Aperito Online Publishing

Pediatrics and Neonatal Care
Open Access

Received : Sep 04, 2013
Accepted: Nov 13, 2013
Published: Dec 18, 2013

http://dx.doi.org/10.14437/PNCOA-1-105 Research Elizabeth Asztalos, Pediatr Neonatal Care 2013: 1:1

Predicting a Positive Neuro developmental Outcome for the Extremely Preterm Infant

Elizabeth Aszlalos[1*] and Alex Kiss[2]

[1]Department of Newborn and Developmental Pediatrics, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

[2]Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

Abstract

Background: Despite the technological and medical advances in perinatal and neonatal care, the rate of preterm birth continues to rise and contribute to the increased costs to the health care systems worldwide. Neonatal clinicians often find themselves trying to determine what neonatal factors are more influential in determining the prognosis of a positive or adverse outcome in this high-risk population.

Objective: The objective of this study was to: 1) to identify neonatal clinical milestones and determine their predictive value for a positive neurodevelopmental outcome; and 2) to determine the individual and combined prognostic effects of these events on the neurodevelopmental outcomes of high risk preterm infants.

Method: Neonatal and neurodevelopmental follow-up data from 437 extremely preterm infants were analyzed in a logistic regression model. The results of the logistic regression models were then validated using bootstrap sampling methods. Specifically, 1000 bootstrap replications of size 400 were selected from the sample and each replication was run replication was run through a logistic regression model. Variables that came out significant in greater than 50% of the 1000 models were considered to have been validated.

Results: In the model, age at which all positive pressure for respiratory support was found to be significant, OR=2.17. 95% CI=1.15-4.11 (p=0.0.18); as well, the need for oxygen support at 36 weeks gestation, OR=0.57. 95% CI=0.33-0.99 (p=0.045); and the presence of periventricular echogenicity, OR=0.23. 95% CI=0.057-0.95 (p=0.043).Both age at which all positive pressure for respiratory support and periventricular echogenicity were found to be significant in more than 50% of simulations (71.1 and 57.0% respectively), with the need of oxygen support at 36 weeks gestation in just under 50% (47.2) . There was no interactive or cumulative effect between the three variables.

Conclusion: Extremely preterm infants who spent less time on any form of positive pressure ventilatory support were more likely to experience a positive neurocognitive outcome. Similarly, those infants who showed no evidence of injury to brain white matter

had an increased likelihood of experiencing a positive neurocognitive outcome but not as high as positive pressure ventilatory support. Utilizing the information from this study once supported and validated by additional studies will assist clinicians in their counselling with parents of these infants during their time in the neonatal care setting.

Keywords: Neurodevelopment outcomes; Preterm infant; Prediction model

***Corresponding author**: Elizabeth Asztalos, MD, Department of Paediatrics, University of Toronto, The Centre for Mother, Infant, and Child Research, Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, M4-230, Toronto, ON M4N 3M5, Canada, E-mail: elizabeth.asztalos@sunnybrook.ca

Introduction

Despite the technological and medical advances in perinatal and neonatal care, the rate of preterm birth continues to rise and contribute to the increased costs to the health care systems worldwide [1-3].

Neonatal clinicians often find themselves trying to determine what neonatal factors are more influential in determining the prognosis of a positive or adverse outcome in this high-risk population. To date, most outcome studies and even clinical trials have evaluated the impact of a single management approach or clinical morbidity on the outcome of a high-risk infant. Preterm infants, smaller and more immature, have benefitted from these modalities in care as they relate to survival but morbidity remains a concern [4-9].

In parallel with the advances made in neonatal intensive care, various scoring systems have been developed initially to compare the performance of different hospitals in a risk-adjusted fashion [10-16]. These scoring systems aimed to determine if they could be predictive of survival and any long term neurodevelopment di_culties in the preterm infant. There are limitations to these scoring systems. Most include physiologic parameters taken in the first 12-24 hours of life. If the parameters are abnormal and contribute to an abnormal score then it certainly can be predictive of an adverse outcome; however, the same could not always be said of the opposite, i.e. should physiologic parameters be within acceptable range, can this be predictive of a normal outcome?

The objective of this study was to: 1) to identify neonatal clinical milestones and determine their predictive value for a positive neurodevelopmental outcome; and 2) to determine the individual and combined prognostic effects of these events on the neurodevelopmental outcomes of high risk preterm infants.

Methods

Study population

The study population included extremely preterm infants (born at < 29 weeks gestation) admitted to the Neonatal Intensive Care Unit (NICU) at the Sunnybrook Health Sciences Centre (SHSC) between January 1, 2005 and December 31, 2008 inclusive. The NICU is one of three tertiary care NICUs in the Greater Toronto Area (Toronto, Ontario, Canada) that serves a catchment area of greater than 70,000 births annually

Data collection

Information was collected prospectively on respiratory disease management including time off oxygen and all forms of positive pressure support, feeding achievements, as well as morbidity outcomes related to intracranial findings, retinopathy of prematurity, and bronchopulmonary dysplasia (Table 1).

Following the initial discharge home from the NICU, the infants were seen in the Neonatal Follow-up Clinic on a series of scheduled visits over the first 2 years of life. The children underwent a neurodevelopmental assessment utilizing the Bayley Scales of Infant Development-3rd edition (BSID-III) [17] at 18-24 months corrected age. Approval for data collection was obtained from the Research Ethics Board for Sunnybrook Health Sciences Centre.

Table 1: Neonatal Characteristics and Morbidity

Neonatal Characteristics and Morbidity	N=437
Gestational age at birth (weeks)(mean) (sd))	26.4 (1.32)
Birthweight (grams)(mean)(sd)	914 (218)
	n (%)
Male Female	223 (51) 214 (49)
Bronchopulmonary Dysplasia (O requirementsat 36 weeks corrected gestational age)	87 (20)
Moderate (O2+PPV 32-34weeks gestational age)	31 (7)
Severe(O2+ PPV ≥35weeks gestational age)	17 (4)
Severe ROP (stage 4, 5, need for laser therapy)	1 (<1)
NEC (Bell stage ≥2)	35 (8)
PDA	249 (57)
Sepsis	166 (38)
Meningitis	5 (1)
Severe IVH (Grade 3, 4, intraparenchymal involvement)	19 (4)
Periventricular echogenicity	17 (4)
Ventriculomegaly	43 (10)
Late ventriculomegaly (≥34 weeks gestational age)	24 (5)

Outcome definitions

The neurodevelopmental outcome measures for this study were the cognitive and language composite scores on the BSID-III. The BSID-III is a norm-referenced instrument to assess cognitive, language, motor functions, social-emotional, and adaptive behaviours [17]. The cognitive scale consists of 91 items, which are scaled and converted to a composite score. The language scale consists of two subtests: receptive communication and expressive communication. The receptive communication subtest assesses an infant's auditory acuity and his/her ability to understand and respond to verbal stimuli, while the expressive communication subtest assesses the infant's ability to vocalize, name pictures and objects, and communicate with others. The two subtests are scaled and combined to form a composite score. The composite cognitive and language scores are age-standardized with a mean score of 100 and a standard deviation of 15. For the purposes of this project, a score of 100 was used as the cut-off for the cognitive and language composite scores. A score of 100 has been found to be similar to a Mental Developmental Index score of 85 (1 standard deviation from the normative value of 100) on the 2nd version of the Bayley Scales of Infant Development [18].

Data analysis

Descriptive statistics were run on all variables of interest with continuous variables summarized using means and standard deviations and categorical variables summarized using counts and proportions.

Two binary outcome variables of interest were created, one for cognition and the other for language. The variables of interest were created such that those having a score greater than or equal to 100 on either cognition or language were compared to those with scores below 100. Logistic regression models were run on the cohort to assess which variables of interest were predictive of either outcome. Continuous variables found to be significant associated with the outcome measures were dichotomized and tested across the range of possible cut-points using Receiver Operating Characteristic (ROC) curves to determine at which cut-off point sensitivity would be greater than 80%. A new binary predictor variable was then created on this basis. The results of the logistic regression models were then validated using bootstrap sampling methods. Specifically, 1000 bootstrap replications of size 400 were selected from the sample and each replication was run through a logistic regression model. Variables that came out significant in greater than 50% of the 1000 models were considered to have been validated

All data analyses were conducted using SAS v9.3 (SAS Institute Inc, Cary, NC).

Results

Population

During the period of study, 672 infants with a gestation age < 29 weeks were admitted to the NICU. Of these, 539 infants survived to discharge; 38infants did not attend the follow-up clinic and 64 did not information on the BSID-III, leaving a total of 437 infants for whom both neonatal and follow-up data were available and were included in the analysis (Figure 1). The characteristics of the population studied are presented in table 1.

Model development and validation

A logistic regression model was run to predict cognition where cognition was treated as a binary outcome (≥100, <100). The variables inserted in the model (neonatal milestones and morbidity) are listed in table 2. Positive pressure ventilation included any and all forms of ventilatory support including direct (via endotracheal) and indirect (nasal) methods. Full enteral feeds were defined as the infant receiving all nutritional support by nasogastric feedings and none by intravenous. An intravenous in place for antibiotics but no parenteral nutrition was included as being at full enteral feeds. Periventricular echogenicity was defined as the presence of any echogenicity in a cranial ultrasound in the first 2 weeks of life that was seen on both sagittal and coronal views. Ventriculomegaly and late ventriculomegaly was defined as any enlargement of the lateral ventricles (unilateral and bilateral) with or without an accompanying intraventricular haemorrhage in any cranial ultrasound during the hospital stay.

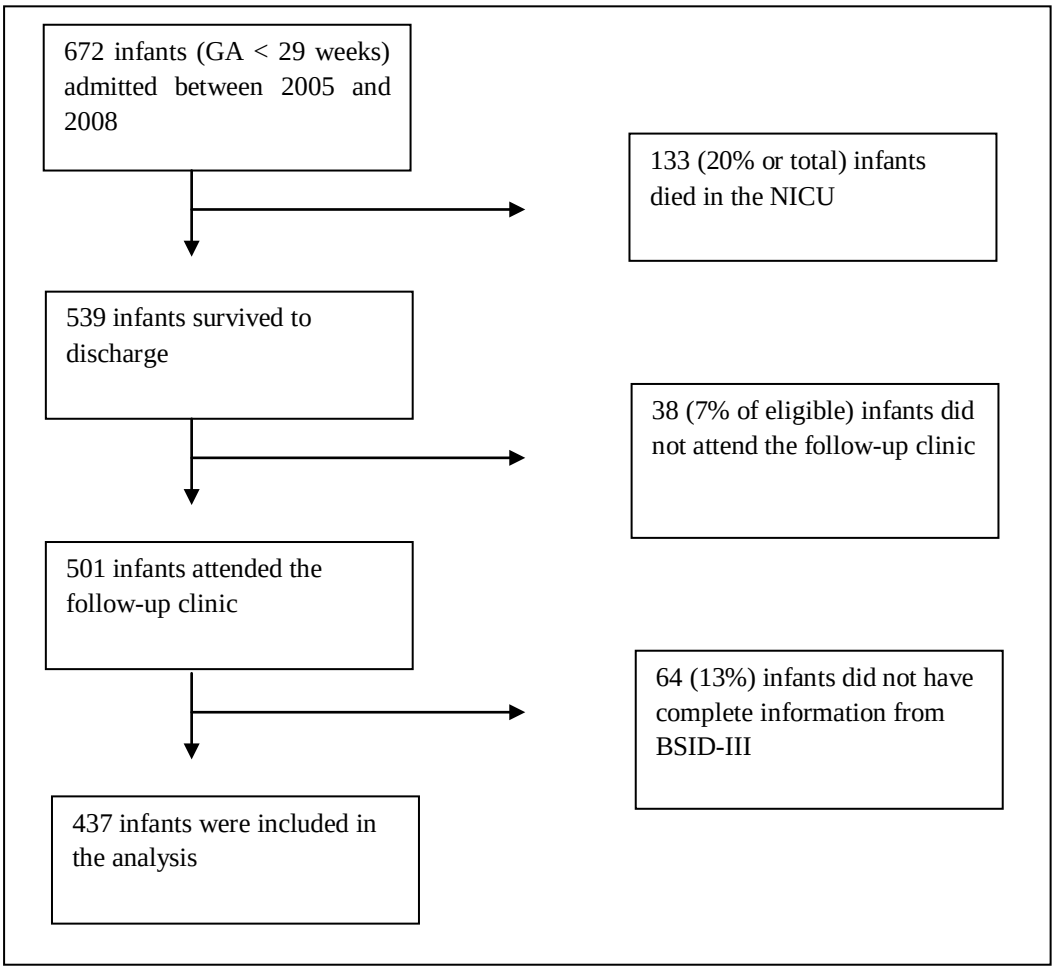

Figure 1: Outline of Population

Table 2: Variables inserted into Model

Variable (Milestones)

- Age (days) for all positive pressure ventilation discontinuation (nasal and endotracheal)
- Age (corrected gestation weeks) for all positive pressure ventilation discontinuation (nasal and endotracheal)
- Age (days) for full enteral feeds
- Age (corrected gestation weeks) for full enteral feeds
- Age (days) birth weight regained
- Age (corrected gestation weeks) birth weight regained Variable (Neonatal Morbidity)

Variable (Neonatal Morbidity)

- Oxygen at 36 weeks corrected weeks gestation
- Severe Retinopathy of prematurity (stage 4, 5, or requiring any treatment)
- Severe intraventricular hemorrhage (grade 3, 4)
- Periventricular echogenicity
- Ventriculomegaly
- Late ventriculomegaly (persistent after 34 weeks gestation)
- Hydrocephalus
- Necrotising enterocolitis (Bell stage ≥ 2)
- Patent Ductus Arteriosus
- Sepsis
- Meningitis

Prior to analysis the variables were tested for multicollinearity using tolerance statistics. Multicollinearity was not found to be a concern (i.e. no tolerance statistics <0.4) and therefore no variables were excluded from consideration. Table 3 lists the odds ratios and their associated confidence limits produced in the model. The cut-off point sensitivity for age in days off all positive pressure was less than 14 days of life; for corrected age in weeks to achieve full feeds was 28 weeks gestation; and corrected age at which birth weight was regained was 27 weeks gestation. In the model, age at which all positive pressure for respiratory support was found to be significant, OR=2.17. 95% CI=1.15-4.11 (p=0.018); as well, the need for oxygen support at 36 weeks gestation, OR=0.57. 95% CI=0.33-0.99 (p=0.045); and the presence of periventricular echogenicity, OR=0.23. 95% CI=0.057-0.95 (p=0.043).The variables were then validated by means of running 1000 bootstrap simulations of size 400. Table 3 shows the percentage of the 1000 simulations in which each variable came out to be statistically significant. Both age at which all positive pressure for respiratory support and periventricular echogenicity

were found to be significant in more than 50% of simulations (71.1 and 57.0% respectively), with the need of oxygen support at 36 weeks gestation in just under 50% (47.2) . There was no interactive or cumulative effect between the three variables.

A similar process was completed to predict language outcomes where language was treated as a binary outcome (>=100, <100). However, no variables were found to demonstrate the same degree of significance as seen with cognition.

Table 3: Odds Ratio Estimates and Bootstrap simulations

Effect	Point Estimate	95% Confidence Limits	P-Value	**Percentage of simulations in which significant**
Age off all positive Pressure (days)	2.17*	1.15, 4.11	0.018	71.1*
Corrected age full feeds	1.46	0.75, 2.87	ns	31.2
Corrected age birth weight regained	1.74	0.89, 3.37	Ns	45.6*
Oxygen at 36 weeks corrected age	0.57*	0.33, 0.99	0.045	47.2*
Sepsis	1.16	0.74, 1.80	Ns	8.8
Patent ductusarteriosus	1.25	0.79, 1.99	Ns	12.5
Ventriculomegaly	0.53	0.20, 1.41	ns	36.3
NEC	0.74	0.48, 1.13	ns	27.5
Hydrocephalus	0.27	0.06, 1.27	ns	36.2
Late Ventriculomegaly (after 34 weeks gestation)	1.32	0.35, 5.04	ns	8.5
Periventricular echogenicity	0.23*	0.06, 0.95	0.043	57.0*
Periventricular leukomalacia	0.26	0.03, 2.54	ns	2.7

extremely preterm infants continue to be at high-risk of an adverse neurodevelopmental outcome of almost 50%, with numbers of 40% related to cognitive or language delay [19]. These numbers

have not changed dramatically from previous studies over the previous decade [20-22]. Clinicians are often faced with discussing adverse neurodevelopmental di_culties in the presence of clear evidence of injury or severe morbidity. However, there is an equal number of infants who do not experience significant neurodevelopmental challenges. Yet the ability for clinicians to counsel on these infants is challenging as there is less evidence available to support discussions along this direction.

Our objective for this study was to determine whether there were specific neonatal events or milestones, when reached or achieved, were associated with a positive neurodevelopmental outcome. Cognition as determined by the cognitive composite score from the BSID-III was chosen as it is an assessment tool used very commonly in clinical and research settings. The results of this study demonstrated that less time overall for an infant to require positive pressure ventilatory support was the most significant milestone/event associated with having a cognition score of 100 or greater at 18-24 months corrected age. The need for oxygen support at 36 weeks gestation or beyond was not as significant. Although not as significant was the presence of echogenicity in the periventricular area on cranial ultrasound during the first 2 weeks of life. The need for oxygen at 36 weeks gestation and after has been associated with a higher probability of an adverse neurodevelopmental outcome in past studies but more recently it is now recognized that not oxygen alone but oxygen and persistent need for prolonged positive pressure support contributes more strongly to an adverse outcome [22-25]. The results from this study supports that reduction in time for positive pressure support can, in fact, be supportive of a positive neurodevelopmental outcome. Similarly, evidence of white matter injury has been strongly associated with an adverse outcome, both motor and cognitive [6, 26-28]. The absence of early evidence of injury can also be supportive of a positive outcome whereas that has not always been the case.

It is important to recognize that there are many factors that can contribute to cognitive development in this vulnerable population. Birth weight and gestational age at birth have been repeatedly found to contribute a major role in both survival and neurodevelopmental outcome. Social factors have been identified to play a critical role and maternal education is a critical contributor as well as support post discharge [29].

The study was completed on data from infants from a single perinatal centre. The use of antenatal corticosteroids for this cohort was close to 90% and birth weight and gestational age at birth did not contribute to the analysis. As such, it is important to recognize this limitation that this represents for the results to apply in other clinical settings. However, additional studies using a more population-based cohort to demonstrate whether these findings persist are necessary. If these findings persist, it will support ensuring approaches and practices in care that will focus on reducing the impact of ventilatory management for this group of vulnerable infants.

In conclusion, we were able to identify a neonatal event/milestone that may be helpful in identifying preterm infants with a higher probability of experiencing a positive neurodevelopment outcome as it relates to cognition. Extremely preterm infants who spent less time on any form of positive

pressure ventilatory support were more likely to experience a positive neurocognitive outcome. Similarly, those infants who showed no evidence of injury to brain white matter as demonstrated by echogenicity on cranial ultrasounds in the first 2 weeks of life had an increased likelihood of experiencing a positive neurocognitive outcome but not as high as positive pressure ventilatory support. These findings from this study can suggest two important approaches in care. First, approaches in respiratory and ventilatory management should focus on total time on any form of positive pressure support and not just on oxygen need at or beyond 36 weeks gestation. Secondly, it is important to ensure approaches and strategies in care are in place during the perinatal and early neonatal period to minimize any impact on the vulnerable preterm brain. Only then will we be able to start seeing greater numbers of vulnerable preterm infants experiencing a positive neurodevelopmental outcome. Utilizing the information from this study once supported and validated by additional studies will assist clinicians in their counseling with parents of these infants during their time in the neonatal care setting.

Acknowledgement

We thank the staff of the Neonatal Follow-up Clinic (Dr. Paige Church, Maureen Luther, Laura Cooper, Denise Hohn, and Pat Maddelena) at the Sunnybrook Health Sciences Centre for their diligent and compassionate work in following the children after discharge from the NICU. This project was supported by a grant from the Alva Foundation, Toronto, Ontario, Canada.

References

1. Public Health Agency of Canada (2012) Perinatal Health Indicators for Canada, Ottawa, Canada.
2. Highlights of 2010-2011 Selected Indicators describing the birthing process in Canada (2012) Canadian Institute for Health Information.
3. Canadian Institute for Health Information. Giving Birth in Canada: The Costs.
4. Saigal S, Doyle LW (2008) An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 371: 261-269.
5. Ehrenkranz RA, Younes N, Lemons JA, Fanaroff AA, Donovan EF, et al. (1999) Longitudinal growth of hospitalized very low birth weight infants. Pediatrics 104: 280-289.
6. Schmidt B, Asztalos EV, Roberts RS, Robertson CM, Sauve RS, et al. (2003) Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. JAMA 289: 1124-1129.
7. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, et al. (2006) Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics 117: 1253-1261.
8. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, et al. (2004) Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 292: 2357-2365.
9. Joseph KS, Kramer MS, Allen AC, Cyr M,

Fair M, et al. (2000) Gestational age-and birthweight-specific declines in infant mortality in Canada, 1985-94. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. Paediatr Perinat Epidemiol 14: 332-339.

10. The International Neonatal Network (1993) The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. The International Neonatal Network. Lancet 342: 193-198.
11. Rautonen J, Mäkelä A, Boyd H, Apajasalo M, Pohjavuori M (1994) CRIB and SNAP: assessing the risk of death for preterm neonates. Lancet 343: 1272-1273.
12. Korner AF, Stevenson DK, Kraemer HC, Spiker D, Scott DT, et al. (1993) Prediction of the development of low birth weight preterm infants by a new neonatal medical index. J Dev Behav Pediatr 14: 106-111.
13. Scheiner AP, Sexton ME (1991) Prediction of developmental outcome using a perinatal risk inventory. Pediatrics 88: 1135-1143.
14. Brazy JE, Eckerman CO, Oehler JM, Goldstein RF, O'Rand AM (1991) Nursery Neurobiologic Risk Score: important factor in predicting outcome in very low birth weight infants. J Pediatr 118: 783-792.
15. Pasman JW, Rotteveel JJ, Maassen B, de Graaf R, Kollée LA(1998) Neonatal risk factors and risk scores including auditory evoked responses. Eur J Pediatr 157: 230-235.
16. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD; National Institute of Child Health and Human Development Neonatal Research Network (2008) Intensive care for extreme prematurity--moving beyond gestational age. N Engl J Med 358: 1672-1681.
17. Bayley N (2007) Manual for the Bayley Scales of Infant Development.(3rd Edn.) The Psychological Corporation, San Antonio, Texas, USA.
18. Anderson PJ, De Luca CR, Hutchinson E, Roberts G, Doyle LW; Victorian Infant Collaborative Group (2010) Underestimation of developmental delay by the new Bayley-III Scale. Arch Pediatr Adolesc Med 164: 352-356.
19. Schmidt B, Whyte RK, Asztalos EV, Moddemann D, Poets C, et al. (2013) Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. JAMA 309: 2111-2120.
20. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, et al. (2001) Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 344: 1966-1972.
21. Whyte RK, Kirpalani H, Asztalos EV, Andersen C, Blajchman M, et al. (2009) Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion. Pediatrics 123: 207-213.
22. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, et al. (2006) Caffeine for Apnea of Prematurity. N Engl J Med 20: 2112-2121.
23. Jobe AH, Bancalari E (2001)

Bronchopulmonary dysplasia. Am J Respir Crit Care Med 163: 1723-1729.

24. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, et al. (2005) Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics 116: 1353-1360.
25. BhandariA,BhandariV(2009)Pitfalls,problems,andprogressinbronchopulmonary dysplasia. Pediatrics 123: 1562-1573.
26. Neil JJ, Inder TE (2004) Imaging perinatal brain injury in premature infants. Semin Perinatol 28: 433-443.
27. El-Dib M, MassaroAN, BulasD, AlyH(2010)Neuroimagingandneurodevelopmental outcome of premature infants.Am J Perinatol 27: 803-818.
28. Boardman JP, Craven C, Valappil S, Counsell SJ, Dyet LE, et al. (2010) A common neonatal image phenotype predicts adverse neurodevelopmental outcome in children born preterm. Neuroimage 52: 409-414.
29. Ko G, Shah P, Lee SK, Asztalos E (2013) Impact of maternal education on cognitive and language scores at 18 to 24 months among extremely preterm neonates. Am J Perinatol 30: 723-730.