlikely to enhance the neuro-protective effect of cooling after birth asphyxia.

<table>
<thead>
<tr>
<th>CPT Codes / HCPCS Codes / ICD-10 Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by &quot;+&quot;:</td>
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</tbody>
</table>

CPT codes covered if selection criteria are met:
<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>99184</td>
<td>Initiation of selective head or total body hypothermia in the critically ill neonate, includes appropriate patient selection by review of clinical, imaging and laboratory data, confirmation of esophageal temperature probe location, evaluation of amplitude EEG, supervision of controlled hypothermia, and assessment of patient tolerance of cooling</td>
</tr>
</tbody>
</table>

**CPT codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38204 - 38205, 38207 - 38215, 38230, 38240, 38242</td>
<td>Bone marrow or stem cell services/procedures-allogenic</td>
</tr>
<tr>
<td>38241</td>
<td>Hematopoietic progenitor cell (HPC); autologous transplantation</td>
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<tr>
<td>97810 - 97814</td>
<td>Acupuncture</td>
</tr>
<tr>
<td>99481</td>
<td>Total body systemic hypothermia in a critically ill neonate per day (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>99482</td>
<td>Selective head hypothermia in a critically ill neonate per day (List separately in addition to code for primary procedure)</td>
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**HCPCS codes not covered for indications listed in the CPB:**

**There are no specific codes for allopurinol:**

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0153</td>
<td>Injection, adenosine, 1 mg (not to be used to report any adenosine phosphate compounds)</td>
</tr>
<tr>
<td>J0881</td>
<td>Injection, darbepoetin alfa, 1 microgram (non-ESRD use)</td>
</tr>
<tr>
<td>J0882</td>
<td>Injection, darbepoetin alfa, 1 microgram (for ESRD use)</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>J0885</td>
<td>Injection, epoetin alfa, (for non-ESRD use), 1000 units</td>
</tr>
<tr>
<td>J0887</td>
<td>Injection, epoetin beta, 1 microgram</td>
</tr>
<tr>
<td>J0888</td>
<td></td>
</tr>
<tr>
<td>J3230</td>
<td>Injection, chlorpromazine HCl, up to 50 mg</td>
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<tr>
<td>J3475</td>
<td>Injection, magnesium sulfate, per 500 mg</td>
</tr>
<tr>
<td>J7502</td>
<td>Cyclosporine, oral, 100 mg</td>
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<tr>
<td>J7515</td>
<td>Cyclosporine, oral, 25 mg</td>
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<tr>
<td>J7516</td>
<td>Cyclosporine, parenteral, 250 mg</td>
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<tr>
<td>J7604</td>
<td>Acetylcysteine, inhalation solution, compounded product, administered through DME, unit dose form, per gram</td>
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<tr>
<td>Q4081</td>
<td>Injection, epoetin alfa, 100 units (for ESRD on dialysis)</td>
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</tbody>
</table>

**ICD-10 codes covered if selection criteria are met:**

- P91.62 Moderate hypoxic ischemic encephalopathy [HIE]
- P91.63 Severe hypoxic ischemic encephalopathy [HIE]

**The above policy is based on the following references:**

4. Schulze SM, Rao S, Patole SK. A systematic review of cooling for neuroprotection in neonates with hypoxic ischemic encephalopathy - are we there yet? BMC


40. Yang D, Kuan CY. Anti-tissue plasminogen activator (tPA) as an effective therapy of neonatal hypoxia-ischemia with and without inflammation. CNS Neurosci Ther. 2015;21(4):367-373.


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0812
Hypoxic Ischemic Encephalopathy

There are no amendments for Medicaid.