

The EPIBEL Study: Outcomes to Discharge From Hospital for Extremely Preterm Infants in Belgium

Piet Vanhaesebrouck, MD, PhD*; Karel Allegaert, MD‡; Jean Bottu, MD§; Christian Debauche, MD||; Hugo Devlieger, MD, PhD‡; Martine Docx, MD¶; Anne François, MD#; Dominique Haumont, MD**;
Jacques Lombet, MD‡‡; Jacques Rigo, MD, PhD‡‡; Koenraad Smets, MD, PhD*;
Inge Vanherreweghe, MD**; Bart Van Overmeire, MD, PhD§§; and Patrick Van Reempts, MD, PhD§§,
for the EPIBEL Study Group

ABSTRACT. *Objective.* To determine mortality and morbidity at discharge from the hospital of a large population-based cohort of infants who were born at ≤ 26 weeks' gestation.

Methods. Perinatal data were collected on extremely preterm infants who were alive at the onset of labor and born between January 1, 1999, and December 31, 2000, in all 19 Belgian perinatal centers.

Results. A total of 525 infants were recorded. Life-supporting care was provided to 322 liveborn infants, 303 of whom were admitted for intensive care. The overall survival rate of liveborn infants was 54%. Of the infants who were alive at the age of 7 days, 82% survived to discharge. Vaginal delivery, shorter gestation, air leak, longer ventilator dependence, and higher initial oxygen need all were independently associated with death; gender, plurality, and surfactant therapy were not. Among the 175 survivors, 63% had 1 or more of the 3 major adverse outcome variables at the time of discharge (serious neuromorbidity, chronic lung disease at 36 weeks' postmenstrual age, or treated retinopathy of prematurity). The chance of survival free from serious neonatal morbidity at the time of hospital discharge was $<15\%$ (21 of 158) for the admitted infants with a gestation <26 weeks.

Conclusions. If for the time being prolongation of pregnancy is unsuccessful, then outcome perspectives should be discussed and treatment options including nonintervention explicitly be made available to parents of infants of <26 weeks' gestation within the limits of medical feasibility and appropriateness. *Pediatrics* 2004; 114:663–675; *extreme prematurity, mortality, morbidity, population-based cohort.*

ABBREVIATIONS. BW, birth weight; GA, gestational age; EPT, extremely preterm; NICU, neonatal intensive care unit; OR, odds

From the *Department of Neonatology, University Hospital Ghent, Ghent, Belgium; ‡Department of Neonatology, University Hospital Gasthuisberg, Leuven, Belgium; §Department of Neonatology of Luxembourg, Luxembourg; ||Department of Neonatology, Cliniques Universitaires St-Luc, Brussels, Belgium; ¶Department of Neonatology, Algemeen Ziekenhuis Middelheim, Antwerp, Belgium; #Department of Neonatology, Centre Hospitalier St Vincent-St Elisabeth, Rocourt, Belgium; **Department of Neonatology, Centre Hospitalier Universitaire St-Pierre, Brussels, Belgium; ‡‡Department of Neonatology, University Hospital Liège, Liège, Belgium; and §§Department of Neonatology, Antwerp University Hospital, Antwerp, Belgium.

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Address correspondence to Piet Vanhaesebrouck, MD, PhD, Department of Neonatology, University Hospital Ghent, De Pintelaan 185 B-9000 Ghent, Belgium. E-mail: piet.vanhaesebrouck@ugent.be

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ratio; CI, confidence interval; ROP, retinopathy of prematurity; CLD, chronic lung disease; CS, cesarean section; IQR, interquartile range; PDA, patent ductus arteriosus; $F_{I_{O_2}}$, fraction of inspired oxygen; CPAP, continuous positive airway pressure; NEC, necrotizing enterocolitis; ICH, intracranial hemorrhage; PVL, periventricular leukomalacia; IP, intestinal perforation; CNN, Canadian Neonatal Network; IPPV, intermittent positive pressure ventilation.

The critical decision to start active perinatal treatment for the fetus or neonate at the limit of viability is one of the most challenging dilemmas for obstetricians and pediatricians in contemporary perinatal practice. There is a trade off—changing over time—whereby survival of extremely preterm infants is achieved at the expense of disability in later childhood. Published rates of severe neurodevelopmental disability in the 1990s ranged from 17% to 45% and from 12% to 35% for infants who were born at 24 and 25 weeks of gestation, respectively.¹ Therefore, individualized decisions should be based not only on the infant's condition at birth but also on relevant outcome data and parental counseling. However, recent information regarding the outcome of infants who are born at extremely low gestational age is rare, and available reports are quickly dated. Moreover, most of the previously published outcome data on which health care professionals have to rely for advising parents are based on data for which birth weight (BW) rather than gestational age (GA) served as the basis of comparison, including a significant number of more mature small-for-gestational-age infants with a different outcome profile and thus not useful for prenatal decisions.² In addition, most previous reports were not population based, as they examined pooled data over several years of a small number of infants who were treated in different ways.^{3–7}

The aim of the present study was to examine GA-specific outcomes of a large population-based cohort of infants who were born at ≤ 26 weeks' gestation and cared for in all 19 perinatal centers of Belgium between January 1999 and December 2000 and to compare the results with those of other geographic GA-based cohorts available in the literature.^{8–15}

METHODS

Study Population and Data Abstraction

During a 2-year period (January 1, 1999, to December 31, 2000), data of all inborn births with a GA between 22 and 26 completed

weeks, ie, up to 26 weeks and 6 days' postmenstrual age, were collected in all perinatal centers in Belgium. During the same period, another 58 extremely preterm (EPT) infants with similar GA were admitted to the 19 centers after postnatal transfer within the first 24 hours. These outborn infants (16% of EPT infants admitted) are not included in additional analysis. Belgium has a population of ~10 million people and nearly 115 000 annual births.

GA was defined as the best obstetric estimate using the information on the record form. The expected date of delivery was based on the last menstrual period of the mother or on the results of an ultrasound performed before 20 weeks' gestation, whichever was available. If both were available and the expected date of delivery derived from ultrasound scans differed from that based on last menstrual period by >14 days, then the scan gestation was used.

A standardized data set of 82 items, including demographic information about the mother and a large number of perinatal data until death, was used. A list of all items collected is provided in the Appendix. A birth, especially at the margins of viability, may arbitrarily be reported as a live birth or later as a neonatal death or fetal death depending on which definition is chosen by the professionals present at birth. This will affect reporting of mortality and outcome around this gestational age.¹⁶ Therefore, data were collected on all pregnancies with at least 1 fetus \geq 22 weeks' GA showing signs of life at the onset of labor, resulting in a birth, death, or alive and whether admitted or not to the neonatal intensive care unit (NICU). Infants who were reported as dying "during delivery" eventually include also those fetuses or infants for which before birth it was unquestionably decided by the parents and the physician(s) involved (gynecologist and/or neonatologist) not to resuscitate the infant at birth.

Amnionitis was suspected when at least 2 of the following clinical signs and symptoms were present: foul-smelling vaginal discharge or amniotic fluid, uterine tenderness, maternal and/or fetal tachycardia, maternal fever, and leukocytosis. Definite diagnosis was based on histologic evidence and/or culture.

Full data collection was completed for all infants who were admitted to 1 of the 19 Belgian NICUs and for all infants who were still alive at the onset of labor in 14 of the 19 units. In the remaining 5 centers, data on nonadmitted neonates were not collected because of incomplete obstetric data or no access to the obstetric file.

Data Validation

Data were entered into a computer database (Filemaker Pro) by the local neonatal staff members and sent by electronic mailing to the coordinator (P.V.). Records with missing information were returned twice for correction or verification. Data were regarded as missing when after a second return and after a personal contact with the responsible neonatologist in each unit the investigators concluded that the data were unobtainable. Items that were ambiguous or improbable were discussed with the person who provided the data and errors were corrected. During analysis, outliers and any data that seemed unlikely were double-checked. The proportional geographic distribution of our study population was checked by the zip code of the mother's domicile (Spearman $r^2 = 0.67$; $P < .01$).

Statistical Data Analysis

All analyses were performed using SPSS 11.0.¹⁷ Group differences on continuous measures were examined by the Wilcoxon test (2 groups) and Kruskal-Wallis test (>2 groups). Differences on categorical measures were analyzed with χ^2 analyses or logistic

regression as appropriate. Outcomes were analyzed by 100-g BW intervals. GA was investigated both as a continuous variable and categorically as completed weeks. Logistic regressions were used to identify associations among perinatal independent risk factors and the major outcome variables (death before discharge and serious short-term morbidity in survivors). The results are expressed as adjusted odds ratios (ORs) and 95% confidence intervals (CIs). The significance level was not changed when multiple comparisons were performed. The level of statistical significance for all analyses was set at $P = .05$ using 2-tailed comparisons.

Outcomes

Clinicians were asked whether a formal decision had been made to provide intensive care, when this decision was discussed, and who had participated in the decision-making process. When the decision was not to provide intensive care, the reason for that particular decision was requested as listed in the Appendix. Institutional Review Board approval was obtained for each termination of pregnancy at the discretion of the local authorities. The primary cause of death was recorded using standard definitions listed in the Appendix. More than 1 cause of death could be recorded in the database. No data were collected on postmortem examination. Survival was calculated at 7 and 28 days after birth and at discharge. Cerebral ultrasound scans were reported locally and classified as to the presence and extent of hemorrhage, ventriculomegaly, and/or hydrocephaly and signs of leukomalacia as listed in the Appendix. Cases with retinopathy of prematurity (ROP) stage III and more (international classification¹⁸) and their treatment (oxygen, cryotherapy, or laser) were noted. Oxygen dependence and chronic lung disease (CLD) were recorded at 28 days postnatally and at 36 weeks of postmenstrual age. Special care (nutritional or respiratory) needed at discharge from the hospital was registered for all infants who were discharged alive. A discretionary estimate of the overall clinical neurologic state by clinical examination at discharge was recorded locally as normal, abnormal, suspicious, or unknown.

RESULTS

One hospital reported no live births between 22 and 26 weeks of gestation during the study period. In the other 18 hospitals, 525 births were recorded (Table 1). A total of 350 (66.6%) infants died. A total of 222 (42.3%) nonsurviving infants were not admitted to the NICU, 203 (91%) of whom died after the onset of labor or immediately at birth and 19 (9%) infants in the delivery room after active resuscitation. Of the 303 neonates who were admitted to the NICU, 42.2% died before discharge and 175 (57.8%) were still alive at discharge from hospital.

Of the 525 births, 212 (40%) originated from mothers who were booked at the local maternity hospital. A total of 273 (52%) came from mothers who were transferred prenatally or during labor to the perinatal center. From the 40 births that remained, the origin was not provided.

Stay in the NICU of the 303 admitted infants accounts for 19 684 hospital days, with a mean (\pm standard deviation) of 96 (\pm 24) days for the 175 survi-

TABLE 1. Survival to Discharge From the Hospital of Reported Live Births by Gestation

Gestation, wk	<i>n</i>	Died Intrapartum, <i>n</i> (%)	Born Alive, <i>n</i> (%)	Died in Delivery Room, <i>n</i> (%)	NICU Admitted, <i>n</i> (%)	Died in NICU, <i>n</i> (%)	Survival Rate of Live Births, <i>n/N</i> (%)
22	72	70 (97.2)	2 (2.8)	1 (50)	1 (1.4)	1 (50)	0/2 (0)
23	71	53 (74.6)	18 (25.4)	5 (27.8)	13 (18.3)	12 (66.7)	1/18 (5.5)
24	101	36 (35.6)	65 (64.3)	11 (16.9)	54 (53.5)	35 (53.9)	19/65 (29.2)
25	115	25 (21.7)	90 (78.3)	0 (0)	90 (78.3)	40 (44.5)	50/90 (55.5)
26	166	19 (11.4)	147 (88.6)	2 (1.3)	145 (87.4)	40 (27.2)	105/147 (71.5)
Total \leq 26	525	203 (38.7)	322 (61.3)	19 (5.9)	303 (57.7)	128 (39.8)	175/322 (54.3)

vors (17 421 days [89%]) and a mean (\pm standard deviation) of 14 (\pm 9) days for the 128 deceased infants (2263 days [11%]). Of the nonsurvivors, 40% (51 of 128) died before 48 hours, 69% (89 of 128) died before 7 days, and 89% (114 of 128) died before 28 days. The number of ventilator days was 4204 for the group of admitted infants, 68% (2841) of whom were used for the 175 surviving infants.

Maternal and Infant Characteristics

Of the 525 infants recorded, 154 (29%) were part of a multiple pregnancy: 125 from a twin pregnancy (45 complete sets), 25 from a triplet pregnancy (6 complete sets), and 4 from 1 complete set of a quadruplet. Twenty-one percent of the mothers were older than 35 years at the time of delivery. Assisted reproduction techniques were used in 18% of the infants admitted. Seventy percent of the mothers of admitted infants were primiparous and parity did not differ by plurality ($P = .45$).

In only 32% of all pregnancies, no complications were reported. Sixty-nine percent (210 of 303) of the infants who were admitted were born after threatening preterm labor. Placental abruption and cerclage were present in the history of 7% and 6%, respectively. Preterm premature rupture of membranes was present from the maternal history in 37% (195 of 525) of all infants recorded and in 22% (66 of 303) of the infants admitted. Chorioamnionitis was suspected in 33% (101 of 303) and proved in another 9% (28 of 303) of the infants admitted. Preeclamptic toxemia was present in the history of 8%. The rates of complications of pregnancy did not differ by gestational age. Tocolytics were used in 51% (267 of 525) of all infants recorded and in 77% (134 of 175) of the surviving infants. Data on the use of prenatal steroids are not available in this study.

Thirty-five percent of the cesarean sections (CSs) were multiple births. Forty-one percent (124 of 303)

of the NICU-admitted infants were born by CS. Forty percent (30 of 79) of the admitted singletons who were born by CS died. Secondary or urgent CS (91 of 124) was more common at higher gestation ($P < .0005$). Fifty-seven percent (83 of 145) of the admitted infants with a gestation of 26 weeks were born by CS. CS rate varied widely among centers, ranging from 14% to 75% (median \pm interquartile range [IQR]: 41 \pm 23%). There was a significant positive correlation between CS rate and survival rate for NICU-admitted infants ($r^2 = .49$, $P < .001$). CS rate was also positively correlated with the admission rate for live-born infants in 13 NICUs where informative data were available ($r^2 = .55$ for paired data [Wilcoxon signed rank test]; $P < .05$).

The proportion of liveborn infants who were admitted for intensive care rose with increasing gestation ($P < .0001$; Table 1). Thirty-five percent (107 of 303) of the admitted infants were part of a multiple pregnancy. Fifty-four percent (163 of 303) of the admissions were male. Seventeen percent (90 of 525) of all infants and 7% (20 of 303) of admitted infants were reported to have major congenital abnormalities. Thirteen of the latter group died before discharge. For the admitted infants, mean BW was 563, 660, 757, and 831 g at ≤ 23 , 24, 25, and 26 weeks of gestation, respectively.

Illnesses and Interventions

Clinical characteristics, interventions, and separate outcome variables are shown in Table 2. The proportion of intubated infants who had hyaline membrane disease and/or respiratory insufficiency and received surfactant did not increase with higher gestation (88%–93% of infants with a gestation of 24–26 weeks; $P = .45$). The number of ventilator days (median \pm IQR) of surviving infants of 24 weeks of gestation (37 \pm 27) was significantly higher compared with the duration of ventilation in infants of 25

TABLE 2. Clinical Characteristics, Interventions, and Separate Outcome Variables in NICU-Admitted Infants and Infants Discharged Alive

	NICU-Admitted Infants ($n = 303$), n or n/N (%)	Infants Discharged Alive ($n = 175$), n (%)
Major congenital malformation	20 (6.6)	7 (3.9)
Perinatal sepsis (<72 h of life)	45 (15)	19 (11)
Idiopathic respiratory distress syndrome	261 (86.1)	146 (83.4)
Endotracheal ventilation	283 (93.3)	154 (87.9)
Surfactant therapy	236 (77.8)	131 (74.8)
Air leak syndrome	66 (21.7)	28 (15.9)
CLD at postnatal age of 28 d	—	143 (82)
CLD at postmenstrual age of 36 wk	—	78 (44.5)
Postnatal steroid therapy	139 (45.8)	103 (58.8)
Erythropoietin treatment	—	31 (17.7)
ICH grade 1–2*	70/280 (24.9)	46 (26.2)
ICH grade 3–4	70/280 (24.9)	21 (11.9)
Cystic PVL	21 (6.9)	17 (9.7)
Treated hydrocephaly (permanent shunt)	—	12 (6.8)
Abnormal or suspect neurologic status at discharge	—	50 (28.5)
Surgical duct ligation	28 (9.2)	19 (10.8)
Treated ROP (laser or cryocoagulation)	—	35 (19.9)
Surgical NEC or IP	44 (14.5)	28 (15.9)
Abdominal surgery	53 (17.4)	40 (23)
Permanent renal insufficiency†	11 (3.6)	1 (.5)

* At least 1 ultrasound scan performed in 280 of the 303 admitted infants.

† Serum level of creatinine >1.5 mg/dL at time of discharge or death.

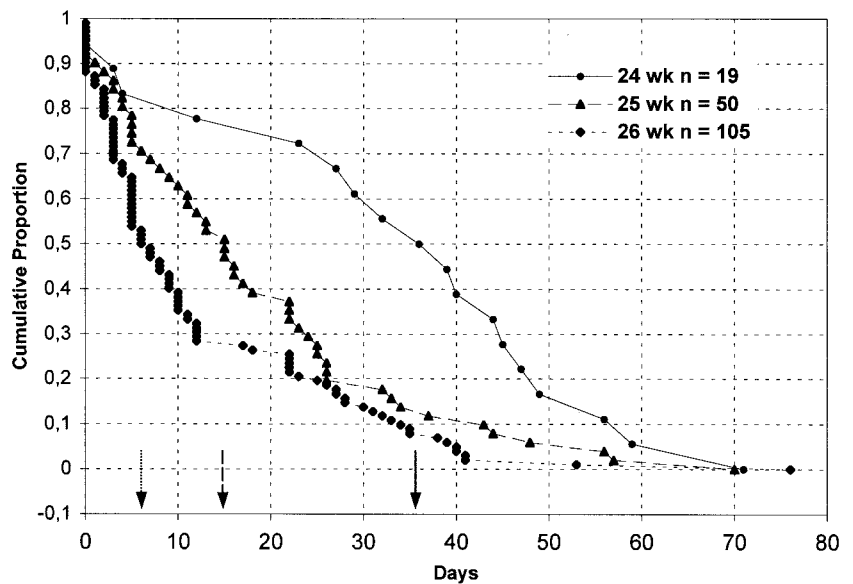


Fig 1. Cumulative proportion of endotracheal ventilatory support according to GA in infants who were discharged alive: arrows indicate the median duration of ventilatory support in surviving infants of 24, 25, and 26 weeks' gestation, respectively (24 vs 25 and 26 weeks' gestation + 25 vs 26 weeks' gestation: $P < .005$).

weeks (15 ± 21) and 26 weeks' gestation (6 ± 19 ; $P < .005$). Figure 1 illustrates the proportional decrease of ventilatory support in surviving infants.

Patent ductus arteriosus (PDA) was reported in 43% of infants who were admitted. Seventy-six percent were treated with a nonsteroidal anti-inflammatory drug (mainly indomethacin), 20 (15%) were treated with medication and ligation, and 8 (6%) were treated with ligation alone.

There was no difference in the postnatal use of steroids with increasing gestational age or in the age (median \pm IQR: 7 ± 14 days) at which steroids were started in infants of different maturity. Steroid therapy in survivors was given for a median (\pm IQR) duration of 19 (± 8) days.

Outcomes

Death Rates, Causes of Death, and Survival

A total of 222 (42.3%) patients were not admitted to the NICU, 203 (91%) of whom were reported to have died after the onset of labor and 19 (9%) in the delivery room after intentional resuscitation. Eighty-four intrapartum deaths were late terminations of pregnancy, mainly (68%) because of the detection of a major congenital or hereditary fetal anomaly. Of the 303 neonates who were admitted to the NICU, 128 died before discharge and 175 were discharged alive from the hospital. After 1 week, 71% of the admitted infants were still alive (Table 3). Rates of survival for NICU-admitted infants are 62% at 28

days of age and 58% at discharge. Expressed as a percentage of reported live births, survival to discharge at ≤ 23 weeks was 5% (1 of 20), at 24 weeks was 29%, at 25 weeks was 56%, and at 26 weeks was 72%. There is a significant intercenter variation in survival rate of admitted infants ranging from 32% to 93% with a median (\pm IQR) value of 52% (± 21). In the 14 units that included all intentionally resuscitated live births (288 infants), median (\pm IQR) survival rate (50% [± 17]) was significantly ($P < .01$) less than the rate (64% [± 32]) in the units that reported only on NICU-admitted infants (34 infants). Most deaths in the NICU occurred early in the postnatal course (Fig 2). The probability to survive until discharge from hospital for the 1-week survivors ranges from 20% at < 24 weeks to $\sim 90\%$ at 26 weeks of gestation. After 28 days of survival, the chance to be discharged alive is 83% for infants of 24 weeks up to 99% for infants of 26 weeks' gestation (χ^2 trend, $P < .0005$ for both groups).

The primary causes of death were mainly cerebral hemorrhage (28%), pulmonary insufficiency (27%), infection (16%), intractable hypotension or shock (13%), and congenital malformation (7%). A combination of respiratory insufficiency, cerebral hemorrhage, and/or infection accounted for 52% of the death rate of admitted infants.

Intensive care was sustained until death in 50% (64 of 128) of the nonsurviving infants who were admitted to the NICU. Life-supporting care was with-

TABLE 3. Survival to 7 and 28 Days for All Admissions and Actual Survival at Discharge for Survivors at Both Ages

GA	NICU Admissions, <i>n</i>	7 Days After Birth		28 Days After Birth		Discharged Alive From Hospital, % (<i>n</i>)
		% Alive at 7 Days (<i>n</i>)	% (\pm SE) of 7-Day Survivors Discharged From Hospital	% Alive at 28 Days (<i>n</i>)	% (\pm SE) of 28-Day Survivors Discharged From Hospital	
≤ 23	14	35.7 (5)	20 (± 12)	28.5 (4)	25 (± 10)	7.1 (1)
24	54	53.7 (29)	65.5 (± 6)	42.5 (23)	82.6 (± 6)	35.1 (19)
25	90	69.9 (63)	79.3 (± 4)	62.2 (56)	89.2 (± 5)	55.5 (50)
26	145	80.6 (117)	89.7 (± 2)	73.1 (106)	99.0 (± 3)	72.4 (105)
All	303	70.6 (214)	81.7 (± 5)	62.3 (189)	92.5 (± 4)	57.7 (175)

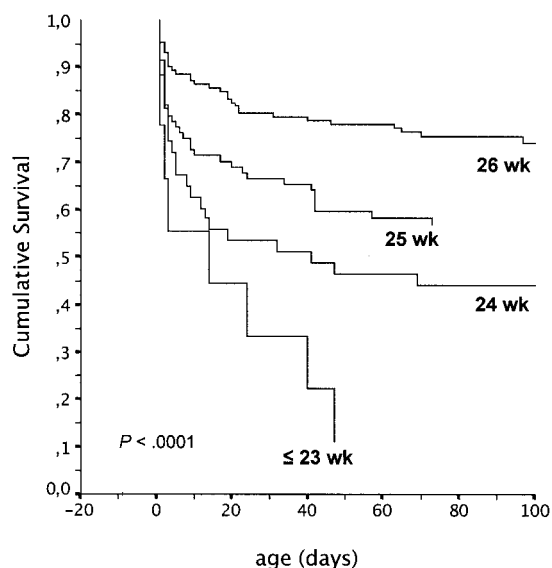


Fig 2. Survival distributions for GA ($P < .0001$) of all infants who were admitted to NICUs ($n = 145$ at 26 weeks, 90 at 25 weeks, 54 at 24 weeks, and 13 at ≤ 23 weeks).

drawn in 39% (50 of 128), mainly because of severe brain hemorrhage or intractable respiratory insufficiency. For the remaining 14 deaths, no answer was provided. The results of logistic regression analyses estimating the independent relationships between perinatal risk factors and death in the NICU-admitted infants are shown in Table 4. Vaginal delivery, lower gestation, air leak, number of days on a respirator, and higher minimal fraction of inspired oxygen (FiO_2) within the first 12 hours of life still remained significantly associated with death in the multivariate model. Death rate was not affected by the use of surfactant therapy, gender, and plurality.

Major Complications of Prematurity and Morbidity

The incidence of major complications of prematurity is shown in Table 2. The incidence of major cerebral hemorrhage (grade 3–4) was inversely correlated with GA in the group of admitted infants ($P < .0005$) but not in the survivors. CLD at 36 weeks'

postmenstrual age as the separate outcome variable was significantly associated with GA (OR: 0.52; 95% CI: 0.28–0.76; $P < .05$), surfactant therapy (OR: 2.43; 95% CI: 1.62–6.38; $P < .005$), and the number of days on the respirator (OR: 1.38; 95% CI: 1.28–1.48; $P < .001$) in a multivariate analysis using the same independent variables as in the previous analysis (intra-uterine transfer, medically assisted conception, premature rupture of membranes >24 hours, mode of delivery, gender, gestation, BW, multiple, air leak, endotracheal ventilation, days on the ventilator, surfactant, and minimal and maximal FiO_2 in first 12 hours). Seventeen infants (10%) were discharged on home oxygen therapy ($n = 12$) or other respiratory support (1 continuous positive airway pressure [CPAP], 1 positive pressure ventilation, and 3 tracheostomies).

Threshold retinopathy was diagnosed in 35 (19.9%) patients. Six additional patients were treated with oxygen for prethreshold disease in line with the STOP-ROP study.¹⁹ Laser therapy was used in 7 infants and cryotherapy in 28 other infants. BW and GA were significantly lower in threshold cases compared with survivors without ROP ($P < .004$ and $< .02$, respectively). Additional analysis of independent risk factors for threshold retinopathy in this cohort of EPT infants is reported by Allegaert et al.²⁰

Hearing deficit was diagnosed in 9 (5%) patients by brainstem evoked response audiometry and was suspected in another 16 (9%) infants. However, 23% (41 of 175) of all survivors either were not screened for audition or data were unknown.

An outcome scale to discharge was constructed (Fig 3). Short-term "intact" survival was pinned down as a survival without neurologic sequelae and without specific intensive care complications at the time of hospital discharge. Seventy-two percent, 56%, and 35% of the admitted infants with a gestational age of 26, 25, and 24 weeks, respectively, were discharged alive. After subtraction of all surviving infants with serious neurologic sequelae (see legend to Fig 3), the remaining groups represent 50%, 32%, and 19% of the infants admitted, respectively. Fi-

TABLE 4. Results of Univariate and Multivariate Analyses of Perinatal Risk Factors Associated With Death Before Discharge in 303 NICU-Admitted Infants

Variable (All Yes/No Unless Stated)	Univariate Analysis		Multivariate Analysis (Forward Stepwise)	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Intrauterine transfer	1.25 (0.70–2.22)	.444		
Medically assisted conception	0.92 (0.40–2.14)	.859		
PROM (>24 h)	0.69 (0.33–1.45)	.335		
CS vs vaginal delivery	0.40 (0.22–0.74)	.003	0.41 (0.23–0.74)	.003
Male gender	1.17 (0.65–2.10)	.588		
Gestation (per wk)	0.36 (0.25–0.50)	$< .0005$	0.35 (0.23–0.51)	$< .0005$
BW (per 100 g)	0.99 (0.99–1.00)	.49		
Multiple	1.10 (0.57–2.14)	.761		
Air leak syndrome (<48 h)	2.01 (1.02–3.98)	.044	2.13 (1.10–4.12)	.024
Endotracheal ventilation	1.24 (0.30–5.08)	.758		
Days on the ventilator	0.96 (0.94–0.98)	.001	0.96 (0.95–0.98)	.001
Surfactant therapy	1.43 (0.62–3.28)	.396		
Minimal $FiO_2 <12$ h	0.20 (0.10–0.40)	$< .0005$	0.18 (0.09–0.34)	$< .0005$
Maximal $FiO_2 <12$ h	0.59 (0.30–1.13)	.114		

PROM indicates premature rupture of membranes.

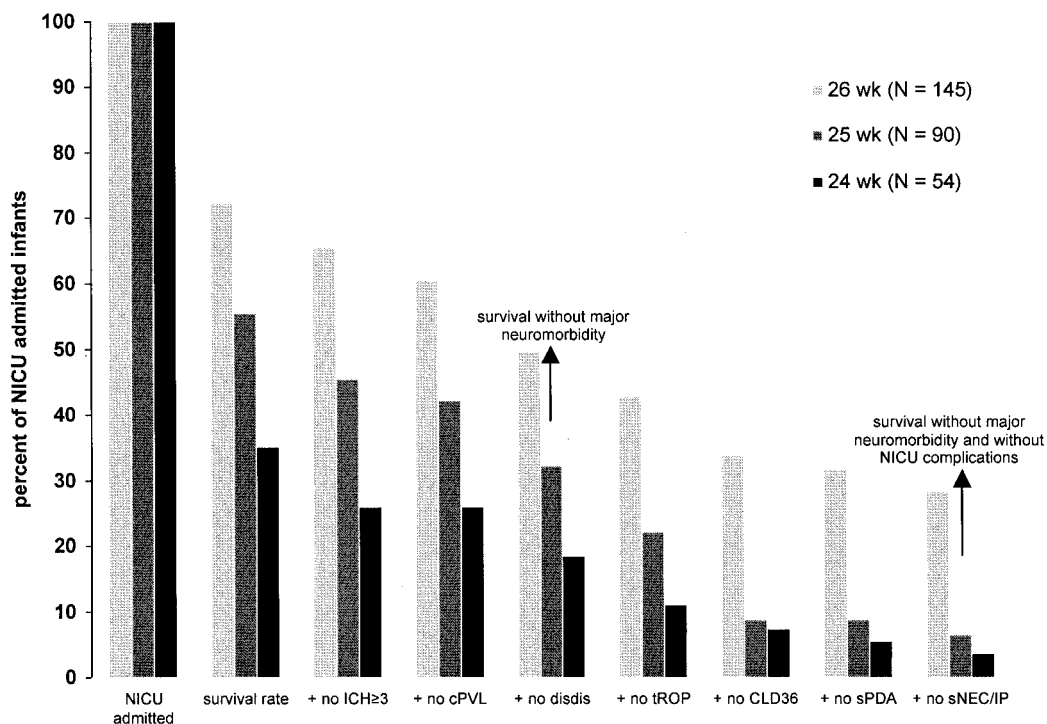


Fig 3. Cumulative short-term outcome scale at the time of discharge for admitted infants with a GA of 24 to 26 weeks. Severe neurologic sequelae are ICH grade 3 and 4 or shunted hydrocephaly (ICH ≥ 3), cystic PVL (cPVL), and discharge disability present or suspected (disdis). NICU-related complications are treated ROP (tROP), CLD at 36 weeks' postmenstrual age (CLD36), surgical ligation of PDA (sPDA), and surgical NEC (sNEC) or IP.

nally, after consecutive deduction of infants with specific NICU complications (sequentially minus treated ROP, CLD, duct ligation, and surgical necrotizing enterocolitis [NEC] or gut perforation) from the corresponding groups of surviving infants free of neurologic sequelae, 28% of the infants with a gestation of 26 weeks could be defined as short-term intact survivors. For the infants of 25 and 24 weeks' gestation, 7% and 4% are left as intact survivors, representing 6 of 90 and 2 of 54 admitted infants, respectively.

Short-term outcome of the 175 infants who were discharged alive in different NICUs is shown in Fig 4. Fifty-eight percent (± 20) is the median (\pm IQR) rate of survival without serious neuromorbidity. The median (\pm IQR) survival rate without any major neurologic sequelae and also free of NICU-related complications is 20% (± 21).

All 3 of the major adverse outcomes—serious neuromorbidity, CLD at 36 weeks' postmenstrual age, and treated ROP—occurred in 10 (6%) infants, and 2 of the 3 adversities occurred in 40 (23%) other infants (Fig 5). One of these 3 major adverse outcomes was observed in another 61 (20%) infants who were discharged from the hospital. The occurrence of >1 of these major adverse outcome variables was significantly higher in the group of admitted infants with a gestation of 24 to 25 weeks compared with the admitted group with a gestational age of 26 weeks (χ^2 , $P = .014$). Of the 35 surviving infants with threshold ROP, 74% (26 of 35) had at least 1 major comorbidity. Surgical duct ligation was an isolated specific event in 4 surviving infants, and laparotomy for NEC or bowel perforation was a single complication for 9

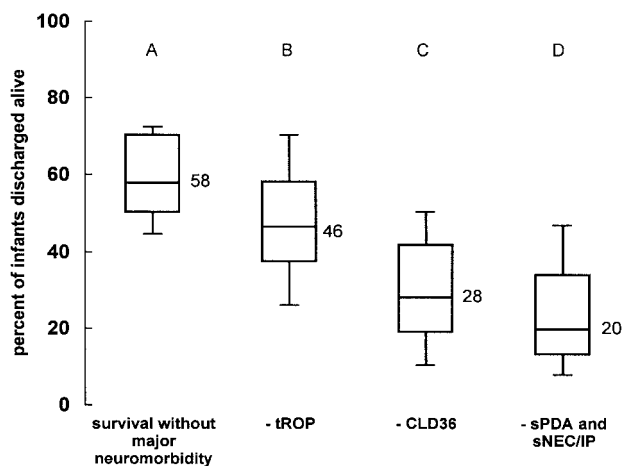


Fig 4. Short-term outcome of the 175 infants who were discharged alive: box-and-whisker plots (median \pm IQR) for survival without major neuromorbidity (58% \pm 20; A), survival without severe neurologic sequelae and without tROP (46% \pm 21; B), survival without neuromorbidity, tROP, and CLD (28% \pm 23; C), and survival without neuromorbidity, tROP, CLD, and sPDA or NEC/IP (20% \pm 21; D).

other infants. Of the 19 surviving infants with a surgical duct closure, 74% were oxygen dependent at 36 weeks' postmenstrual age.

Logistic regression analysis was performed using the same independent variables as in the previous analysis with, at this time, serious neuromorbidity (intracranial hemorrhage [ICH] grade 3 or 4, cystic periventricular leukomalacia [PVL], and discharge disability present or suspect) and typical NICU-related complications (treated ROP, CLD at 36 weeks'

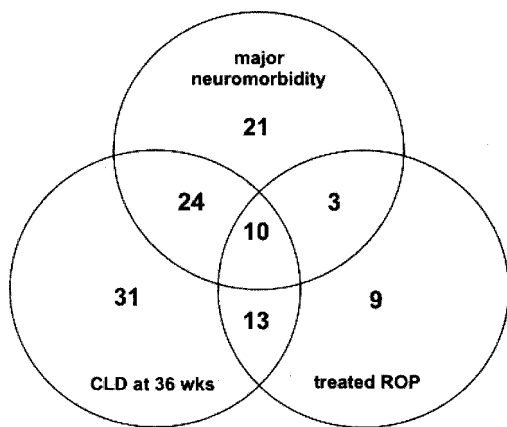


Fig 5. Diagram showing the incidence of multiple major morbidity in all survivors ($n = 175$) to discharge from the hospital: major neuromorbidity (ICH \geq grade 3, cPVL, hydrocephaly treated by permanent shunt, and discharge disability present or suspected), CLD at 36 weeks, and treated ROP.

postmenstrual age, PDA ligation, and surgical NEC/intestinal perforation [IP]) as separate outcome variables (Table 5). Multivariate analysis showed a significant association of the duration of endotracheal ventilation with serious neuromorbidity in the group of surviving EPT infants. In the multivariate model, 2 variables—days on the respirator and maximal FiO_2 during first 12 hours—were significantly associated with the occurrence of specific NICU-related complications.

Growth Rate

BW and body weight at the time of discharge from the hospital were plotted on a population-specific growth chart²¹ and on Lubchenco's fetal growth curve²² for 153 of the 175 surviving infants for whom both weight data and time intervals were available (Fig 6). Postnatal weight gain expressed as g/kg/day (median \pm IQR) during the hospital stay in 96 survivors of 26 weeks' gestation (10.7 ± 2.6) was not significantly different from that in 57 surviving infants with a gestation of 24 to 25 weeks (10.3 ± 3 ; $P = .85$). Sixteen percent (24 of 153) of these survivors

were small for gestational age (BW <10th centile). Body weight at discharge was <10th centile (65 of 120) of the population-specific intrauterine growth curve and, for survivors discharged at a postmenstrual age >42 weeks, <10th centile (25 of 33) of the gender-specific postnatal Euro-Growth chart.²³ Overall growth restriction at the time of discharge was present in 59% (90 of 153) of the infants.

DISCUSSION

The overall survival rate of a population-based cohort of liveborn infants who were ≤ 26 weeks' GA was 54%. Mortality was high in the first few days at all GAs but most impressive in infants below 24 weeks' gestation. GA-specific survival curves of this geographic cohort should help physicians in their discussions with parents on survival probabilities and policy makers in planning resource allocation (Fig 2, Table 3). Thirty-three percent of the survivors showed serious neuromorbidity, and only 37% were free of major neonatal morbidity (major neuromorbidity, CLD at 36 weeks of postmenstrual age, and treated ROP).

Many studies limit and base outcome data of EPT infants on BW, confounding the effects of extremely preterm birth with those of intrauterine growth restriction. Moreover, many previous studies—besides not being population-based—omitted (or did not include) termination of pregnancy, fetal deaths, or delivery room deaths, thus exaggerating survival by 100% and 56% at 23 and 24 weeks, respectively, as stated by Evans and Levene.²⁴ This type of selection bias could lead to inaccurate counseling of pregnant women as to the survival potential of a possible viable or nonviable fetus. In the present study, 13 of the 18 units reported not only on NICU admissions but also on all live births, intrapartum deaths, and terminations of pregnancy. A significant difference in survival rate was calculated depending on the denominator used.

Chan et al¹¹ emphasized the impact of EPT infants on resource use consuming 11% of total NICU patient days and 20% of mechanical ventilator use. Our

TABLE 5. Results of Univariate and Multivariate Analyses of Prenatal and Postnatal Risk Factors Associated With Serious Neuromorbidity and Specific NICU-Related Complications as Separate Outcomes (Defined in Text) in the 175 Surviving EPT Infants

Independent Risk Factor (All Yes/No Unless Stated)	Outcome Serious Neuromorbidity				Outcome NICU-Specific Complications			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Intrauterine transfer	0.99 (0.48–2.02)	.98			0.78 (0.34–1.80)	.566		
Medically assisted conception	1.95 (0.66–5.74)	.22			2.98 (0.75–11.13)	.122		
PROM (>24 h)	0.46 (0.18–1.14)	.09			0.83 (0.30–2.30)	.731		
CS vs vaginal delivery	0.56 (0.25–1.28)	.17			0.42 (0.17–1.06)	.067		
Male gender	1.08 (0.52–2.22)	.83			1.22 (0.53–2.80)	.636		
Gestation (per wk)	0.91 (0.61–1.35)	.66			0.97 (0.61–1.53)	.905		
BW (per 100 g)	1.00 (0.99–1.00)	.24			0.99 (0.99–1.00)	.050		
Multiple	0.63 (0.27–1.47)	.29			0.53 (0.20–1.40)	.201		
Air leak syndrome	1.20 (0.46–3.11)	.70			5.32 (1.06–26.71)	.042		
Endotracheal ventilation	0.67 (0.14–3.14)	.61			1.68 (0.39–7.23)	.485		
Days on the ventilator	1.03 (1.00–1.05)	.01	1.03 (1.01–1.05)	.002	1.07 (1.02–1.13)	.007	1.07 (1.02–1.12)	.002
Surfactant therapy	1.76 (0.61–5.05)	.28			0.66 (0.21–2.07)	.481		
Minimal FiO_2 <12 h	2.43 (0.73–8.05)	.14			2.32 (0.56–9.62)	.244		
Maximal FiO_2 <12 h	0.53 (0.24–1.16)	.11			0.32 (0.13–0.76)	.010	0.37 (0.17–0.79)	.011

PROM indicates premature rupture of membranes.

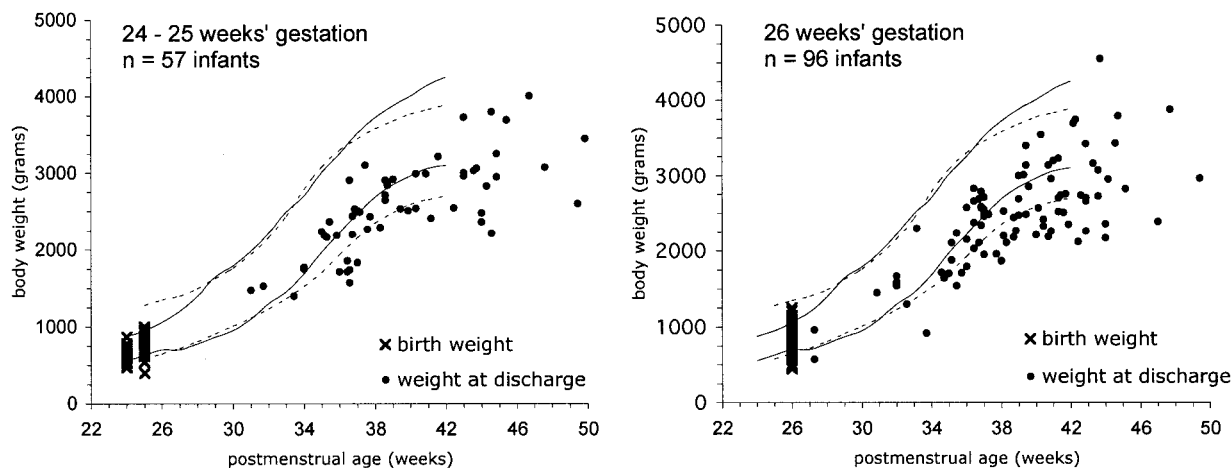


Fig 6. BW and body weight at discharge from the hospital for surviving infants of 26 weeks' gestation (right-sided diagram) and 24 to 25 weeks (left-sided diagram) plotted on a population-specific growth chart (p_{10} and p_{90} intrauterine growth standards for Belgian infants with permission from Devlieger et al²¹ and for comparison on Lubchenco's fetal growth curve²² [stippled lines for 10th and 90th centiles]).

EPT infants represent only 2% of all NICU admissions in Belgium, but they occupy ~10% of the 332 NICU beds available. During the study period, 16% of all mechanical ventilator days in Belgian NICUs are "consumed" by infants with a GA ≤ 26 weeks (data provided by the Belgian Society of Neonatologists and Pediatric Intensivists). However, in NICUs, most expenditure, even among the smallest infants, is allocated to the surviving infants, in contrast to adult medical intensive care for the oldest patients at greatest risk, where more than half of the intensive care bed-days are spent on those who will not survive.²⁵

Thirty-five percent of the 303 infants who were admitted were part of a multiple pregnancy. In other population-based studies (United Kingdom, Canada, New Zealand, France), this number ranged from 23% to 29%.^{8,11-13} This strong association of extreme prematurity with multiple-gestation pregnancies in different surveys suggests a probable link with the use of assisted reproduction techniques. However, multiple gestation in these EPT infants was not associated with outcome variables (survival and short-term major neuromorbidity or NICU-specific complications). This is in accordance with the results of a large single-center study in which neonatal outcomes (survival, ICH, CLD, PDA, NEC, and ROP) of EPT infants from multiple gestations were not significantly different from those of singletons.²⁶ A high rate of obstetric complications was found particularly for preterm premature rupture of membranes and amnionitis similar to the findings in the EPICure study.⁸ Tocolytics were used liberally (>70%) in the patients who were admitted, in contrast with only 22% of the mothers who were admitted in the EPICure cohort.⁸ Contrary to the UK-Ireland cohort, we could not find any association between the use of tocolytics and survival, incidence of brain ultrasound abnormalities, or CLD. Because the prevalence of tocolytics' use is so obviously different in these 2 study groups, other yet unknown variables may have been involved to explain these divergent results.

CS was associated with higher survival in our study group of admitted patients but not with short-term outcomes (serious neuromorbidity and specific NICU complications). In contrast, CS was not associated with higher survival in the EPICure cohort.⁸ In the Canadian geographic cohort of infants from 22 to 25 weeks' gestation, the CS rate was 33% overall and 47% for infants of 25 weeks' GA.¹¹ The Canadian NICU Network found that abdominal delivery in EPT infants was associated with less severe ICH.²⁷ In a recent large, single-hospital study on 278 deliveries at 22 to 25 weeks, CS was associated with increased in-hospital mortality.⁴ In a prospective observational multicenter study on 713 singleton births, Bottoms et al²⁸ reported that the willingness to perform a CS between 22 and 25 weeks' gestation for fetal indications was linked to an increased chance of survival with serious morbidity. We showed a higher rate of survival in admitted infants after CS and a correlation of the CS rate with the admission rate of liveborn EPT infants. This may either mean the willingness of the obstetrician to perform a CS with an ensuing active commitment of the neonatologist to—at least temporarily—save the life of the EPT infant or that the wishes of the parents and an active treatment attitude of the neonatologist—whether based on supposed better outcomes locally or not—induce less reluctance on the side of the obstetrician to perform a CS for the previsible infant. The data of this study do not permit any additional conclusion on this subject. However, it illustrates that the approach to obstetric management significantly influences the outcome of EPT infants and that in these cases, patients and physicians should be aware of the impact of that approach. For the time being, systematic review of controlled trials up to 2003 shows that a policy of elective CS delivery in the very small infant undoubtedly increases the perioperative risks of maternal morbidity, but it remains unclear whether these are offset by benefits for the infant. Recruitment difficulties will probably hamper a clear answer to this question in the near future.²⁹

As in the UK-Ireland cohort, we did find an im-

portant number of admitted infants (25 [8%]) with a BW below the recommended lower limit of 500 g set by the World Health Organization for routine collection of perinatal data.⁸ Nine (36%) of these 25 infants survived to be discharged from hospital.

The association of early clinical condition variables (early air leak and a high minimal F_{iO_2} in the first 12 hours) with death, as well as with serious neuromorbidity and specific complications, suggests that these markers of risk can at least partially help in early postnatal informed decision making, ie, of considering withdrawal of intensive care. Lower gestation is significantly associated with death but not with major neuromorbidity or with characteristic NICU complications in their most severe form of presentation. In 39% (50 of 128) of the admitted infants who did not survive, withdrawal of curative intensive care was planned. Differences in this end-of-life decision policy may partially explain the large variation in survival rate between units. This may also be the case as seen in the large interhospital variation in delivery room survival rates (range: 41%–82%) as demonstrated by Chan et al¹¹ and in the present study (range: 33%–75%). Of 106 informative cases (data not shown) in 12 different NICUs, we could also find large differences in ethical practice with regard to the decisions of withholding curative care in the delivery room. In some units, a well-established GA of ≤ 24 completed weeks was an elective criterion for non-resuscitation. In other units, this decision was never or seldom taken. Parental refusal to initiate full resuscitation was exceptional (2 cases) and reported in only 1 NICU. From our data, it seems that parenchymal cerebral bleeding contributed largely to the number of infants who died as a result of withdrawal of intensive care, thereby significantly reducing the numbers of survivors with major ICHs from 25% in the patients who were admitted to 12% in survivors. This was also clearly demonstrated in the EPICure study.⁸

In the Canadian cohort¹¹ and the present study, almost two thirds of the surviving infants received postnatal steroids for prevention of CLD. Seventy-two percent of the EPICure cohort survivors received steroids postnatally.⁸ It is important to realize that all infants in these studies were born before the new millennium. It is since then almost clear that the risks of this treatment in currently used doses outweigh the benefits.³⁰

Although on physiologic grounds the absence of any beneficial effect of surfactant treatment before 26 weeks might be presumed, the administration of surfactant has been estimated to benefit some EPT infants.^{4,31,32} Eighty-four percent of admitted infants in the EPICure study⁸ and 78% in ours received surfactant, but death rates were not affected by the use of surfactant. This is in contrast to the retrospective study by Ferrera et al³² reporting an improvement in survival from 55% to 73% for the infants (23–26 weeks) who were treated compared with those who were not treated with surfactant. A large retrospective cohort study of 891 liveborn infants of 23 to 26 weeks' gestation (421 presurfactant and 470 postsurfactant) in Canada showed no secular change in overall mortality since the introduction of rescue therapy with natural surfactant.³³ In both the EPICure and our EPIBEL study, the use of surfactant was associated with a higher frequency of CLD at 40 and 36 weeks' postmenstrual age, respectively. The question of routinely adopting a policy of treating all infants of 23 to 26 weeks' gestation with surfactant undoubtedly requires additional exploration.

Population-based surveys on infants who are born before 28 weeks' gestation are scarce worldwide. Table 6 is an overview of recently published GA-specific population-based surveys of EPT infants who were born since 1990. The survival rates of our population-based cohort are within the range of other European and Australian surveys. However, the survival rates of liveborn EPT infants in a large geographic survey of 17 Canadian NICUs were remarkably higher than the average figures from European and Australian data.¹¹ These data should be interpreted cautiously as they almost exclusively come from large tertiary-level regional referral centers recruiting significant numbers (mean of 30 infants ≤ 25 weeks' gestation per year) of EPT infants out of 22 million people. In our survey, only 6 of 19 NICUs report on >10 admissions per year of infants with a GA ≤ 26 weeks and 5 units on >5 survivors yearly, the highest number in a single unit being 20. These figures emphasize the need for aggregated data to provide reliable information for caregivers and parents to make informed treatment decisions with the best available information. A recent review of the world literature by Hack and Fanaroff revealed that in the 1990s, survival ranged from 2% to 35% at 23 weeks' gestation. At 24 weeks' gestation,

TABLE 6. Rates of Survival for EPT Liveborn Infants (23–25 Weeks) in Population-Based Surveys for Infants Born After 1990

Reference	Region	Year of Birth	Rate of Survival	No. of Liveborn Infants (GA Range)	23 wk, %	24 wk, %	25 wk, %
1	World review	1990–1999			2–35	17–58	35–85
12	New Zealand	1998–1999	At discharge	167 (20–26)	9	72 (24–25 wk)	
11	Canada	1996–1997	At discharge	949	17	44	68
13	France	1997	At discharge	207	0	31	50
9	Wales	1993–1994	At 1 y		4	26	58
10	N. England	1991–1994	At 1 y		2	17	35
8	UK-Ireland	1995	At discharge	1289 (21–25)	11	26	44
14	Australia	1991–1992	At 2 y	401 (23–27)	10	33	58
15	Australia	1992–1993	At 1 y	614 (20–27)	2	31	49
Present study	Belgium*	1999–2000	At discharge	322 (22–26)	5	29	55

* Data on nonadmitted infants were not collected in 5 units.

the range was 17% to 58%, and at 25 weeks' gestation, the range was 35% to 85%.¹

Most of the typical complications of prematurity (ICH, PVL, hydrocephalus, ROP, and CLD) are well-known antecedents of later disability in childhood. Because of the known variability in interpretation for the less severe cases in multicenter studies, we analyzed only the most severe cases reported. Among the 54% (175 of 322) of this study population of liveborn infants (GA \leq 26 weeks) who were discharged from the hospital, 63% (111 of 175) had 1 or more of the 3 major adverse outcome variables (serious neuromorbidity, CLD at 36 weeks' postmenstrual age, or treated ROP). The present study examined infants who were 1 week more mature (\leq 26 weeks) versus $<$ 26 weeks for the EPICure⁸ and Canadian Neonatal Network (CNN) studies.¹¹ Thus, 62% of the surviving infants in the EPICure study had 1 of the 3 major adverse outcome variables. Likewise, severe ROP is similar in rate (14.6%, 17%, and 19.9% for EPICure, CNN, and EPIBEL, respectively) but with 1 week of difference. Notwithstanding the advanced maturity in the EPIBEL study, the figures for CLD at 36 weeks' postmenstrual age seem to show a disproportionately higher rate in the EPICure data: 73% (231 of 314) compared with the 51% (242 of 475) in CNN and 44% (78 of 175) in EPIBEL data. Also, diverging criteria for the lower limit of arterial oxygen saturation used in maintaining chronic oxygen therapy may have interfered with the incidence of CLD observed. In the EPICure group, 31% of the infants were discharged from the hospital with oxygen therapy, contrasting with only 7% (12 of 175) in the EPIBEL infants. Severe cerebral ultrasound abnormalities were obvious in a similar number of infants from the discharged EPICure cohort, EPIBEL, and CNN survey (17%, 17%, and 19%, respectively).

The overall neonatal morbidity rate is very high in EPT infants (Fig 7). In the large Canadian 1996–1997 cohort, 63% (475 of 754) of the NICU-admitted EPT infants survived, but only 23% (109 of 475) of the survivors and 14% of the infants who were admitted

did so without major morbidity defined as the presence of CLD, NEC, \geq grade 3 intraventricular hemorrhage, or \geq grade 3 ROP.¹¹ Morbidity-free survival increased from 11% of survivors at \leq 23 weeks to 29% at 25 weeks. In the New Zealand cohort of high-risk infants who were born in 1998–1999, the survival rate for NICU-admitted infants of $<$ 26 weeks' gestation was 68% (114 of 167). Thirty-eight percent (43 of 114) of the survivors and 26% of the infants who were admitted were discharged without major neonatal morbidity. Morbidity-free survival was 25% (2 of 8) for the survivors of $<$ 24 weeks and 39% (41 of 106) for infants of 24 and 25 weeks' gestation.¹² Major morbidity at discharge was defined here as the presence of CLD, definite NEC, \geq grade 3 intraventricular hemorrhage, PVL, porencephalic cyst, hydrocephalus, or \geq grade 3 ROP. The survival rate was 39% (314 of 811) in the EPICure cohort of NICU-admitted infants, and the comparable rate of survival without major morbidity was 38% (119 of 314) of the survivors and 15% of the NICU-admitted infants.⁸ In the EPIBEL cohort, the corresponding figures for infants of $<$ 26 weeks' gestation are a survival rate of 44% (70 of 158) and free of comparable serious neonatal morbidity in 30% of the survivors and 13% (21 of 158) of the admitted group. Considering survival free of serious neonatal morbidity, the results of most of these geographic cohorts suggest a potential higher risk of neonatal morbidity with improved survival in EPT infants. A rise in neonatal morbidity and later disability in childhood with improved survival leading to no significant change in the number of normal survivors (16% vs 14%) as the proportion of the original population was observed recently as an alarming development comparing the outcome of 192 EPT infants in a large single-center study during an 11-year period.³⁴ Near universal initiation of intensive care in a population-based cohort of EPT infants (23–26 weeks' gestation) who were born during the mid-1980s in central New Jersey ($n = 146$), compared with selective initiation of intensive care for a comparable group of EPT infants in the Netherlands ($n = 141$),

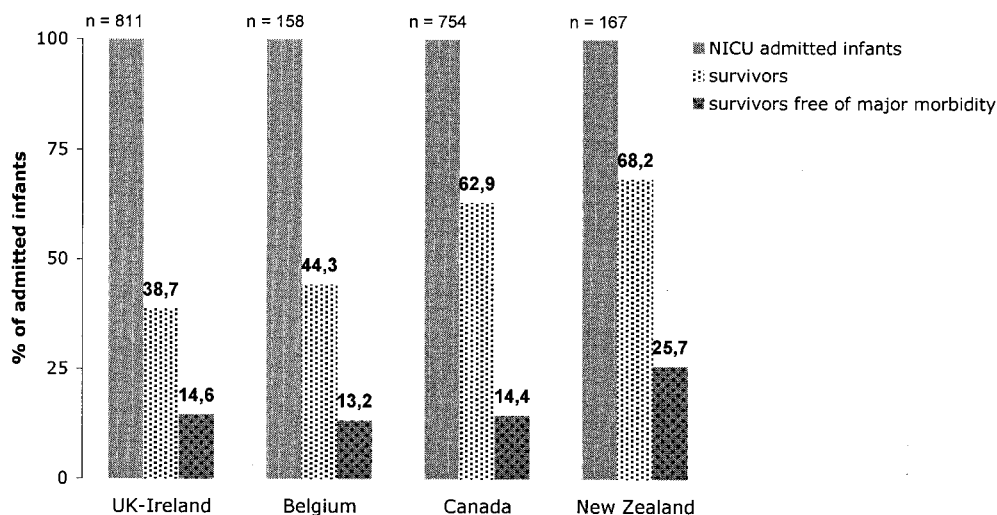


Fig 7. Overall survival rate and survival rate free of major neonatal morbidity at discharge in NICU-admitted infants of $<$ 26 weeks' gestation in recently published population-based cohorts of EPT infants (Canada,¹¹ New Zealand,¹² and UK-Ireland⁸).

was associated with a doubling of survival (46% vs 22%) but a 4 times higher prevalence of disabling cerebral palsy among survivors (17.2% vs 3.4%).³⁵ Although markers of major neonatal morbidity are well-known antecedents of later disability in childhood, in-hospital morbidity is not equivalent to childhood disability. In current published literature, rates of severe disability vary between 17% and 45% for those who are born at 24 weeks of gestation and between 12% and 35% at 25 weeks.¹ Disability rate for the EPICure infants at the median age of 30 months corrected for GA was 51% (159 of 314), and 23% had severe disability.³⁶ However, follow-up at these early ages may not discern all impairments as in middle to late childhood more disability may become apparent.³⁷ Neonatal health status is an important variable indicating neurocognitive and school performance outcomes in low BW infants.³⁷ The significance of these findings for the future health and development of the children in our study will become apparent only after additional follow-up in progress.

Postnatal growth during the NICU stay of this cohort of EPT infants did not achieve even the lower end of what is reported for intrauterine weight gain, which is 14 to 20 g/kg/day.³⁸ Almost every infant showed a major shift to the right on the reference chart, and nearly two thirds of the survivors developed moderate to severe malnutrition during the hospital stay (Fig 6). Recent studies suggest that cumulative nutritional deficit during the early weeks of life is the major determinant of postnatal growth deficit³⁹ and that early aggressive nutrition including high protein and energy supplies from the first day of life allowed improvement in postnatal growth in EPT infants.⁴⁰ Nevertheless, appropriately designed interventional studies are still needed to evaluate the safety and the medium- and long-term benefit of such a nutritional policy.

No institution in Belgium has a large experience with survival and long-term outcome data for EPT infants, compared with neonatal referral centers in Australia and North America. Survival free of major morbidity in this vulnerable patient group is so poor that it can be argued that additional centralization would enable more experience to be gained in a restricted number of tertiary-level NICUs. Also, fear remains as higher survival rates for infants with borderline viability may be achieved only at the expense of disability in childhood. Whether quality of life could be improved remains to be proven. Outborn EPT infants have poorer outcomes than inborn infants, even after adjustment for differences in baseline population risks and admission illness severity.^{11,41} As in Belgium still 16% of these EPT infants are transferred postnatally, a more consistent referral policy could be one more possible improvement in perinatal care. Consistently and undoubtedly clear from all population-based cohorts and also single-center studies of EPT infants is that outcome improves markedly between 24 and 26 weeks. Therefore, all efforts should by priority be focused on prolonging pregnancy. New potent tocolytics with fewer side effects for mother and fetus, such as oxy-

tocin receptor antagonists, seem to be promising in delaying advancement of EPT labor.⁴² From the data on survival and neonatal morbidity of this and other cohort studies of EPT fetuses and infants, for the time being, it can be concluded that if prolongation is unsuccessful, then outcome perspectives should be discussed and treatment options including nonintervention explicitly be made available to parents of infants of <26 weeks' gestation within the limits of medical feasibility and appropriateness.^{43,44} However, as there seems to be a continuing trend toward improved outcomes, longitudinal studies will remain important for monitoring continuing changes in EPT outcomes.¹¹

APPENDIX

The following are data items that are included in the standardized form for all inborn infants who are admitted to a NICU. Items that require an answer yes or no are indicated y/n, and ranges of options are given in parentheses. At the end of the record, there is an opportunity for the information to be amplified with free text.

For all 525 records: perinatal center number; year of admission; date of birth; date of admission; mother's birthday; zip code of mother's home; origin (inborn, inborn-antenatal transfer, inborn-intrauterine transfer); conception (spontaneous, insemination, hormonal induction, in vitro fertilization, unknown); number of previous pregnancies (G); number of live births (P); complications of pregnancy (none, cerclage, abruptio placentae, diabetes, hospitalization during third trimester, hypertension after week 20, threatening preterm labor, placenta previa, preeclampsia, other major disease, unknown); tocolysis (none, inapplicable, betamimetics, indomethacin, other nonsteroidal anti-inflammatory drugs, MgSO₄, antibiotics, unknown); interval rupture of membranes (peripartum, uncertain, <12 hours, 12-24 hours, 24 hours-7 days, 7-14 days, >14 days, unknown); hydramnion (normal, anhydramnion, oligohydramnion, polyhydramnion, unknown); amnionitis (none, yes, suspect, unknown); modus of delivery (spontaneous vaginal, vaginal breech, elective CS, urgent or secondary CS, instrumental delivery, CS after instrumental traction, other); gender (boy, girl, undetermined); GA (completed weeks); Apgar scores at 1 and 5 minutes, respectively; resuscitation (none, bag and mask, endotracheal ventilation, perfusion and/or drugs, cardiac massage, no data); BW (grams); multiple pregnancy (no, 1 of twins, 2 of twins, etc, unknown); congenital anomalies (n/y); infection (none, fetal, perinatal [<72 hours of life], unknown); why intensive care was not provided (inapplicable; because GA <23 weeks; because GA was 23 or 24 weeks; refusal of parents; decided by parents and gynecologist; decided by parents and neonatologist; decided by parents, gynecologist, and neonatologist; other [please fill in comments]); died intrapartum; unknown); acquired gastrointestinal disorders (none, NEC [Bell criteria stage ≥II], gastrointestinal perforation[s], gastrointestinal hemorrhage, prolonged paralytic ileus, meconium disease, inguinal hernia[s], other); conjugated hyperbiliru-

binemia (none, surgical condition, parenteral nutrition associated, infection, error of metabolism, idiopathic or nonclassified, other); days of total parenteral nutrition; start of enteral feeding; feeding type (mother's milk, formula, mixed); abdominal surgery (none, intestinal surgery, urogenital surgery, other); intestinal surgery (intestinal surgery for NEC, intestinal surgery for gut perforation, emergency surgery for inguinal hernia, elective surgery for inguinal hernia, other); intestinal sequelae (none, yes, dead, unknown); type of sequelae (inapplicable, stoma during hospital stay, stoma at discharge, [semi]elementary nutrition at discharge, other); weight at discharge/death; primary respiratory disorder(s) (none, hyaline membrane disease, acquired pneumonia, congenital pneumonia, pulmonary hemorrhage, persistent pulmonary hypertension, lung edema, chronic amnion leak syndrome, other); air leak (none, unilateral pneumothorax, bilateral pneumothorax, interstitial emphysema, pneumomediastinum, pneumopericardium, gaseous embolism, other); endotracheal ventilation (none, yes, inapplicable, unknown); days of endotracheal ventilation; surfactant (y/n; prophylactically or rescue?); minimal (inapplicable, $\leq 40\%$, $41\% - 60\%$, $61\% - 90\%$, $91\% - 100\%$, unknown) and maximal (inapplicable, $\leq 40\%$, $41\% - 80\%$, $81\% - 90\%$, $91\% - 100\%$, unknown) F_{iO_2} during first 12 hours of life; number of days on nasal CPAP; postnatal day nasal CPAP was arrested; last day of oxygen therapy; CLD at 28 days postnatally (none, type I, type II, inapplicable) and type of treatment provided (inapplicable, ambient air, $F_{iO_2} \leq 40\%$, $F_{iO_2} > 40\%$, CPAP, intermittent positive pressure ventilation [IPPV]); CLD at 36 weeks of postmenstrual age (none, type I, type II, inapplicable) and type of treatment provided (inapplicable, ambient air, $F_{iO_2} \leq 40\%$, $F_{iO_2} > 40\%$, CPAP, IPPV); systemic steroid therapy (none, yes, inapplicable, unknown); postnatal age (days) at the onset of steroid treatment, number of steroid therapy days; persistent ductus arteriosus (none, fluid restriction/diuretics, indomethacin, other nonsteroidal anti-inflammatory drugs, surgery); use of inotropics (none; prophylactic dopamine $\leq 5 \mu\text{g}/\text{kg}/\text{min}$; dopamine therapeutic dose $> 5 \mu\text{g}/\text{kg}/\text{min}$; therapeutic dose of dopamine and dobutamine; therapeutic dose of dopamine, dobutamine, and other; other; unknown); number of transfusions; erythropoietin therapy (none, yes, no data); thoracic surgery (none, cardiac surgery, pulmonary surgery, esophageal surgery, other); cardiac surgery (ductus arteriosus ligation, palliative shunt, corrective cardiac surgery, other); renal insufficiency (none, transitory, prolonged (at postnatal age > 7 days), permanent (= at discharge); biochemical disorders (none, persistent or recurrent hypoglycemia [$< 40 \text{ mg}/\text{dL}$], persistent severe hyperglycemia [$> 200 \text{ mg}/\text{dL}$], persistent moderate hyperglycemia [$> 150 \text{ mg}/\text{dL}$], severe metabolic acidosis [maximal base deficit ≤ -15], moderate metabolic acidosis [maximal base deficit ≤ -10], severe hyponatremia [$< 125 \text{ mEq}/\text{L}$], moderate hyponatremia [$< 130 \text{ mEq}/\text{L}$], severe hypernatremia [$> 160 \text{ mEq}/\text{L}$], moderate hypernatremia [$> 150 \text{ mEq}/\text{L}$], other); hydrocephaly (none, external, communicating, supratentorial); type of

treatment (y/n) for hydrocephaly (inapplicable, external drain, Rickham catheter, ventriculoperitoneal shunt, ventriculoatrial shunt, endoscopic therapy, serial lumbar punctures \pm drugs, other); cerebral hemorrhage (none, grade 1 [subependymal], grade 2 [limited intraventricular], grade 3 [large intraventricular hemorrhage with ventricular dilatation], grade 4 [frontoparietal intraparenchymatous echodensity], other, no data); leukomalacia (none, isolated echodensities > 7 days, regular echodensities + ventriculomegaly, irregular echodensities and no ventriculomegaly, irregular echodensities and ventriculomegaly, cystic PVL, cystic subcortical/mixed leukomalacia); treatment of indirect hyperbilirubinemia (none, phototherapy, 1 exsanguinotransfusion, multiple exsanguinotransfusions, intravenous immunoglobulins, other); clinical evaluation at discharge (normal, abnormal, suspicious, dead, unknown); neurosensorial hearing deficit (none, yes, uncertain, not tested, dead, unknown); ROP stage $\geq \text{III}$ (none, yes, not tested, dead, unknown); ROP treatment (inapplicable, oxygen, cryotherapy, laser, unknown); date of discharge; type of discharge (inapplicable, home, referring neonatal or pediatric unit, other NICU, internal transfer to the pediatric department, center for functional readaptation, died, other, unknown); special care at discharge (none, inapplicable, oxygen therapy, CPAP, IPPV, tracheostomy, tracheostomy and IPPV, parenteral nutrition, tube feeding, partial tube feeding, gastrostomy feeding, other); death (y/n); date of death; causes of death (inapplicable, congenital malformation, perinatal asphyxia, obstetric trauma, infection, cerebral hemorrhage, leukomalacia, shock, respiratory insufficiency, inborn error of metabolism, fetal hydrops, perioperative complication, iatrogenic cause, unexpected death, unexplained, other cause(s)); place of death (inapplicable, NICU, delivery room, cardiac surgery unit, pediatric department, other hospital department, referring hospital, baby-lance, at home, unknown); application of care (inapplicable, application of curative care until death, abstention, withdrawal of curative care, unknown).

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versitaire des Enfants Reine Fabiola (ULB-Brussels): Denise Blum, Anne-Britt Johansson; Hôpital Erasme Cliniques Universitaires (ULB-Brussels): Anne Pardou, Danièle Vermeylen; Cliniques Universitaires St-Luc (UCL-Brussels): Gaston Verellen, Christian Debauche (Principal Investigator); Institut Médical E. Cavell (Brussels): Eliane Damis, Marc Flausch; Antwerp University Hospital: Patrick Van Reempts (Principal Investigator), Bart Van Overmeire (Principal Investigator); University Hospital Gasthuisberg Leuven: Hugo Devlieger (Principal Investigator), Karel Allegaert (Principal Investigator); University Hospital Ghent: Piet Vanhaesebrouck (Principal Investigator), Koenraad Smets (Principal Investigator); University Hospital Liège: Jacques Rigo (Principal Investigator), Jacques Lombet (Principal Investigator).

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