Outcome of infants born at < 32 weeks' gestation in a single-centre level III neonatology unit – relation to feeding strategy

Ursula Kiechl-Kohlendorfer ⓘ**,
Marlene Biermayr, Ulrike Pupp Peglow and
Elke Griesmaier**

Abstract

Objective: This study aimed to determine survival, neonatal morbidity, and outcomes at 1 and 2 years in children who were born very preterm, and to analyse any relation to enteral feeding.

Methods: We performed a prospective, observational study on very preterm infants (range: 23–31 weeks' gestation) born at Innsbruck Medical University Hospital, Austria, between 2007 and 2014 (n = 557).

Results: The overall survival rate was 94.6%. Survival rates were 77.8%, 78.6%, 90.9%, and 90.9% among those born at 24, 25, 26, and 27 weeks, and 97.3%, 95.3%, 98.3%, and 100% among those born at 28, 29, 30, and 31 weeks of gestation, respectively. The overall prevalence of chronic lung disease among survivors was 7.3%. The prevalence of necrotizing enterocolitis requiring surgery, intraventricular haemorrhage grades 3 and 4, and severe retinopathy of prematurity was 3.1%, 2.1%, and 6.2%, respectively. There was no difference in short-term morbidity or neurodevelopmental outcome at 1 or 2 years of corrected age between infants who were fed with human milk at discharge and those who were formula-fed.

Conclusion: In the current study, mortality and short-term morbidity rates were low. No differences regarding feeding strategy were detected.

Department of Paediatrics II, Division of Neonatology,
Medical University of Innsbruck, Innsbruck, Austria

Corresponding author:
Ursula Kiechl-Kohlendorfer, Medical University of
Innsbruck, Anichstrasse 35, Department of Paediatrics II,
Division of Neonatology, 6020 Innsbruck, Austria.
Email: ursula.kohlendorfer@i-med.ac.at

Introduction

The number of neonates surviving very preterm birth has gradually increased because of advances in perinatal and neonatal care. However, increasing survival is associated with an increased awareness of morbidity outcomes in these children.

Most of the large cohort studies that reported the outcome of very preterm-born children exclusively focussed on mortality and short-term morbidity of those born before 27 weeks' gestation.[1,2] Even though children who are born between 27 and 31 weeks have a lower relative risk for adverse outcomes, they comprise a much larger proportion of preterm births, and in absolute numbers, they account for most children with deficits.[3] Therefore, up-to-date and reliable population-based information on outcome including the very preterm group is of special importance for caregivers.

The use of human milk compared with preterm infant formula in very preterm infants (born < 32 weeks' gestation) during hospitalization is associated with reduced in-hospital morbidity. This morbidity includes lower rates of necrotizing enterocolitis (NEC),[4–6] chronic lung disease (CLD), and severe retinopathy of prematurity (ROP),[6] as well as improved neurodevelopmental outcomes.[7,8] Therefore, the effect of the enteral feeding strategy during the hospital stay should be considered in analyses of outcome data.

Therefore, this study aimed to report survival rates and survival without short-term morbidity in all live-born very preterm infants in a geographically defined area. We also included data on neurodevelopmental outcomes at 1 and 2 years old and focussed on the effect of feeding strategy on outcome data.

Methods

Participants

The study survey area was Tyrol, which is a state in western Austria with 750,000 inhabitants and approximately 7500 live births per year. All infants who were born before 32 completed weeks of pregnancy at Innsbruck Medical University Hospital, which is the only neonatal intensive care unit in the geographical region, were enroled. The study period was between January 2007 and December 2014.

The follow-up study was approved by the ethics committee of the Medical University of Innsbruck (No. AN2013–0086 333/4.2). Informed consent of the participants was not required because the database only contained routine data.

Maternal and neonatal data

The following clinical data were prospectively collected: maternal and neonatal data, including maternal age, maternal years of education, smoking during pregnancy, antenatal steroid use, gestational age (full weeks of gestation), birth weight (g), small for gestational age (SGA), multiple births, sex, postnatal surfactant use, diagnosis of early- and late-onset sepsis, CLD, intraventricular haemorrhage (IVH),

NEC, and severe ROP. Gestational age was calculated from the first day of the last menstrual period. This was compared with assessment of gestational age by ultrasound scans that were performed before 24 weeks. If there was a difference of more than 1 week between menstrual and ultrasound assessment, assessment of the scan was preferred. Growth charts developed by Fenton et al.[9] were used to classify infants as SGA at birth. SGA was defined as a birth weight lower than the 10th percentile for sex and gestational age. Overall mortality was defined as all deaths that occurred after birth and included delivery room and neonatal intensive care unit deaths. Smoking habits during pregnancy (yes/no) were based on self-reported data. All data are available on request.

Short-term outcome

The following major short-time morbidities were analysed. Moderate/severe CLD was defined as oxygen dependence at 36 weeks' postmenstrual age. NEC was defined according to Bell's criteria[10] and classified as medical (clinical symptoms and signs plus evidence of pneumatosis on an abdominal x-ray) or surgical (histological evidence of NEC on surgical specimens of the intestine). IVH was classified according to the method of Papile et al.[11] Cystic periventricular leukomalacia (PVL) was defined by ultrasonographic findings that suggested cystic degeneration of periventricular white matter. ROP was graded according to international classification.[12] A diagnosis of early-onset (≤ 72 hours after birth) or late-onset (> 72 hours) sepsis required signs of generalized infection, a positive blood culture, and antibiotic therapy for 5 or more days.

An adverse short-term outcome was defined as moderate/severe CLD, NEC requiring surgical treatment, IVH grades 3 to 4, and ROP grades 3 to 5.

Long-term outcome

Neurodevelopmental outcome was assessed at 1 and 2 years of corrected age. Neurodevelopmental outcome was determined by neurological examinations and the Bayley Scales of Infant and Toddler Development, second edition (Bayley-II),[13] for infants born between 2007 and 2013, and the third edition (Bayley-III)[14] for infants born in 2014. Bayley-II scores provide psychomotor (PDI) and mental (MDI) developmental indices, Bayley-III scores motor composite, and mental developmental scores (mean of cognitive and language composite scores). The mean score is 100, and a score of < 85 (>1 standard deviation [SD] below the mean) and ≥ 70 (≤ 2 SDs below the mean) indicates a delay and a score of < 70 (> 2 SDs below the mean) indicates abnormal development. Delayed neurodevelopmental outcome was defined as a score of < 85 and ≥ 70. Abnormal neurodevelopmental outcome was defined as a score of < 70 on either the PDI or the MDI of the Bayley-II or the motor composite or mental developmental score of the Bayley-III. Cerebral palsy was classified by the Gross Motor Function Classification.[15] Patients with cerebral palsy (grades 2–5) were included in the group of infants with an abnormal outcome. No children had blindness or sensorineural hearing loss that required a hearing aid.

All cognitive tests were performed by one of two experienced psychologists.

Enteral feeding regime

Enteral feeding was started in all infants on their first day of life. In neonates with a birth weight of less than 1000 g, only donor human milk or mother's milk was used in the first 4 weeks of life. A human milk fortifier was added at a feeding volume of 100 mL/kg (Prolacta +4; Prolacta Bioscience Inc., City of Industry,

CA, USA). Thereafter, mother's milk (if available) and a bovine fortifier or infant formula were provided. In children with a birth weight between 1000 g and 1500 g, mother's milk or donor human milk if available was used. A bovine fortifier was added at a total feeding volume of 100 mL/kg. Infants who weighed more than 1500 g received mother's milk if available or formula and a bovine fortifier for a total feeding volume of 100 mL/kg. The total feeding volume was increased by 10 to 20 mL/kg/day depending on a physical examination of the stomach, meconium passage, and gastric residuals.

The two feeding groups were classified as any human milk (human milk with either fortifier or formula) or formula (formula only) based on feeding in the previous 24 hours before discharge from hospital. Data on feeding before discharge were retrospectively collected from the patients' records.

Statistical analysis

Data analysis was performed with SPSS software, version 20.0, for Windows (IBM Corp., Armonk, NY, USA). Categorical data were compared using the chi-square or Fisher's exact test. Multivariate risk profiles according to feeding strategy at discharge from hospital were computed by means of logistic regression analysis. The multivariate model was adjusted for maternal age, smoking during pregnancy, antenatal steroids, gestational age, birth weight, SGA, and late-onset sepsis.

Results

During the study period, there were 557 live births, of which 30 children died. Of the remaining 527 children, 459 (87.1%) and 442 (83.9%) attended follow-up visits at 1 and 2 years old. There were no significant differences in maternal age, maternal education, antenatal steroid use, gestational age, birth weight, sex, SGA, early- and late-onset sepsis, CLD, severe IVH, PVL, ROP, and NEC between non-participants and participants. Smoking during pregnancy was significantly more prevalent in non-participants than in participants ($p < 0.001$), whereas surfactant was more frequently used in participants than in non-participants ($p = 0.006$).

Table 1 shows maternal and pre-, peri-, and neonatal data for the population of children who were born very preterm according to the feeding group at discharge from hospital.

The formula group had a significantly higher prevalence of low maternal age (< 23 years) ($p = 0.001$), low maternal education (< 12 years) ($p = 0.032$), smoking during pregnancy ($p = 0.027$), SGA ($p = 0.002$), and ROP grades 3 and 4 ($p = 0.001$), whereas the use of antenatal steroids was significantly lower ($p = 0.005$) than in the human milk group. Mean gestational age and birth weight were significantly lower in the formula group than in the human milk group (both $p < 0.001$). No significant differences were found regarding all other maternal and pre-, peri-, and postnatal variables between these two groups.

Survival

The overall survival rate of all infants in the neonatal wards was 94.6%. Survival rates in infants who were born at 23, 24, 25, 26, 27, and 28 weeks of gestation were 20.0%, 77.8%, 78.6%, 90.9%, 90.9%, and 97.3%, respectively. The survival rates were 95.3% and 98.3% in those born at 29 and 30 weeks of gestation. All of the children who were born at 31 weeks of gestation survived. There was no significant difference in the survival rate over the 8-year study period.

Table 1. Sociodemographic and neonatal characteristics of preterm infants with a gestational age of fewer than 32 weeks according to feeding strategy at discharge from hospital

Variable	Any human milk (n = 429), n (%) or mean ± SD	Formula (n = 98), n (%) or mean ± SD	p value
Maternal age < 23 years	28 (6.5)	17 (17.3)	0.001
Low educational level of the mother (< 12 years)	162 (45.5)	47 (58.8)	0.032
Smoking during pregnancy	98 (23.0)	33 (33.7)	0.027
Multiple births	163 (38.8)	35 (35.7)	0.570
Antenatal steroids	389 (92.0)	80 (82.5)	0.005
Gestational age (weeks)	29.1 ± 1.9	28.2 ± 2.0	<0.001
Birth weight (g)	1304 ± 391	1032 ± 313	<0.001
SGA	54 (12.7)	26 (26.5)	0.002
Male sex	229 (53.4)	43 (43.9)	0.089
Surfactant treatment	233 (55.2)	60 (61.2)	0.280
CLD	29 (6.8)	9 (9.2)	0.421
IVH (all grades)	55 (13.0)	13 (13.3)	0.938
IVH (grades 3–4)	7 (1.7)	4 (4.1)	0.133
PVL	14 (3.3)	2 (2.0)	0.748
NEC	14 (3.4)	6 (6.3)	0.237
ROP (grades 3–4)	19 (4.6)	13 (13.3)	0.001
Early-onset sepsis	12 (2.8)	1 (1.0)	0.301
Late-onset sepsis	25 (5.9)	8 (8.2)	0.394

SD: standard deviation; SGA: small for gestational age; CLD: chronic lung disease; IVH: intraventricular haemorrhage; PVL: periventricular leukomalacia; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity. The p values were obtained by Fisher's exact test or the t test, as appropriate. For all variables, except for educational level of the mother, the proportion of missing data was < 5%. The proportions of missing data were as follows: 0.2% for maternal age < 23 years; 17.3% for low educational level of the mother; 0.4% for smoking during pregnancy; 1.7% for multiple births; 1.3% for antenatal steroids; 1.3% for surfactant treatment; 0.9% for CLD, IVH, and PVL; 2.8% for NEC; 2.5% for ROP; 0.8% for early-onset sepsis; and 1.3% for late-onset sepsis. There were no missing data for gestational age, birth weight, sex, and SGA.

Short-term morbidity

The prevalence of CLD, NEC requiring surgery, IVH grades 3 and 4, PVL, and severe ROP was 7.3%, 3.1%, 2.1%, 3.1%, and 6.2%, respectively. The overall NEC rate was 3.9%. Overall survival that was free of an adverse short-term outcome was 86.5%. The rates of adverse short-term outcomes according to the two feeding groups are shown in Table 1.

Formula feeding at discharge from hospital was related to an increased risk of adverse short-term outcome (p = 0.002).

However, in the multivariate model after adjustment for maternal age at birth, smoking during pregnancy, antenatal steroids, gestational age at birth, birth weight, SGA, and late-onset sepsis, this significance was lost (Table 2). When we separately focussed on children with different gestational ages (23–26 weeks, n = 77; 27–29 weeks, n = 113; and 30–31 weeks, n = 337) there was also no significant association between the feeding strategy at discharge and short-term morbidity after adjustment for the above-mentioned variables.

Table 2. Multivariable associations between formula feeding at discharge and adverse outcome

Variable	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Adverse short-term outcome	2.40 (1.36–4.24)	0.002	1.08 (0.53–2.21)	0.825
Delayed outcome at 1 year	1.03 (0.59–1.80)	0.918	0.88 (0.48–1.64)	0.696
Abnormal outcome at 1 year	1.12 (0.46–2.69)	0.807	0.63 (0.23–1.78)	0.388
Delayed outcome at 2 years	1.52 (0.78–2.96)	0.217	1.22 (0.59–2.51)	0.600
Abnormal outcome at 2 years	2.05 (0.96–4.37)	0.064	1.75 (0.73–4.17)	0.207

Adverse short-term outcome: moderate/severe CLD, NEC requiring surgical treatment, IVH grades 3 to 4, ROP grades 3 to 5; delayed outcome: Bayley-II psychomotor developmental index (PDI) and/or mental developmental index (MDI) ≥ 70 and < 85 or Bayley-III motor composite score and/or mental developmental score (mean of cognitive and language composite scores) ≥ 70 and < 85; abnormal outcome: Bayley-II PDI and/or MDI < 70 or Bayley-III motor composite score and/or mental developmental score < 70. Patients with cerebral palsy (grades 2–5) were included in the group of infants with an abnormal outcome. CI: confidence interval; OR: odds ratio derived from logistic regression analysis of risk variables for an adverse outcome. The multivariate model was adjusted for maternal age, smoking during pregnancy, antenatal steroids, gestational age, birth weight, small for gestational age, and late-onset sepsis.

Table 3a. Neurodevelopmental outcome at 1 year of corrected age in preterm infants with a gestational age of less than 32 weeks according to feeding strategy at discharge from hospital

Variable	Any human milk (n = 374), n (%)	Formula (n = 85), n (%)
Delayed outcome	97 (25.9)	21 (24.7)
Abnormal outcome	30 (8.0)	7 (8.2)

Table 3b. Neurodevelopmental outcome at 2 years of corrected age in preterm infants with a gestational age of less than 32 weeks according to feeding strategy at discharge from hospital

Variable	Any human milk (n = 362), n (%)	Formula (n = 80), n (%)
Delayed outcome	52 (14.4)	14 (17.5)
Abnormal outcome	30 (8.3)	11 (13.8)

Delayed outcome: Bayley-II psychomotor developmental index (PDI) and/or mental developmental index (MDI) ≥ 70 and < 85 or Bayley-III motor composite score and/or mental developmental score (mean of cognitive and language composite scores) ≥ 70 and < 85; abnormal outcome: Bayley-II PDI and/or MDI < 70 or Bayley-III motor composite score and/or mental developmental score < 70. Patients with cerebral palsy (grades 2–5) were included in the group of infants with an abnormal outcome.

Long-term morbidity

Neurodevelopmental outcomes at corrected ages of 1 and 2 years are shown in Tables 2, 3a, and 3b. Full assessment of motor and cognitive abilities at 1 year of corrected age was available in 459 (87.1%) of the 527 children. A total of 247 (66.0%) children in the human milk group and 57 (67.1%) in the formula group achieved normal Bayley scores in motor and mental developmental indices (range: 85–115). At this time, there were no significant differences in developmental delay (Bayley scales ≥ 70 and < 85) and abnormal development (Bayley score < 70) between the human milk and formula groups. At a corrected age of 2 years, 442 (83.9%) of the 527 children were tested. A total of 280 (77.3%) children in the human milk group and 55 (68.8%) in the formula group achieved a normal developmental outcome in motor and mental scores. There was a trend towards a better outcome at 2 years old in the human milk group compared with the formula group, but this was not significant. There were no significant

differences in long-term outcome when we separately focussed on different gestational ages (23–26 weeks, 27–29 weeks, and 30–31 weeks) between the feeding groups.

Discussion

The overall survival rate of all live-born infants was 94.6% in this population-based cohort of very preterm-born children between 2007 and 2014. Survival rates in the extremely preterm age group (born at < 28 weeks' gestation) were also high at 77.8% among those born at 24 weeks of gestation, and over 90% in those with a gestational age of more than 26 weeks. Survival rates of live-born infants in population-based cohort studies greatly vary, especially regarding extremely preterm infants,[1,16–29] with rates ranging from 35%[25,29] to 70%[1], and from 59%[29] to 81%[1] for those at 25 weeks of gestation. High overall survival rates in our children at a gestational age of 24 weeks or higher may reflect advances in perinatal and neonatal care with high rates of antenatal corticosteroids (90.2%) and surfactant use (56.3%). Our survival rate for this group is low (20%) compared with that in countries with active resuscitation for neonates born at 23 weeks of gestation (Sweden). However, during the last 3 years, we already changed our practice in favour of proactive treatment and the future survival rate of these very immature neonates will probably be higher.

The overall rate of survival that was free of an adverse short-term outcome (moderate/severe CLD, NEC requiring surgical treatment, IVH grades 3–4, and ROP grades 3–5) was 86.5% in our study. The overall prevalence of moderate/severe CLD, severe NEC, IVH grades 3 to 4, and severe ROP was 7.3%, 3.1%, 2.1%, and 6.2%, respectively. The outcome results in the EPIPAGE-2 cohort study were similar to those in our study, with a rate of survival that was free of an adverse short-term outcome of 82.9% for those born between 23 and 31 weeks of gestation.[27] Furthermore, the prevalence of moderate/severe CLD, severe NEC, IVH, and severe ROP was 8.0%, 3.7%, 5.3%, and 1.2%, respectively. Other studies that only focussed on extremely preterm infants reported markedly higher frequencies of short-term morbidities.[16,20,30] The prevalence of severe CLD in other studies ranged from 25%[30] to 44%,[20] and the prevalence of severe ROP ranged from 8%[16] to 34%.[30] The lowest prevalence of severe IVH in extremely preterm infants was 6.0% in a Swedish study,[19] 6.9% in a Dutch Study,[16] and 5.3% in another study that included extremely preterm and very preterm infants.[27] The mean incidence of NEC was reported to be 7% to 10% among extremely preterm infants.[31] In the EPIPAGE-2 cohort, the rate of severe NEC was 3.7% in children born between 23 and 31 weeks of gestation.[27]

A total of 335 (75.8%) of 442 children showed normal motor and mental development at a corrected age of 2 years. Reported rates of no developmental impairment or disability using Bayley assessment at 2 years old in surviving infants vary from 70.6% in the Netherlands[16] to 52.1% in Australia,[32] and 42% in Sweden.[18] All of these studies reported outcomes of extremely preterm infants only. The EPIPAGE-2 cohort study reported a much better outcome, where 80.5% of all children born between 23 and 31 weeks of gestation survived without neuromotor or sensory disability at 2 years of corrected age.[33] However, Bayley assessment for the definition of outcome was not used in this cohort. Generally, developmental outcomes are difficult to compare because of different testing methods and different definitions of disability used.

Our study showed no difference in neurodevelopmental outcome at 1 and 2 years

of age between the human milk and formula groups as assessed with Bayley-II and Bayley-III. This result might be explained by the high breastfeeding rate of 81.4% at discharge from hospital. This finding may also be explained by the local feeding strategy using only human milk in neonates who weighed less than 1000 g and mother's milk or donor milk if available in neonates who weighed 1000 to 1500 g. Our results are in accordance with a recently published study by O'Connor et al.[34] These authors did not find an improved outcome in very low birth weight infants at 18 months of corrected age when supplemental donor milk instead of formula was provided as a supplement to mother's milk. The authors concluded that if donor milk is used in settings with high provision of mother's milk, improved neurodevelopmental outcome should not be considered a treatment goal.

The strengths of this study include the population-based cohort design with prospective enrolment of infants who were born not only extremely preterm, but also very preterm. These outcomes have been reported infrequently. Moreover, the effect of feeding during hospital stay was included in the outcome data. Specialists in paediatrics and paediatric neurology performed the follow-up examinations and certified psychologists administered the Bayley-II and Bayley-III tests.

A limitation of our study is the number of children who were lost to follow-up, although follow-up rates at 1 and 2 years of age were high at 87.1% and 83.9%, respectively. However, we found a social bias in participation, with more mothers who smoked during pregnancy refusing to participate in follow-up. Another limitation is the early age at follow-up because cognitive and academic problems may become evident later.[35] Additionally, our study focussed on outcome differences regarding feeding strategy and was not a randomized, controlled trial. However, randomization between human milk and formula would not have been possible for ethical reasons. Moreover, only differences in outcome between those fed with any human milk and those fed with formula at discharge were calculated. This is because the precise amount of human milk could not be extracted from patients' records retrospectively.

This study provides the first complete description of outcome of very preterm infants who were born in Tyrol. To compare these data with those of other populations, the Austrian healthcare system and policy on treatment of very preterm infants must be considered. Healthcare in Austria is accessible for all people and everyone has health insurance coverage. Perinatal care is well structured and offered to every pregnant woman. This health system may lead to better care in pregnancy and might also be an explanation for good outcome data in very preterm infants.

Conclusions

Our population-based study of very preterm infants shows that mortality and short-term morbidity rates are low. There is no difference in short-term morbidity or neurodevelopmental outcome at 1 or 2 years of corrected age between infants who are fed with human milk at discharge and those who are formula-fed. Advances in perinatal and neonatal care, as well as the high rate of human milk feeding during hospital stay, play an important role in a successful strategy for low rates of complications in these children.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

ORCID iD

Ursula Kiechl-Kohlendorfer (iD) http://orcid.org/0000-0003-0433-6196

References

1. EXPRESS Group, Fellman V, Hellström-Westas L, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA* 2009; 301: 2225–2233.
2. Bolisetty S, Dhawan A, Abdel-Latif M, et al. Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. *Pediatrics* 2014; 133: 55–62.
3. Larroque B, Ancel PY, Marret S, et al. Neurodevelopmental disabilities and special care of 5-year-old children born before 33 weeks of gestation (the EPIPAGE study): a longitudinal cohort study. *Lancet* 2008; 371: 813–820.
4. Schanler RJ, Shulman RJ and Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. *Pediatrics* 1999; 103: 1150–1157.
5. Schanler RJ, Lau C, Hurst NM, et al. Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants. *Pediatrics* 2005; 116: 400–406.
6. Maayan-Metzger A, Avivi S, Schushan-Eisen I, et al. Human milk versus formula feeding among preterm infants: short-term outcomes. *Am J Perinatol* 2012; 29: 121–126.
7. Vohr BR, Poindexter BB, Dusick AM, et al. Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. *Pediatrics* 2006; 118: e115–e123.
8. Vohr BR, Poindexter BB, Dusick AM, et al. Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. *Pediatrics* 2007; 120: e953–e959.
9. Fenton TR and Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr* 2013; 13: 59.
10. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg* 1978; 187: 1–7.
11. Papile LA, Burstein J, Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 gm. *J Pediatr* 1978; 92: 529–534.
12. An international classification of retinopathy of prematurity. Committee for the classification of retinopathy of prematurity. *Arch Ophthalmol* 1984; 102: 1130–1134. (https://www.ncbi.nlm.nih.gov/pubmed/6547831)
13. Bayley N. *Bayley scales of infant and toddler development*. 2nd ed. San Antonio, TX: Psychological Corporation, 1993.
14. Bayley N. *Bayley scales of infant and toddler development*. 3rd ed. San Antonio, TX: Harcourt Assessment, 2006.
15. Palisano RJ, Hanna SE, Rosenbaum PL, et al. Validation of a model of gross motor function for children with cerebral palsy. *Phys Ther* 2000; 80: 974–985.
16. de Waal CG, Weisglas-Kuperus N, van Goudoever JB, et al. Mortality, neonatal morbidity and two year follow-up of extremely preterm infants born in The Netherlands in 2007. *PLoS One* 2012; 7: e41302.
17. Larroque B, Breart G, Kaminski M, et al. Survival of very preterm infants: epipage, a population based cohort study. *Arch Dis Child Fetal Neonatal Ed* 2004; 89: F139–F144.
18. Serenius F, Källén K, Blennow M, et al. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. *JAMA* 2013; 309: 1810–1820.
19. Markestad T, Kaaresen PI, Rønnestad A, et al. Early death, morbidity, and need of

treatment among extremely premature infants. *Pediatrics* 2005; 115: 1289–1298.

20. Vanhaesebrouck P, Allegaert K, Bottu J, et al. The EPIBEL study: outcomes to discharge from hospital for extremely preterm infants in Belgium. *Pediatrics* 2004; 114: 663–675.

21. Chan K, Ohlsson A, Synnes A, et al. Survival, morbidity, and resource use of infants of 25 weeks' gestational age or less. *Am J Obstet Gynecol* 2001; 185: 220–226.

22. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD neonatal research network. *Pediatrics* 2010; 126: 443–456.

23. Costeloe KL, Hennessy EM, Haider S, et al. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ* 2012; 345: e7976. doi: 10.1136/bmj.e7976

24. Boland RA, Davis PG, Dawson JA, et al. Predicting death or major neurodevelopmental disability in extremely preterm infants born in Australia. *Arch Dis Child Fetal Neonatal Ed* 2013; 98: F201–F204. doi: 10.1136/archdischild-2012–301628

25. Berger TM, Steurer MA, Woerner A, et al; Swiss neonatal network. Trends and centre-to-centre variability in survival rates of very preterm infants (<32 weeks) over a 10-year-period in Switzerland. *Arch Dis Child Fetal Neonatal Ed* 2012; 97: F323–F328.

26. Younge N, Goldstein RF, Cotten CM, et al. Survival and neurodevelopment of periviable infants. *N Engl J Med* 2017; 376: 1890–1891. doi: 10.1056/NEJMc1703379

27. Ancel PY, Goffinet F, EPIPAGE-2 Writing Group, et al. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. *JAMA Pediatr* 2015; 169: 230–238. doi: 10.1001/jamapediatrics.2014.3351

28. Mercier CE, Dunn MS, Ferrelli KR, et al. Neurodevelopmental outcome of extremely low birth weight infants from the Vermont Oxford network: 1998–2003. *Neonatology* 2010; 97: 329–338. doi: 10.1159/000260136

29. Field DJ, Dorling JS, Manktelow BN, et al. Survival of extremely premature babies in a geographically defined population: prospective cohort study of 1994–9 compared with 2000–5. *BMJ* 2008; 336: 1221–1223. doi: 10.1136/bmj.39555.670718.BE

30. EXPRESS Group. Incidence of and risk factors for neonatal morbidity after active perinatal care: extremely preterm infants study in Sweden (EXPRESS). *Acta Paediatr* 2010; 99: 978–992. doi: 10.1111/j.1651–2227.2010.01846.x

31. Thompson AM and Bizzarro MJ. Necrotizing enterocolitis in newborns: pathogenesis, prevention and management. *Drugs* 2008; 68: 1227–1238.

32. Doyle LW, Roberts G, Anderson PJ, et al. Outcomes at age 2 years of infants < 28 weeks' gestational age born in Victoria in 2005. *J Pediatr* 2010; 156: 49–53.e1. doi: 10.1016/j.jpeds.2009.07.013

33. Pierrat V, Marchand-Martin L, Arnaud C, et al. Neurodevelopmental outcome at 2 years for preterm children born at 22 to 34 weeks' gestation in France in 2011: EPIPAGE-2 cohort study. *BMJ* 2017; 358: j3448. doi: 10.1136/bmj.j3448

34. O'Connor DL, Gibbins S, Kiss A, et al. Effect of supplemental donor human milk compared with preterm formula on neurodevelopment of very low-birth-weight infants at 18 months: a randomized clinical trial. *JAMA* 2016; 316: 1897–905. doi: 10.1001/jama.2016.16144

35. Aarnoudse-Moens CS, Oosterlaan J, Duivenvoorden HJ, et al. Development of preschool and academic skills in children born very preterm. *J Pediatr* 2011; 158: 51–56.