89 Neonatal diseases I

John Pardalos

APNEA OF PREMATURITY

Apnea of prematurity is a condition frequently seen in preterm infants. It is defined as a cessation in breathing for more than 20 seconds, or less than 20 seconds if it is associated with bradycardia and/or cyanosis (1). The incidence of this disorder increases with decreasing gestational age, but luckily most infants outgrow this disorder by the time they reach 35 to 36 weeks postconceptional age. Over the last 20 years, the prevalence of this disorder has increased as smaller, more preterm infants are now surviving. With advances in ventilator management and surfactant therapy, many preterm infants are currently being extubated within days of admission to the neonatal intensive care unit. The goal is to keep them off the ventilators to prevent potential trauma to the developing lungs. As a result, neonatologists are faced with a dilemma about when is the frequency of apnea high enough to require reintubation.

For decades, neonatologists have been looking for ways to treat these infants without resorting to mechanical ventilation. Many times these infants are placed on some type of positive pressure device post-extubation to help the infants maintain adequate respiratory dynamics while using minimal pressures to achieve this. Some of the various devices used to accomplish this include nasal prong continuous positive airway pressure [CPAP (NCPAP)], nasal prong CPAP with a rate (known as NIPPV), SiPAP, and high-flow nasal cannula. These devices provide positive pressure to the infant's airway that helps stent the airways open, allowing for easier flow of air into and out of the lungs, which helps prevent obstructive apnea. NIPPV generates increased pharyngeal pressure intermittently based on the peak inspiratory pressure and rate that may activate the dilator muscles of the pharynx and stimulates respiratory drives to abort the apnea spell (2). In studies comparing NIPPV with NCPAP, it was noted that those infants treated with NIPPV had a greater reduction in the number of apneic spells compared with those treated with NCPAP (2–5).

Since the 1970s, methylxanthines have been used to treat apnea of prematurity. Over the years, various methylxanthines have been used including theophylline, aminophylline, and caffeine. Currently, caffeine is most commonly used due to a wide therapeutic window with fewer risks of side effects. We do not have to draw levels with caffeine compared with theophylline and aminophylline. The mechanism of action of methylxanthines is unknown, but they have been shown to decrease apneic events, increase minute volumes, improve respiratory system compliance, reduce diaphragmatic fatigue, and act as a diuretic (6,12,14). In fact those infants treated with caffeine required mechanical ventilation, noninvasive ventilation, and/or supplemental oxygen therapy for 1 week less on average compared with those infants treated with placebo. Those infants treated with

caffeine, however, did show slower weight gain compared with the placebo group at least initially (7,13,14).

Another concern with methylxanthines was that they may interfere with the neurodevelopmental outcome of infants. In animal models, adenosine was noted to protect the brain from energy failure or cell death during hypoxia and ischemia and methylxanthines inhibit adenosine receptors (8). The Caffeine for Apnea of Prematurity (CAP) trial was conducted to see what short- and long-term risks and benefits caffeine provided infants. The trial found that caffeine reduced the incidence of bronchopulmonary dysplasia and decreased the need for supplemental oxygen therapy and assisted ventilation of any type. The CAP trial followed these patients to 2 years of life and found that caffeine also improved the neurodevelopmental outcome at 18 to 21 months of age. Caffeine was noted to decrease the incidence of cerebral palsy and cognitive delay but no change in death, severe hearing loss, or bilateral blindness was found (6,8,12,13). The study did find that those infants who were started on caffeine while they were still on some type of respiratory support had the greatest improvement in their neurodevelopmental outcomes (6).

Other medications used to attempt to treat apnea of prematurity include carnitine and doxapram. Carnitine deficiency can be a cause of apnea in infants and adults but no trial has shown that supplementation with carnitine made a difference in the frequency of apnea (9,10). Doxapram is another respiratory stimulant that has been used to treat apnea of prematurity. Doxapram must be administered intravenously, however, and potentially has the following side effects: seizures, liver dysfunction, and gastrointestinal irritation, which has limited its use. In a recent Cochrane review that compared the use of doxapram versus methylxanthine in the treatment of apnea found no difference between the two medications (11).

LATE PRETERM NEWBORNS

Infants born at 34 0/7 weeks to 36 6/7 weeks of gestation were called near-term until 2005 when the National Institute of Child Health and Human Development of the National Institutes of Health held a workshop entitled "Optimizing Care and Outcome of the Near-Term Pregnancy and the Near-Term Newborn Infant." At this workshop, a decision was made to call these infants late preterm infants to signify that even though these infants many times were of the physical size of term infants, physiologically and metabolically they were immature (15,16). When compared with term infants, late preterm infants are more likely to have respiratory distress, temperature instability, hypoglycemia, hyperbilirubinemia, apnea, sepsis, and feeding problems. They were also noted to have higher mortality and rehospitalization rates during the newborn period (15–20). Therefore, it is important that late

preterm infants not be treated like healthy term infants but monitored closely to make sure that if they develop any morbidities noted above, they are treated promptly.

Between 1990 and 2005, the overall preterm birth rate increased by 20% from 10.6% in 1990 to 12.7% in 2005. During this same time period, the late preterm infant birth rate increased by 25% from 7.3% in 1990 to 9.1% in 2005. In 2005, 71% of all preterm births (<37 0/7 weeks of gestation) occurred in the late preterm gestation (34 0/7 to 36 6/7 weeks) group (21). Three factors that may have contributed to this increase in the overall preterm birth rate as well as the late preterm birth rate include increased percentage of women waiting until later in life to have children, increased use of assisted reproductive technology to have children, and increased rates of multiple births (twins, triplets, etc.). These three factors are interrelated, and it is difficult to ascertain the effect on the preterm birth rate by any one factor. Studies have shown that preterm delivery frequency is higher in women less than 16 years old and in those over 35 years old by 2% to 4% compared with the rate seen in women 21 to 24 years old. In addition, studies have shown that using assisted reproductive technology to become pregnant increases the risk of multiple births, which are more likely to deliver prematurely but this increased risk of preterm birth is also seen with singleton births conceived using assisted reproductive technology (22).

As stated previously, late preterm infants have a higher mortality rate compared with term infants (16,17,21–25). From 1995 to 2002, the overall infant mortality rate (0–364 days) for late preterm infants decreased from 9.5 per 1000 to 7.9 per 1000 and for term infants it decreased from 3.0 per 1000 to 2.4 per 1000. Congenital malformations accounted for 42% of the deaths in the late preterm infants and 31% in the term infants (23). In a study conducted by Young et al., all infants born in Utah between 1999 and 2004 with a gestational age of 34 to 42 weeks were evaluated to see whether they died prior to their first birthday. They also found that the most common reason for the death of infants during their first year of life was due to birth defects. In addition, they determined the early neonatal (1–7 days), neonatal (1–28 days), and infant (1–365 days) mortality rates by gestational age excluding infants with birth defects. In all three categories, they found that the 34-week-gestational-age infants had the highest mortality rate while the 39- to 41-week-gestational-age infants had the lowest rates. For example, infants without birth defects had an early neonatal mortality rate of 1.27 per 1000 at 34 weeks of gestation, 1.06 per 1000 at 35 weeks of gestation, 0.66 per 1000 at 36 weeks of gestation but a rate of 0.08 per 1000 at 40 weeks of gestation. This gave a risk ratio of 3.25, 3.21, and 2.69 at 34, 35, and 36 weeks of gestation respectively when compared with 40 weeks of gestation. Infants in this study had a neonatal mortality rate of 1.90 per 1000 at 34 weeks of gestation, 1.41 per 1000 at 35 weeks of gestation, 0.99 per 1000 at 36 weeks of gestation, but a rate of 0.22 per 1000 at 40 weeks of gestation. This gave a risk ratio of 3.24, 3.20, and 2.68 at 34, 35, and 36 weeks of gestation respectively when compared with 40 weeks of gestation. These infants had an infant mortality rate of 3.79 per 1000 at 34 weeks of gestation, 3.16 per 1000 at 35 weeks of gestation, 2.55 per 1000 at 36 weeks of gestation, but a rate of 0.80 per 1000 at 40 weeks of gestation. This gave a risk ratio of 4.62, 3.91, and 3.14 at 34,

35, and 36 weeks of gestation respectively when compared with 40 weeks of gestation (24). When birth weight was taken into account, the neonatal and infant mortality rates again decreased with increasing gestational age from 34 to 41 weeks of gestation. Those infants who were small for gestational age (SGA) at any gestational age had the highest mortality rate. Late preterm infants who were SGA were 44 times more likely to die during the first 28 days of life and 21 times more likely to die during the first year of life compared with term appropriate-for-gestational-age (AGA) infants. When infants with congenital anomalies were excluded, late preterm infants who were SGA continued to have a higher risk of dying compared with term AGA infants during both the neonatal and infant periods (25).

When late preterm infants are born, there are a variety of potential complications that they are at a higher risk of developing compared with their term counterparts for which they need to be monitored closely. In a study by Wang et al. in 2004, they looked at infants born between October 1997 and October 2000 at Massachusetts General Hospital and randomly selected 90 late preterm infants (35 0/7 to 36 6/7 weeks of gestational age) and 95 term infants (37 to 40 weeks of gestational age) who met the inclusion criteria. They found that the late preterm infants were more likely to have temperature instability (10% vs. 0%; OR: infinite), hypoglycemia (15.6% vs. 5.3%; OR: 3.30; 95% CI: 1.1–12.2), require intravenous infusion (26.7% vs. 5.3%; OR: 6.48; 95% CI: 2.27–22.91), respiratory distress (28.9% vs. 4.2%; OR: 9.14; 95% CI: 2.9–37.8), and were clinically jaundiced (54.4% vs. 37.9%; OR 1.95; 95% CI: 1.04–3.67) compared with the term infants. The late preterm infants were also more likely to require a sepsis evaluation compared with the term infants (36.7% vs. 12.6%; OR: 3.97; 95% CI: 1.82–9.21). Even though more of the late preterm infants ended up receiving a full 7-day course of antibiotics, it was not statistically significant (20). Because of these morbidities, late preterm infants are more likely to have prolonged hospitalizations (required hospitalization after their mother was discharged). In a study by Pulver et al., they found that 75% of 34-week-gestational-age infants, 50% of 35-week-gestational age, and 25% of 36-week-gestational-age infants had a prolonged hospitalization. The average length of stay for these infants was 12.6, 6.1, and 3.8 days for 34-, 35-, and 36-week-gestational-age infants respectively (18).

In a study by Shapiro-Mendoza et al., they looked for risk factors that increased the morbidity rate in singleton late preterm infants who were considered healthy at birth. These infants were considered healthy if they were discharged before a fourth-night hospital stay, weighed at least 2000 g at birth, and did not have any significant health problems or procedures. They found that having an Asian/Pacific Islander mother, being firstborn, being breastfed at discharge, having a mother with complications at labor and delivery, and having a public payer source at the time of delivery all increased the risk of a neonatal morbidity. They also found that these healthy late preterm infants had a 4.8% risk of being readmitted to the hospital and 1.3% had an observation stay within 28 days of life. They found that those infants who were breastfed were more likely to require readmission to the hospital or have an observation stay due to inadequate weight gain, jaundice, or

feeding problems (19). Therefore, it is important to make sure that healthy late preterm infants are truly feeding well prior to discharge from the hospital and have close follow-up after discharge to prevent the need for readmission to the hospital.

At 34 weeks of gestation, the brain weighs about 65% that of a term infant's brain and very few sulci and gyri are present, so studies have been conducted to look at the long-term neurologic outcome of late preterm infants. These studies have found that late preterm infants have worse neurologic outcomes compared with term infants. For example, in a study by Woythaler et al., they looked at 6300 term and 1200 late preterm infants at 24 months of age. They looked at the mental developmental index (MDI) and psychomotor developmental index (PDI) on the Bayley Scales of Infant Development Short Form—Research Edition. These indices have a mean score of 100 with a standard deviation of 15, so a score less than 70 indicates significant delay and a score of 70 to 84 indicates mild delay. In this study, they found that the late preterm infants had a mean score of 85 and the term infants had a mean score of 89 on the MDI while on the PDI, the mean scores were 88 and 92 for the late preterm and term infants respectively. About 21.2% of the late preterm infants and 16.4% of the term infants had a score <70 on the MDI while 6.1% of the late preterm infants and 6.5% of the term infants had a score <70 on the PDI. When they controlled for gestational age, plurality, maternal race, education, marital status, depression, prenatal care, primary language, infant gender, poverty level, delivery type, fetal growth, and any breastmilk feedings, the adjusted odds (95% CI) of a late preterm infant having more severe mental developmental delay (MDI score <70) was 1.51 (95% CI: 1.26–1.82) and milder mental developmental delay (MDI score 70–84) was 1.43 (95% CI: 1.22–1.67) compared with a term infant. In addition, the adjusted odds ratio that a late preterm infant having more severe psychomotor developmental delay (PDI score <70) was 1.56 (95% CI: 1.29–1.88) and milder psychomotor developmental delay (PDI score 70–84) was 1.58 (95% CI: 1.37–1.83) compared with a term infant (26). In another study by Morse et al., they looked at healthy late preterm infants (spent <72 hours in the hospital at birth) to see whether they were ready for kindergarten. They looked at 7152 healthy late preterm infants and 152,661 term infants and found that the late preterm infants had a 36% higher risk of developmental delay or disability, a 19% higher risk of suspension in kindergarten, and a 10% to 13% higher risk of having disability in pre-kindergarten, requiring exceptional student education or requiring retention in kindergarten (27). These studies show that even though these late preterm infants appear healthy at birth, they should be monitored closely and placed in early educational interventions if they start to show delays to help improve their outcomes.

As you can see, late preterm infants should not be treated like term infants. They have a higher risk of developing neonatal morbidities, require rehospitalization, and have poor neurologic outcomes. These infants need to be monitored closely throughout their childhood, and if they start to develop any issues, they need to be treated quickly to allow them to have the best possible outcome.

THERAPEUTIC HYPOTHERMIA

Hypoxic-ischemic encephalopathy (HIE) occurs in infants when cerebral perfusion is impaired resulting in hypoxic injury to the brain. It occurs in 3 to 5 per 1000 live births with moderate or severe HIE occurring in 0.5 to 1 per 1000 live births (28,29). HIE accounts for 23% of the 4 million neonatal deaths globally each year (28,30).

Studies have shown that neuronal death following a hypoxic-ischemic injury occurs in two phases. Initially, the lack of oxygen causes primary energy failure that results in neuronal death via necrosis or apoptosis. Necrosis is characterized by swelling of the plasma membrane until the cell eventually ruptures releasing intracellular toxins while apoptosis is a slower form of neuronal death due to a less severe or prolonged hypoxic event often described as cell suicide. Once reperfusion of the brain occurs, the energy levels in the neurons “normalize.” This period is characterized by normal blood pressure and intracellular pH, transient improvement in cellular edema, and an absence of seizures. Then a second energy failure occurs during which delayed neuronal death occurs. This is caused by hyperemia, cytotoxic edema, mitochondrial failure, accumulation of excitotoxins, apoptosis, nitric oxide synthesis, free radical damage, and cytotoxic actions of activated microglia. It is this secondary energy failure that leads to the highest proportion of neuronal death and leads to encephalopathy and seizures. Therefore, the time between the primary and secondary energy failures provide a window of opportunity to provide some intervention that may prevent the more devastating secondary event from occurring (28,31).

Scientists have been looking for interventions that could be initiated during this therapeutic window to try to improve the outcome of infants who suffer from HIE, but to date, nothing has shown promise except for hypothermia. Hypothermia has been shown to modify cells programmed for apoptosis leading to their survival. It may also protect neurons by reducing their metabolic rate, attenuating the release of excitatory amino acids (glutamate and dopamine), ameliorating the ischemia-impaired uptake of glutamate and decreasing the production of toxic nitric oxide and free radicals (28,29). Studies in animal models have shown that a 2°C to 3°C drop in the temperature of the brain after a hypoxic-ischemic event decreased energy expenditure, improved subsequent performance testing, and/or decreased histologic neuronal loss (29). Other studies found that the earlier the hypothermia was initiated, the better the outcome. This neuroprotective effect of hypothermia was seen up to 6 hours post insult. Still other studies found that moderate hypothermia of the brain in the 32°C to 34°C range that was continued for 24 to 72 hours again had the best outcomes in animal models. Temperatures lower than this range revealed an increase in potential systemic adverse effects such as mortality, hypoglycemia, decreased cardiac contractility and cardiac output, sinus bradycardia, hypotension, ventilation–perfusion mismatch, increased blood viscosity, coagulopathy, acid/base imbalance, electrolyte imbalance, and increased risk of infections (31).

Currently there are two ways to provide hypothermia to neonates, selective brain cooling or total body cooling. Recently there were four large multicenter randomized control trials that were conducted to evaluate the effect of

hypothermia in neonates with moderate or severe HIE using one of these two methods of hypothermia. The CoolCap trial included 234 infants who were ≥ 36 weeks of gestational age with moderate to severe HIE and abnormal amplitude-integrated electroencephalography (aEEG). These infants were randomized to either receive selective head cooling for 72 hours with a goal rectal temperature of 34°C to 35°C or standard care. Therapy with hypothermia was to be initiated within 6 hours of birth. The inclusion criteria were an Apgar score of ≤ 5 at 10 minutes after birth, continued need for resuscitation including endotracheal or mask ventilation at 10 minutes after birth, or severe acidosis defined as a pH < 7.00 or a base deficit of ≥ 16 mmol/L on either a cord gas or an arterial or venous sample drawn within 60 minutes of birth. Eligible infants were then assessed for clinical evidence of moderate or severe HIE using the Sarnat criteria (lethargy, stupor, or coma with one or more of the following symptoms: hypotonia, abnormal reflexes (including oculomotor or pupillary), an absent or weak suck, or clinical evidence of seizures. Next an aEEG was used to determine whether the infant had a moderate or severely abnormal aEEG tracing for 20 minutes prior to initiation of hypothermia. Those infants who were randomized to hypothermia were kept cool for 72 hours and then gradually rewarmed by no more than 0.5°C/hr until the infant's temperature was normal (36.5 – 37.5°C). They ended up with 116 infants who were treated with hypothermia and 118 who received standard therapy. These infants were followed for 18 months and they found no difference in the primary outcomes of death or severe disability, but when they looked at the subset of infants with moderately abnormal aEEG, those who were cooled had an improved outcome ($n = 172$, odds ratio 0.42; 95% CI 0.22–0.80; $p = 0.009$) (32).

The NICHD Neonatal Research trial included 208 infants who were ≥ 36 weeks of gestational age with moderate-to-severe HIE. These infants were randomized to either receive whole-body cooling for 72 hours with a goal esophageal temperature of 33.5°C or standard care. Therapy with hypothermia was to be initiated within 6 hours of birth. The inclusion criteria were infants with severe acidosis defined as a pH < 7.00 or a base deficit of ≥ 16 mmol/L on either a cord gas or any blood sample drawn within 60 minutes of birth or those infants with a pH of 7.01 to 7.15, a base deficit of 10 to 15.9 mmol/L, or no blood gas available with additional criteria of an acute perinatal event (e.g., late or variable decelerations, cord prolapse, cord rupture, uterine rupture, maternal trauma, hemorrhage, or cardiorespiratory arrest), and either an Apgar score of ≤ 5 at 10 minutes after birth, or continued need for resuscitation including endotracheal or mask ventilation at 10 minutes after birth. Eligible infants were then assessed for clinical evidence of moderate or severe HIE or seizures. HIE was defined as having one or more signs in at least three of the following six categories: level of consciousness, spontaneous activity, posture, tone, primitive reflexes (suck or Moro), and autonomic nervous system (pupils, heart rate, or respirations). Those neonates that were randomized to hypothermia were kept cool for 72 hours and then gradually rewarmed by no more than 0.5°C/hr until the infant's temperature was normal (36.5 – 37.0°C). They ended up with 102 infants who were treated with hypothermia and 106 who received standard therapy. These infants were followed for 18 to 22 months and

they found death or moderate/severe disability occurred in 44% of the hypothermia group and 62% of the control group (risk ratio 0.72; 95% CI 0.54–0.95; $p = 0.01$). Death occurred in 24% of the hypothermia group and 37% of the control group and cerebral palsy occurred in 19% of the hypothermia group and 30% of the control group (33).

The TOBY trial included 325 infants who were ≥ 36 weeks of gestational age with moderate to severe HIE. These infants were randomized to either receive whole-body cooling for 72 hours with a goal rectal temperature of 33.5°C or standard care. Therapy with hypothermia was to be initiated within 6 hours of birth. The inclusion criteria were infants with severe acidosis defined as a pH < 7.00 or a base deficit of ≥ 16 mmol/L on either a cord gas or any blood sample drawn within 60 minutes of birth or an Apgar score of ≤ 5 at 10 minutes after birth or continued need for resuscitation including endotracheal or mask ventilation at 10 minutes after birth. Eligible infants were then assessed for clinical evidence of moderate or severe HIE (indicated by lethargy, stupor, or coma) and either hypotonia, abnormal reflexes (including oculomotor or pupillary), an absent or weak suck, or clinical seizures. Finally, they had to have an abnormal aEEG pattern on a 30-minute tracing. Those infants who were randomized to hypothermia were kept cool for 72 hours and then gradually rewarmed by no more than 0.5°C/hr until the infant's temperature was normal (37.0°C). They ended up with 163 infants who were treated with hypothermia and 162 who received standard therapy. These infants were followed for 18 months and they found death or moderate/severe disability occurred in 45% of the hypothermia group and 53% of the control group (risk ratio 0.86; 95% CI 0.68–1.07; $p = 0.17$). Survival without neurologic abnormalities was improved in the hypothermia group (risk ratio 1.57; 95% CI 1.16–2.12; $p = 0.003$). In addition, cerebral palsy was decreased in the hypothermia group (risk ratio 0.67; 95% CI 0.47–0.96; $p = 0.03$) and improved outcomes were noted on the MDI and the PDI of the Bayley Scales of Infant Development II ($p = 0.03$ for each) (34).

As you can see, when you look at these three randomized control trials, hypothermia appears to decrease the mortality rate or major disability at 18 months of age especially in those infants with only moderate HIE (28). This was confirmed in the neo.nEURO.network trial, which included 111 infants who were ≥ 36 weeks of gestational age with moderate to severe HIE. These infants were randomized to either receive whole-body cooling for 72 hours with a goal rectal temperature of 33.5°C or standard care. Therapy with hypothermia was to be initiated within 6 hours of birth. The inclusion criteria were infants with at least one of the following criteria: severe acidosis defined as a pH < 7.00 or a base deficit of ≥ 16 mmol/L on either a cord gas or arterial blood gas drawn within 60 minutes of birth, or an Apgar score of less than 5 at 10 minutes after birth, or continued need for resuscitation including endotracheal or mask ventilation at 10 minutes after birth. Eligible infants were then assessed for clinical evidence of moderate or severe HIE (indicated by lethargy, stupor, or coma) and at least one of the following criteria: hypotonia, abnormal reflexes (including oculomotor or pupillary), an absent or weak suck, or clinical seizures. Finally, they had to have an abnormal standard EEG or aEEG pattern on a

30-minute tracing. Those infants who were randomized to hypothermia were kept cool for 72 hours and then gradually rewarmed by no more than 0.5°C/hr until the infant's temperature was normal (37.0°C). They ended up with 53 infants who were treated with hypothermia and 58 who received standard therapy. Both groups were treated with either morphine or fentanyl to reduce the discomfort due to the HIE or the hypothermia. These infants were followed for 18 to 21 months, and they found death or severe disability occurred in 51% of the hypothermia group and 83% of the control group (odds ratio 0.21: 95% CI 0.09–0.54; $p = 0.001$). This was even true in the severe HIE group (odds ratio 0.17: 95% CI 0.05–0.57; $p = 0.005$) (35). As you can see from these studies, hypothermia appears to help improve the outcomes of infants with HIE more so with those who are moderately affected, but hypothermia is not a cure-all and more studies combining hypothermia with other neuroprotective interventions need to be conducted.

REFERENCES

1. American Academy of Pediatrics Committee on Fetus and Newborn. Apnea, sudden infant death syndrome, and home monitoring. *Pediatrics* 2003; 111: 914–17.
2. Lin C, Wang S, Lin Y, Yeh T. Efficacy of nasal intermittent positive pressure ventilation in treating apnea of prematurity. *Pediatr Pulmonol* 1998; 26: 349–53.
3. Barrington KJ, Bull D, Finer NN. Randomized trial of nasal synchronized intermittent mandatory ventilation compared with continuous positive airway pressure after extubation of very low birth weight infants. *Pediatrics* 2001; 107: 638–41.
4. Lemyre B, Davis PG, DePaoli AG. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for apnea of prematurity. *Cochrane Database Syst Rev* 2008.
5. Friedlich P, Lecart C, Posen R, et al. A randomized trial of nasopharyngeal-synchronized intermittent mandatory ventilation versus nasopharyngeal continuous positive airway pressure in very low birth weight infants after extubation. *J Perinatol* 1999; 19: 413–18.
6. Davis PG, Schmidt B, Roberts RS, et al.; for the Caffeine for Apnea of Prematurity Trial Group. Caffeine for apnea of prematurity trial: benefits may vary in subgroups. *J Pediatr* 2010; 156: 382–7.
7. Schmidt B, Roberts RS, Davis P, et al.; for the Caffeine for Apnea of Prematurity Trial Group. Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006; 354: 2112–21.
8. Schmidt B, Roberts RS, Davis P, et al.; for the Caffeine for Apnea of Prematurity Trial Group. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007; 357: 1893–902.
9. Kumar M, Kabra NS, Paes B. Role of carnitine supplementation in apnea of prematurity: a systematic review. *J Perinatol* 2004; 24: 158–63.
10. Kumar M, Jubra NS, Paes B. Carnitine supplementation for preterm infants with recurrent apnea. *Cochrane Database Syst Rev* 2008.
11. Henderson-Smart DJ, Steer PA. Doxapram versus methylxanthine for apnea in preterm infants. *Cochrane Database Syst Rev* 2011.
12. Henderson-Smart DJ, DePaoli AG. Methylxanthine treatment for apnoea in preterm infants. *Cochrane Database Syst Rev* 2011.
13. Henderson-Smart DJ, Davis PG. Prophylactic methylxanthines for endotracheal extubation in preterm infants. *Cochrane Database Syst Rev* 2011.
14. Henderson-Smart DJ, DePaoli AG. Prophylactic methylxanthine for prevention of apnoea in preterm infants. *Cochrane Database Syst Rev* 2011.
15. Raju TNK, Higgins RD, Stark AR, Leveno KJ. Optimizing care and outcomes for late-preterm (near-term) infants: a summary of the workshop sponsored by the national institute of child health and human development. *Pediatrics* 2006; 118: 1207–14.
16. Engle WA, Tomashek KM, Wallman C, the Committee on Fetus and Newborn. "Late-preterm" infants: a population at risk. *Pediatrics* 2007; 120: 1390–401.
17. Khashu M, Narayanan M, Bhargava S, Osioviich H. Perinatal outcomes associated with preterm birth at 33 to 36 weeks' gestation: a population-based cohort study. *Pediatrics* 2009; 123: 109–13.
18. Pulver LS, Denney JM, Silver RM, Young PC. Morbidity and discharge timing of late preterm newborns. *Clin Pediatr* 2010; 49: 1061–7.
19. Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M, et al. Risk factors for neonatal morbidity and mortality among "healthy," late preterm newborns. *Semin Perinatol* 2006; 30: 54–60.
20. Wang ML, Dorer DJ, Fleming MP, Catlin EA. Clinical outcomes of near-term infants. *Pediatrics* 2004; 114: 372–6.
21. Reddy UM, Ko C, Raju TNK, Willinger M. Delivery indications at late-preterm gestations and infant mortality rates in the United States. *Pediatrics* 2009; 124: 234–40.
22. Raju TNK. Epidemiology of late preterm (near-term) births. *Clin Perinatol* 2006; 33: 751–63.
23. Tomashek KM, Shapiro-Mendoza CK, Davidoff MJ, Petrini JR. Differences in mortality between late-preterm and term singleton infants in the United States, 1995–2002. *J Pediatr* 2007; 151: 450–6.
24. Young PC, Glasgow TS, Li X, Guest-Warnick G, Stoddard G. Mortality of late-preterm (near-term) newborns in Utah. *Pediatrics* 2007; 119: e659–65.
25. Pulver LS, Guest-Warnick G, Stoddard GJ, Byington CL, Young PC. Weight for gestational age affects the mortality of late preterm infants. *Pediatrics* 2009; 123: e1072–7.
26. Woythaler MA, McCormick MC, Smith VC. Late preterm infants have worse 24-month neurodevelopmental outcomes than term infants. *Pediatrics* 2011; 127: e622–9.
27. Morse SB, Zheng H, Tang Y, Roth J. Early school-age outcomes of late preterm infants. *Pediatrics* 2009; 123: e622–9.
28. Jacobs SE, Tarnow-Mordi WO. Therapeutic hypothermia for newborn infants with hypoxic-ischemic encephalopathy. *J Paediatr Child Health* 2010; 46: 568–76.
29. Jacobs SE, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 2008.
30. Shah PS, Ohlsson A, Perlman M. Hypothermia to treat neonatal hypoxic ischemic encephalopathy: systematic review. *Arch Pediatr Adolesc Med* 2007; 161: 951–8.
31. Sahni R, Sanocka UM. Hypothermia for hypoxic-ischemic encephalopathy. *Clin Perinatol* 2008; 35: 717–34.
32. Gluckman PD, Wyatt JS, Azzopardi D, et al.; on behalf of the CoolCap Study Group. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomized trial. *Lancet* 2005; 365: 663–70.
33. Shankaran S, Laptook AR, Ehrenkranz RA, et al.; for the NICHD Neonatal Research Network. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 2005; 353: 1574–84.
34. Azzopardi DV, Strohm B, Edwards AD, et al.; for the TOBY Study Group. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med* 2009; 361: 1349–58.
35. Simbruner G, Mittal RA, Rohlmann F, Muche R, for the neo.nEURO.network trial. Systemic hypothermia after neonatal encephalopathy: outcomes of neo.nEURO.network rct. *Pediatrics* 2010; 126: e771–8.