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CME Outcomes for Extremely Premature Infants

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Premature birth is a significant cause of infant and child morbidity and mortality. In the United States, the premature birth rate, which had steadily increased during the 1990s and early 2000s, has decreased annually for 7 years and is now approximately 11.39%. Human viability, defined as gestational age at which the chance of survival is 50%, is currently approximately 23 to 24 weeks in developed countries. Infant girls, on average, have better outcomes than infant boys. A relatively uncomplicated course in the intensive care nursery for an extremely premature infant results in a discharge date close to the prenatal estimated date of confinement. Despite technological advances and efforts of child health experts during the last generation, the extremely premature infant (less than 28 weeks gestation) and extremely low birth weight infant (<1000 g) remain at high risk for death and disability with 30% to 50% mortality and, in survivors, at least 20% to 50% risk of morbidity. The introduction of continuous positive airway pressure, mechanical ventilation, and exogenous surfactant increased survival and spurred the development of neonatal intensive care in the 1970s through the early 1990s. Routine administration of antenatal steroids during premature labor improved neonatal mortality and morbidity in the late 1990s. The recognition that chronic postnatal administration of steroids to infants should be avoided may have improved outcomes in the early 2000s. Evidence from recent trials attempting to define the appropriate target for oxygen saturation in preterm infants suggests arterial oxygen saturation between 91% and 95% (compared with 85%–89%) avoids excess mortality; however, final analyses of data from these trials have not been published, so definitive recommendations are still pending. The development of neonatal neurocritical intensive care units may improve neurocognitive outcomes in this high-risk group. Long-term follow-up to detect and address developmental, learning, behavioral, and social problems is critical for children born at these early gestational ages. The striking similarities in response to extreme prematurity in the lung and brain imply that agents and techniques that benefit one organ are likely to also benefit the other. Finally, because therapy and supportive care continue to change, the outcomes of extremely low birth weight infants are ever evolving. Efforts to minimize injury, preserve growth, and identify interventions focused on antioxidant and anti-inflammatory pathways are now being evaluated. Thus, treating and preventing long-term deficits must be developed in the context of a “moving target.” (Anesth Analg 2015;120:1337–51)

In 2010, more than 1 in 10 of the world's infants, of more than 15 million children, were born prematurely.¹ More than a million of those children died secondary to complications associated with premature birth. Prematurity is the single most important cause of death in the first month of life and is a factor in greater than 75% of pediatric deaths in the neonatal period. As the second leading cause of

death in children younger than 5 years of age,² prematurity remains a global health problem. In addition, prematurity is associated with learning and motor disabilities and with visual and hearing impairment, contributing to approximately one-half of disabilities in children. Although preterm birth actually has decreased in the United States during the past 7 years, worldwide rates have increased during the last decade.^{1–4}

The challenges that “graduates” of the neonatal intensive care unit (NICU) present in the setting of anesthesiology and surgery will be discussed from several perspectives: (1) general outcomes of the extremely premature infant; (2) respiratory consequences of prematurity in the pediatric patient; (3) neurologic outcomes and therapies associated with neonatal neurologic intensive care therapies; and (4) selected aspects of term and preterm newborn brain imaging. This review is intended to provide background and historical perspective to the management of infants whose medical needs present a multitude of challenges for various health care professionals.

OUTCOMES OF THE EXTREMELY PREMATURE INFANT

Several definitions are important for clarity in the discussion of premature birth outcomes. First, gestational age is defined as the age of the fetus in terms of pregnancy

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duration in weeks, measured from the first day of the last menstrual period and, by convention, gestation is recorded as completed weeks and never rounded up. For example, an infant who is born at 32 weeks and 4 days is defined as being 32 weeks. The definition of the “estimated date of confinement” (EDC), also known as the due date, is 40 weeks added to the first day of the last menstrual period and estimates the day when the infant will be born.⁵ “Postmenstrual age” (PMA) is the time elapsed between the first day of the last menstrual period and the current day,⁵ and PMA also can be calculated as the gestational age plus the time elapsed after birth (chronologic age). PMA is used clinically during the perinatal period beginning after the day of birth. “Postconceptual age” is not synonymous with PMA.⁵ “Corrected age,” also called the adjusted age, describes children up to 3 years of age who were born preterm. “Corrected age” represents the age of the child since the EDC. “Term” birth is classically defined as 37 to 42 weeks. Recently, a National Institute of Child Health and Human Development (NICHD)-led group proposed subgrouping births between 37 and 39 weeks’ gestation as “early term.”⁶ “Preterm birth” is defined as any birth prior to 37 weeks’ completed gestation or fewer than 259 days since the first day of the mother’s last menstrual period.^{2,3,5,6} Preterm birth often is subdivided further based on birth gestational age. “Late preterm” infants are those born 34 to less than 37 weeks’ gestation, “moderate preterm” is designated as 32 to less than 34 weeks’ gestation, “very preterm” is designated 28 to less than 32 weeks’ gestation, and “extremely preterm,” which is the primary focus of this discussion, is less than 28 weeks’ gestational age^{2,3,5,6} (Table 1).

Other useful definitions include “small for gestational age” (SGA), defined as weight less than 10th percentile at a given fetal gestational age. “Large for gestational age” (LGA) is defined as weight greater than the 90th percentile for duration of gestation. Infants greater than 4500 g at term birth are LGA.⁷ The terms SGA and LGA age do not distinguish among the various ideologies of these conditions. Low birth weight infants can be further classified into very low birth weight, which includes infants less than 1500 g, and extremely low birth weight infants (ELBW), which comprise infants less than 1000 g.

Table 1. Terminology of Prematurity

Label	Definition (weeks completed gestation)
Extremely preterm	<28
Very preterm	28 to <32
Moderate preterm	32 to <34
Late preterm	34 to <37
Early term	37 to <39
Term	38 to <41
Late-term	41 to <42
Post-term	>42
SGA	Weight less than 10th percentile for gestational age
LGA	Weight greater than 90th percentile for gestational age
VLBW	Less than 1500 g
ELBW	Less than 1000 g

SGA = small for gestational age; LGA = large for gestational age; VLBW = very low birth weight; ELBW = extremely low birth weight.

A “live birth” is defined as the complete expulsion or extraction of the product of human conception regardless of the duration of pregnancy, and after such expulsion, the infant breathes or shows other evidence of life such as a beating heart, pulsation of the umbilical cord, or definitive movement of voluntary muscles. “Live birth” does not designate whether the umbilical cord has been cut or the placenta remains attached. Heartbeats need to be distinguished from transient cardiac contractions. Respirations need to be distinguished from fleeting respiratory efforts or gasps. “Fetal death” is death of the product of human conception before complete expulsion or extraction from the mother regardless of the duration of pregnancy. Death is indicated by the fact that after expulsion/extraction, the fetus does not breathe or show any other evidence of life, such as a beating heart or pulsation of the umbilical cord.

Viability often is defined as the gestational age at which there is a 50% chance of survival with or without medical care²; therefore, under current conditions, viability in developed, high-income countries of the world is somewhere between 22 and 24 weeks, whereas viability is closer to 34 weeks’ gestational age in low- and middle-income countries.² Premature birth rate and the relative proportions within the subcategories of extremely preterm, very preterm, and late preterm births vary throughout the world (Fig. 1). The greatest rate of premature birth (close to 18%) is noted in Southeastern Asia.² Worldwide, most preterm births are late preterm.

SURVIVAL AND MORBIDITY

In the United States in 2011, approximately half a million (11.7%) of the 4 million total births were preterm (Fig. 2). The subgroup of extremely preterm births comprise approximately 6% of all preterm births and are less than 1% of all births. Infants born less than 34 weeks comprise almost 60% of infant deaths.^{4,8} Recently, the premature birthrate has decreased. Data for 2013 show a preterm birthrate of 11.39%, compared with a maximum of 12.5% in 2009.⁸ The premature birth rate in the United States ranks in the middle of other nations.² In addition, ethnic and racial disparities in the premature birthrate remain throughout the world. In the United States, non-Hispanic black infants have a premature birthrate closer to 16%, and non-Hispanic white infants have rates closer to 10%.⁹

Over the last generation, a dramatic decrease in infant mortality has been associated with medical innovations in the management of neonates, particularly those born preterm. The specialty of anesthesiology has contributed significantly to those innovations. These contributions include initiation of rational IV fluid therapies; development of artificial airways and breathing circuits; application of mechanical ventilation and airway distending pressure; and development of a resuscitation scoring system, the Apgar score, to aid in the evaluation of the resuscitative efforts of the newborn.

After application of the airway distending pressure by Gregory et al.,¹⁰ many centers in the United States and the developed world began aggressive programs to develop intensive care programs to support the smallest premature infants and to develop follow-up clinics to evaluate the success of these intensive care efforts. In a cohort of 61 infants

Figure 1. Modified with permission from World Health Organization: Born Too Soon: the Global Action Report on Preterm Birth. Geneva, Switzerland: World Health Organization Press, 2012.²

Figure 2. Figure drawn using data from Centers for Disease Control and Prevention.⁴

Table 2. Extremely Low Birth Weight Infant Outcomes

Innovation	Time
CPAP, Mechanical ventilation	1980s
Exogenous surfactant	Early 1990s
Antenatal steroids	Mid/late 1990s
Avoiding postnatal steroids	Early 2000s
Targeted oxygen therapy	Mid 2000s
Systematic care/experience	Continuous

CPAP = continuous positive airway pressure.

born between 500 and 750 g in the latter half of the 1970s, girls (71.4% survival) had better outcomes compared with boys (18.2% survival) and small increments of increasing birth weight and gestational age were strongly associated with improved outcomes.¹¹

Changes in clinical outcomes of extremely premature infants have been significantly influenced by changes in medical care (Table 2). Continuous positive airway pressure (CPAP), mechanical ventilation, exogenous surfactant, and antenatal steroids have improved survival markedly, whereas postnatal administration of steroids to premature infants worsened outcomes.^{12,13} The adverse effects of postnatal steroids became apparent in trials designed to lessen the severity of chronic lung disease in premature infants. Although these studies have shown that a course of high-dose dexamethasone tapered over weeks is associated with smaller head circumference, weak motor skills, lower IQ

scores, and clinically significant disabilities, the role of single-dose or short-term use of either hydrocortisone or dexamethasone has not been established.¹²⁻¹⁴

Most recently, randomized control trials have been published to better delineate the lowest inspired oxygen concentration (comparing target ranges for oxygen saturation of 85%–89% with 91%–95%) that maximizes survival and minimizes eye, pulmonary, and neurocognitive morbidities in premature infants.¹⁵⁻¹⁷ That is, oxygen therapy has been associated with improved survival but greater incidence of chronic lung disease and retinopathy of prematurity (ROP), especially in extremely premature infants.

The results of these randomized controlled, multicenter studies have yielded conflicting evidence. Investigators from the SUPPORT trial (surfactant, positive pressure, and pulse oximetry) conducted in the United States noted that the lower saturation of peripheral oxygen (SpO₂) target group (85%–89%) had a lower incidence of ROP (8.6% vs 17.9%) but a greater rate of mortality (22.1% vs 18.2%) compared with the target group of 91% to 95%.¹⁵ Similar findings were noted in BOOST (Benefits of Oxygen Saturation Targeting) II, a collaboration of United Kingdom, Australia, and New Zealand.¹⁷ However, in the Canadian Oxygen Trial (COT), which included 578 infants, no significant difference in the rate of death or disability at 18 months¹⁶ were identified. Similar findings of no difference in death, major disability, ROP, or chronic lung disease between the 2 target saturation groups also was reported in the 6 regional NICUs from New Zealand (Boost-NZ).^{18,19}

The optimal oxygen saturation during surgery and anesthesia has not been defined. Some of these disparities in these large multicenter studies may have been related to a technical problem with the Massimo pulse oximeter. During these studies, a change in the algorithm was made when it was discovered that the pulse oximeter was reading 2% to 3% greater than the actual value. However, it appears that small differences in SpO₂ target range may influence mortality. Thus, at present in the premature infant, targeting SpO₂ to less than 90% should be avoided. A critical factor in the management of these infants is the inability to maintain saturation in the targeted range. For example, in the oxygen

targeting study involving CPAP, infants targeted for oxygen saturations of 88% to 92% achieved their goal saturation only 31% of the time.²⁰

The innovation epoch framework (Table 2) provides a useful backdrop against which to examine the changing results of outcome studies during the last 20 years. For example, the initial National Institutes of Health and Human Development Neonatal Network study²¹ reported the morbidity and mortality of 1765 premature infants (birth weight 500–1500 g) in the period after the widespread implementation of NICUs and mechanical respiratory support, but before the introduction of exogenous surfactant. Survival dramatically improved with each week of gestational age and for each 100-g increment in birth weight. Specifically, survival in the 500- to 600-g group was only 20% compared with 56% in the 700- to 800-g birth weight group (Fig. 3). Nonsurvivors tended to die within in the first 2 weeks of life, and mortality after 28 days of age was 8%.

Figure 3. Extremely low birth weight infant outcomes of the National Institute of Child Health and Human Development (NICHD) Neonatal Network. Eight centers participated in the NICHD Neonatal Network, 1765 infants born in the middle to late 1980s. Survival significantly improved with each week of increase in gestational age and with each 100-g increment increase in birth weight (data not shown). Figure drawn from data presented in Hack et al.²¹

Of note, length of stay correlated with the gestational age; if the course in the NICU was stable, the extremely premature infant was discharged at approximately the time of the EDC. As observed in previous reports, infant girls had better outcomes compared with male counterparts. Finally, data from these earlier studies often included patients admitted to intensive care nurseries and not infants who died in the delivery room or during transport to the intensive care unit, which tended to skew survival statistics (Fig. 4).

From 1986 to 2004, several large population-based cohort outcome studies (Table 3)^{21–44} included approximately 14,700 ELBW infants from North America, Western Europe, the United Kingdom, Australia, and Japan. Outcomes of observation studies were pooled and then referenced to the Table 2 epochs to show changes in survival over time (Fig. 5). The regression lines for each gestational between 23 and 26 weeks document improved survival rates over time. When the 50% survival rate standard is used, the viability appears to have improved from approximately 25 to 26 weeks in the 1990s to approximately 23 to 24 weeks by the mid-2000s.

Increased survival of extremely premature infants has raised the concern for an increase in the number of children who incur severe acute and chronic morbidities (e.g., intraventricular hemorrhage [IVH], necrotizing enterocolitis [NEC], bronchopulmonary dysplasia [BPD], chronic lung disease, severe visual impairment, hearing impairment, cerebral palsy [CP], and cognitive developmental delay) (Table 4). Eichenwald and Stark⁴⁵ have systematically documented the critical importance of gestational age on survival in a cohort born between 1997 and 2002 by noting short-term survival without complications (NEC, BPD, severe IVH) as a function of narrow ranges of birth weights (approximately 20%, 501–750 g; approximately 50%, 751–1000 g; approximately 70%, 1001–1250 g; approximately 90%, 1251–1500 g). Comparing several eras (1991–1996 vs 1997–2002), the authors concluded that improved survival was accompanied by persistently high rates of morbidity. In a more recent publication, Stoll et al.⁴⁶ reported similar

Figure 4. The figure shows how survival statistics may be distorted depending on the reference denominator used in evaluating mortality risk. Older cohort observations often included only patients admitted to intensive care. These studies did not account for infants who succumbed in the delivery room or on the way to intensive care. In the figure in the left hand panel, survival is referenced to live births (population-based cohort), demonstrating very poor outcome in the less than 500- to 600-g subgroup. When survival is referenced to pediatric intensive care unit admissions as it is on the right-sided panel, outcomes seem much better. Clinicians involved in the surgical and intensive care management of these patients often have this distorted view of survival because he or she sees only the children admitted for care. Figure 6 also displays the significant improvement in survival that occurred with the widespread availability and use of exogenous surfactant. Figure drawn from data presented in Hack et al.²²

Table 3. Large Observational Outcome Cohort Studies from 1986 to 2004

Country	Birth cohort treatment epoch	Reference
United States	1980s	Hack et al. ²⁰
United States	1980s	Hack et al. ²¹
Australia	Early 1990s	Doyle ²²
United States	Early 1990s	Hack et al. ²¹
United Kingdom	Early 1990s	Tin et al. ²³
Australia	Early 1990s	Sutton and Bajuk ²⁴
United States	Mid 1990s	Hintz et al. ²⁵
United Kingdom	Mid 1990s	Draper et al. ²⁶
Denmark	Mid 1990s	Kamper et al. ²⁷
Northern Sweden	Mid 1990s	Håkansson et al. ²⁸
Southern Sweden	Mid 1990s	Håkansson et al. ²⁸
United Kingdom/Ireland	Mid 1990s	Wood et al. ²⁹
Netherlands	Mid 1990s	den Ouden and Anthony ³⁰
Finland	Late 1990s	Tommiska et al. ³¹
Australia	Late 1990s	Doyle ³²
France	Late 1990s	Larroque et al. ³³
United States	Late 1990s	Hintz et al. ²⁵
Belgium	Late 1990s	Vanhaesebrouck et al. ³⁴
Finland	Late 1990s	Tommiska et al. ³¹
Norway	Late 1990s	Markestad et al. ³⁵
United States	Early 2000s	Hintz et al. ³⁶
Germany	Early 2000s	Kutz et al. ³⁷
United States	Early 2000s	Mercier et al. ³⁸
Sweden	Mid 2000s	Serenius et al. ³⁹
Japan	Mid 2000s	Ishii et al. ⁴⁰
Australia	Mid 2000s	Doyle et al. ⁴¹

Figure 5. Extremely low birth weight infant survival. Outcomes of observation studies were pooled, then referenced to the Table 2 epochs to allow visual evaluation of the association of changes in survival over time with the innovations. The regression lines for each gestational age 23 through 26 weeks suggest that survival has improved over time. When the 50% survival rate standard (black dashed line) is used, the figure suggests that viability has improved from approximately 25 to 26 weeks in the 1990s to between 23 and 24 weeks by the mid-2000s. Graphic drawn from data in the references.^{21–44}

results but expanded the dataset to include infants between 22 and 24 weeks of gestation and added several parameters to gauge outcomes (periventricular leukomalacia, ROP > stage 3, early/late sepsis/meningitis, NEC, BPD, and severe IVH). Comparing short-term outcomes in 2003, 2005, and 2007, the authors confirmed that rates of survival without morbidity remained stable over this time period for each

Table 4. Morbidity Risks

ELBW morbidity	Risk	95% CI
Acute/NICU		
Any ROP	63.7	60.6–66.6
Severe ROP	12.3	11.3–13.3
IVH (Grade III–IV)	14.1	13.1–15.2
Surgical NEC	10.1	9.3–11.0
Chronic problems		
BPD (O ₂ at 28 weeks)	42.2	40.4–43.9
BPD (O ₂ at 36 weeks)	38.7	36.9–40.5
Blindness	0.8	0.36–1.62
Hearing loss	3.1	2.1–4.4
Cerebral palsy	6.1	4.7–7.7
Cognitive delay	7.4	5.2–9.4

Data from the 3 recent randomized trials of titrated oxygen therapy^{15–17} are pooled to provide point estimates of morbidity risks with 95% confidence intervals. The risk of bronchopulmonary dysplasia (BPD), defined as “supplemental oxygen needed at 28 weeks’ postmenstrual age,” is 42%. A more strict definition of oxygen BPD, “supplemental oxygen greater than 30% at 36 weeks’ postmenstrual age” places the risk at 39% of patients. ELBW = extremely low birth weight; CI = confidence interval; NICU = neonatal intensive care unit; ROP = retinopathy of prematurity; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; BPD = bronchopulmonary dysplasia.

gestational age (0%, 22 weeks; 5%–11%, 24 weeks; 20%–22%, 25 weeks; 32%–34%, 26 weeks; 44%–46%, 27 weeks; 54%–62%, 28 weeks).

Of note, pooled data from recent randomized, controlled trials of titrated oxygen therapy^{15–17} suggest that from 2000 to 2010, morbidity may have improved gradually in extremely premature infants (Table 4). Because patients may have more than one morbidity, some experts suggest that examining outcomes in this population requires examining the percentage of patients who are spared various morbidities (Fig. 6).³⁵

Thus, even with technological advances the extremely premature infant remains at considerable risk for death (30%–50% mortality) and disability (20%–50%).^{15–17,37} Abitbol and Rodriguez⁴⁷ noted that preterm birth significantly influences the “developmental programming” of health and disease so that abnormalities in organogenesis secondary to preterm birth clearly may influence function throughout a lifetime.

RESPIRATORY OUTCOMES

Alveolar lung development continues into the postnatal period. Prematurity coupled with inflammation, hyperoxia, and volutrauma and barotrauma from mechanical ventilation can interrupt normal pulmonary development and thus create a clinical scenario of chronic lung disease with pathophysiological effects that can extend beyond infancy into adulthood. BPD has been referred to as the “chronic lung disease of the premature.” Although multiple definitions have been proposed, one commonly accepted version includes oxygen dependence at 28 postnatal days and severity and stratification as mild, moderate, or severe at 36 weeks postconceptual age (gestational age <32 weeks) or at 56 days (gestational age >32 weeks) based on supplemental oxygen delivery (i.e., room air, fraction of inspired oxygen 0.22–0.29, and fraction of inspired oxygen > 0.30, respectively).⁴⁸

Understanding the etiology of BPD requires a review of normal lung development. A simplified sequence of

Figure 6. The percentage of extremely premature infants who are spared from various morbidities. The figure represents the cumulative short-term outcome scale at the time of discharge for admitted infants with a gestational age (GA) of 24 to 26 weeks. At the time of hospital discharge, approximately 50% of infants born at 25 weeks' GA leave the hospital without any major neurologic disability versus only 20% of infants born at 24 weeks. Figure modified with permission from Vanhaesebrouck et al.³⁵

development includes several stages: embryonic, pseudo-glandular (8–17 weeks), canalicular (16–23 weeks), sacular (23–32 weeks), and alveolar (overlaps sacular-postnatal)⁴⁸ (Fig. 7).⁴⁹ Because the entire bronchiolar tree is established by 17 to 18 weeks' gestation, destruction of or severe injury to airways postnatally (e.g., supplemental oxygen and/or ventilation) in the extremely premature infant is likely to impart permanent sequelae. Another critical event associated with BPD centers on pulmonary vascularization, which is the hallmark of the canalicular stage of development. Active development of the distal pulmonary circulation includes appearance of lung capillaries by 20 weeks, a time closely proximate to the gestational age of the ELBW infant. Injury to the lung at this phase predisposes the infant to irreversible pulmonary vascular injury and delayed or arrested growth of alveoli.^{48,50}

During the last decade, “new” BPD has been contrasted with “old” BPD. The distinction between new and old has evolved as a result of changes in postnatal care, as well as increased survival of more immature infants (i.e., infants born at earlier stages of pulmonary development). The so-called “new BPD” primarily develops in the ELBW infant (less than 1000 g) born during the late canalicular or early sacular phase.⁴⁸ In contrast, “Old BPD” includes infants from the presurfactant era, of an older gestational age, born during the late sacular and alveolar stages of lung development, and exposed to vigorous mechanical ventilation and supplemental oxygen. The primary pathology of “old BPD” includes intense airway inflammation, fibrosis with severe epithelial injury, and smooth muscle hyperplasia. In contrast, “new BPD” of the ELBW infants evolves in the setting of gentler ventilator strategies, prenatal steroids, and postnatal surfactant. With birth at mid-gestation, ELBW infants undergo the complex process of lung development postnatally. At this immature stage of development, the lung is

extremely susceptible to injury secondary to inflammation/infection, ventilatory support (including CPAP), and even appropriate supplemental oxygen. When postnatal damage occurs during the early sacular or late canalicular stages, the pathology includes fewer but larger alveoli, abnormal vascular growth, but less prominent inflammation, smooth muscle hypertrophy, and fibroproliferation. Thus, “new BPD” is characterized by the prominent arrest of both alveolar septation and vascular development and subsequent reduction in surface area for gas exchange.^{48,50,51} Despite the well-described differences in the pathology of “new” compared with “old” BPD, children born prematurely in different eras seem to have remarkably similar long-term functional pulmonary abnormalities.⁵² That is, during the last 30 years, survivors of BPD seem to display similar patterns of clinical dysfunction that persist into late childhood and early adulthood.

The circulation of the developing lung is critical in establishing the distal airspaces; pulmonary blood vessels promote alveolar growth and development. Vascular endothelial growth factor (VEGF) has been linked to both normal vascular and parenchymal lung development (Fig. 8), and, in experimental BPD models, disrupting VEGF signaling is associated with structural abnormalities.⁵³ Abman⁵³ has suggested that abnormal VEGF signaling may serve as a common pathway for injury associated with a variety of prenatal (e.g., chorioamnionitis, intrauterine growth restriction [IUGR], genetic susceptibility) and postnatal (e.g., mechanical ventilation, supplemental oxygen) factors that converge to produce decreased angiogenesis and alveolarization characteristic of BPD. For example, the abnormal VEGF signaling in the placenta of IUGR fetuses may also predispose them to developing pulmonary hypertension postnatally, especially in the setting of BPD. Check et al.⁵⁴ reported that at least half of patients with BPD-associated

Figure 7. Normal development of the lung. The 5 stages of normal development of the lung; weeks 0 to 6 of gestation comprise the embryonic period, weeks 6 to 16 the pseudoglandular period, weeks 16 to 24 the canalicular period, weeks 25 to 36 the saccular period, and alveolar 36 weeks to postnatal. Pulmonary circulation develops in parallel with lung development.⁴⁹

pulmonary hypertension had a birth weight below the 25th percentile. In a recent review, Mourani and Abman⁵⁵ noted that “pulmonary vascular disease secondary to disruption of normal pulmonary vascular development after preterm birth is an important determinant of the pathobiology of BPD and contributes significantly to morbidity and mortality.” The high incidence of pulmonary hypertension among infants with BPD supports the concept that impaired angiogenesis decreases alveolarization.

Several recent reviews⁵⁶⁻⁵⁹ note that the incidence of pulmonary hypertension among ELBW infants ranges between 17% and 43% and mortality between 14% and 38%. Of importance, only 25% of those with severe BPD and pulmonary hypertension survive to 2 to 3 years of age. In a prospective study, Bhat et al.⁶⁰ reported pulmonary hypertension in 18% of a cohort of ELBW infants (24–27 weeks’ gestation). Similar to others, he noted that IUGR and severe BPD were highly associated with the diagnosis

of pulmonary hypertension. Although 31% of infants were diagnosed by 4 weeks, 66% were not identified until 3 to 4 months. In 58%, pulmonary hypertension persisted to discharge from the intensive care nursery. Although the ELBW infant encounters the greatest risk for BPD and associated pulmonary hypertension, accurately predicting outcomes in specific patients remains elusive; that is, not all infants with severe BPD develop pulmonary hypertension, while others with milder BPD may develop pulmonary hypertension.

BPD: INCIDENCE AND LONG-TERM OUTCOMES

Outcomes in ELBW infants born between 2004 and 2007 demonstrate that even with optimal therapy (e.g., prenatal steroids, appropriate prenatal antibiotics, early treatment with surfactant, “gentle” ventilatory strategies, meticulous monitoring of oxygen administration), BPD persists as a major source of both short- and long-term morbidity.⁴⁶ Stoll et al.⁴⁶ noted that after a 24-week gestation, all infants incurred some degree of BPD (mild, 26%; moderate, 35%; severe, 39%), whereas in the 28-week gestation group, 39% developed BPD (mild, 16%; moderate, 15%; severe, 8%) (Table 5).

Similar to findings from studies from earlier eras, airway obstruction currently persists as a common long-term outcome of the ELBW infant. Based on studies of 11-year-old children from the Epicure cohort (<25 weeks’ gestation, born in 1995), Fawke et al.⁵² noted that abnormally low pulmonary function (forced expiratory volume in 1 second [FEV₁], forced expiratory flow from 25% to 75% of vital capacity, and FEV₁/forced vital capacity more than 2 SD lower than predicted) occurred in 66% of ELBW infants with BPD

Figure 8. Vascular endothelial growth factor (VEGF) signaling in the pathogenesis of neonatal pulmonary vascular disease. Blood vessels in the lung actively promote alveolar growth during development. VEGF contributes to normal lung development and early disruption leads to structural abnormalities. Lung angiogenesis promotes lung development.⁵³

Table 5. Incidence of BPD (%)

	23 Weeks	26 Weeks	28 Weeks	Total
Mild	26	35	16	27
Moderate	35	26	15	23
Severe	39	17	8	18

At 23-weeks’ gestation, all infants incurred some degree of bronchopulmonary dysplasia (BPD) (mild, 26%; moderate, 35%; severe, 39%). Although still prevalent, BPD was less common in the 28-week gestation group (mild, 16%; moderate, 15%; severe, 8%). Incidence of BPD varies markedly among subgroups of infants based on gestational age. Data from reference 45.

compared with 32% of ELBW infants without BPD and 9% of term infants. Of significance, airway obstruction was only partially reversible with bronchodilators, especially in the ex-ELBW infants with BPD. Similarly, Joshi et al.⁶¹ also documented a greater incidence of exercise-induced, bronchodilator-responsive wheezing in 8- to 12-year-old ex-premature infants (<32 weeks' gestation) with histories of BPD. Although airway obstruction and/or hyperreactivity dominate the reported abnormal pulmonary outcome of ex-ELBW infants, decreased alveolar surface area, and decreased effective pulmonary blood flow have also been noted.^{62,63}

In 2 distinct cohorts, Vollsæter et al.⁶⁴ reported FEV₁ over time among 3 groups: term control, ex-ELBW infants with no BPD, and ex-ELBW with BPD in 2 separate cohorts. One cohort was studied at age 10 and 18 years (born between 1991 and 1995) and an older cohort at 18 and 25 years (born between 1982 and 1985) (Fig. 9). In these 2 distinct cohorts of ELBW infants (e.g., later time period more likely to have received prenatal steroids and postnatal surfactant), Vollsæter et al. identified significant airway obstruction that tracked (i.e., no improvement in function) from ages 10 to 18 in one group and between 18 and 25 years in the other. Thus, pulmonary injury associated with ELBW implies persistent dysfunction into adulthood that did not improve over time.

An analogous finding of "tracking of pulmonary dysfunction over time" was noted in the Tucson Children's Respiratory Study, which followed a normal, unselected population (N = 1246) from birth to 22 years, and reported that infants who were in the lowest quartile of function (FEV₁, forced expiratory flow from 25% to 75% of vital capacity, FEV₁/forced vital capacity) at birth remained in that quartile at 11, 16, and 22 years of age.⁶⁵ Thus, factors that occur in utero or in the neonatal period may have pulmonary effects that persist into adult life. For example, Postma and van den Berge⁶⁶ suggested that chronic lung disease (i.e., chronic obstructive pulmonary disease, "COPD") may actually originate during fetal development.

In summary, the lifelong pulmonary injury associated with prematurity is exaggerated in the setting of a history of BPD. The severity of pulmonary dysfunction seems to persist throughout life, with clear separation into 2 groups of ex-ELBW infants (those with versus those without BPD), both of which are distinct from healthy, full-term controls. In the adult, the pulmonary function of the ex-ELBW

infant is abnormal compared with the age-matched ex-term infant, but not as severely abnormal as that associated with the ex-ELBW infant with BPD.^{61,64} The airway obstruction of the ex-premature, especially with BPD, that persists into late childhood and early adulthood is commonly characterized by coughing and wheezing. Such airway hyperresponsiveness may be only partially responsive to treatment (i.e., bronchodilators, anti-inflammatory agents). The long-term outcome of pulmonary hypertension associated with BPD has not been completely defined. BPD may be "the earliest & perhaps the longest lasting lung disease in humans."⁵¹

Although asthma and chronic lung disease of the ex-premature share common clinical features, each has a distinct underlying pathology and etiology. Instead of the eosinophil-mediated inflammation and atopy typical of asthma, the ex-premature infant's recurrent broncho-obstructive symptoms result from abnormal growth and development of the architecture of the lung.^{48,67} Instead of bronchoconstriction, small conductive airways may collapse during expiration because of inadequate supporting parenchyma. High-resolution computed tomography (CT) suggests that adolescent and young adult survivors of BPD have lung changes more closely resembling those of pulmonary emphysema than those seen in asthma.

NEUROLOGIC OUTCOMES

The neurologic sequelae of prematurity and its treatment impart lifelong structural and functional impairments. Similar to the response of the lung, injury to the brain correlates highly with gestational age. Even with the dramatic changes in management during the last 2 decades (e.g., prenatal steroids, avoiding postnatal steroids, easy access to surfactant), the rates of neurodevelopmental abnormalities among ex-preterm infants remain high.⁶⁸ For example, Kobaly et al.⁶⁹ have documented that even with clinical practice changes between the years 2000 and 2003, neurodevelopmental outcomes (mental developmental index [MDI], psychomotor developmental index) did not improve compared to earlier eras, even though the incidence of neurosensory impairment (e.g., deafness requiring aid, blindness, persistent hypo- or hypertonia) decreased. In addition, children with BPD continued to have poorer cognitive performance compared to children without BPD.

Figure 9. Tracking of forced expiratory volume in 1 second (FEV₁) in normal and extremely low birth weight infants (with and without bronchopulmonary dysplasia [BPD]) into early adulthood. FEV₁ in preterm-born subjects, including subjects with BPD and without BPD, compared with subjects born at term.⁶³

VULNERABILITY OF THE PRETERM BRAIN TO INJURY

Pervasive and persistent neuropsychologic deficits are better understood in the context of normal in utero-third trimester brain development. During this period, dramatic cortical, dendritic, and axonal ramifications, as well as glial proliferation and differentiation occur, along with synaptogenesis and myelination. The combined effect of this neurodevelopment is a 4- to 5-fold increase in the volume of cortical gray and white matter.⁷⁰ During the same time period of cortical development, there is a similar proliferation, growth, and migration of granule cells in the cerebellum.⁷¹ At 30 weeks' gestation, the brain has achieved only half of its full-term weight (Fig. 10),⁷² whereas the cerebellum has only reached 35% to 40% of its expected volume at 40 weeks (Fig. 11).⁷³

Similar to development of the lung, blood vessels in the brain develop in parallel with the parenchyma. During the last 16 weeks of gestation, the periventricular network expands with growth of long and short penetrator vessels and formation of extensive anastomoses. At mid-gestation, blood flow to the white matter is only 25% of that to the cortex. Of note, in the ELBW infant, cerebral blood flow is often passive, with more than 95% of ELBW infants demonstrating pressure passive flow at least 20% to 50% of the time.⁷⁴ In recognizing the disturbed autoregulation in the ELBW infant, Greisen⁷⁵ emphasizes that the lower limit of blood pressure associated with intact cerebral autoregulation is especially difficult to pinpoint, at least in part due to the enormous variability in "normal" blood pressure in ELBW infants. Consistent with these data, diffuse white matter injury is identified in >50% of ELBW infants. Deep gray matter growth failure has been noted to accompany white matter injury.^{76,77} Perinatal injuries disrupt the coordinated growth of the whole brain,^{78,79} thus lending a pathologic correlation and possible explanation of the diffuse deficits in higher (executive) cognitive function in survivors of ELBW.

Thus, as with advances in neonatal medicine focused on the avoiding lung injury, developments in supportive care of the central nervous system have contributed to improved survival for critically ill neonates. Nonetheless, similar to the persistent high rate of chronic lung disease, this vulnerable population still remains at high risk for brain injury

Figure 10. Normal brain growth. Brain weight from 20 to 40 (term) gestational weeks is expressed as a percent of term brain weight. For example, at 34 gestational weeks, the overall brain weight is 65% of term weight.⁷²

and consequent adverse outcomes, including CP, cognitive disabilities, and epilepsy.⁸⁰

Volpe⁸¹ emphasizes that "brain injury and impaired brain development" are "inextricably intertwined." Similar to other investigators,^{37,39} he notes that injury at a critical period of rapid development and growth interferes with establishing the intricate microstructural connections throughout the brain (e.g., between basal ganglia and cortex, thalamus and cortex, cerebellum and cortex, pons and cortex, and intracortical). Analogous to long-term pulmonary dysfunction, structural abnormalities of the ELBW infant's brain persist into late childhood, adolescence, and adulthood and correlate with neuropsychological abnormalities. Decreased volumes of the frontal and temporal lobes and the caudate and/or cerebellum have been associated with functional abnormalities. Of importance, disturbed connectivity associated with cognitive impairment increases the risk for inattention and/or hyperactivity, anxiety, and other social and emotional problems.^{81,82}

Neurodevelopmental disability related to cognition is often categorized with the Bayley Scales of Infant Development, a tool used to quantify developmental outcome during the first 3 years of life.^{22,30,83} Cognitive delay, as defined by mean Bayley scores and the proportion of subjects scoring below 70, is increased in extremely premature infants. Pooled estimates from large population-based cohort studies conducted through the late 1990s to the early 2000s suggest an increasing incidence of cognitive delay, with the risk in some studies approaching 50%. However, pooled estimates from large observational studies suggest a risk of 25.2% (95% confidence interval [95% CI]: 20.4–30.5)^{15,21–44,84} (Fig. 12).

The early reports from the NICHD cohort (births < 32 weeks between 1993 and 1998) reported that periventricular leukomalacia, BPD, multiple births, male sex, nonwhite race, maternal education less than 12 years, and IVH were risk factors associated with cognitive delay. Postnatal steroids increased the risk and antenatal steroids decreased the risk of neurodevelopmental disability.⁸⁵ Other collaborative studies of long-term neurocognitive outcome involving

Figure 11. Normal cerebellar growth. Note that cerebellar volume as a function of gestational age reveals the dramatic increase between 24 and 40 weeks' gestation.⁷³

multiple cohorts from various eras confirm that ex-ELBW infants who reached school age scored lower scores on all cognitive and academic scales,^{29,68,86,87} including abnormalities of both attention and emotional problems. Even in the 2004 cohort,²⁹ although most patients had received antenatal steroids, postnatal surfactant, magnesium, and caffeine, 38% developed BPD and 3.7% incurred severe IVH (grade III and IV). In a more recent cohort, Kumar et al.⁸⁶ noted that although 33% of ex-ELBW infants were categorized as having an “unimpaired outcome” at 30 months, MDI scores were markedly skewed toward the low end of normal. That is, only 17% of these infants had an MDI > 101, suggesting that this group with “normal cognitive function” were in fact disadvantaged compared to the control group of ex-term infants.

The neuropsychologic sequelae of preterm birth have been noted to persist into adolescence and adulthood. On the basis of the data from the Multicenter Randomized Indomethacin IVH Prevention Trial, Luu et al.⁸⁷ noted that adolescents had an increased incidence of deficits in “executive function,” which are high-level mental activities that correlate with ability to regulate behavior and cognition for goal-directed activity (e.g., verbal fluency inhibition, cognitive flexibility).

CP AND THE PRETERM INFANT

CP is a nonprogressive motor disability that results in movement disorders such as plegias, spasticity, and dystonia. The exact cause is unknown, but prematurity is significantly associated with CP and it affects 2.5 of every 1000 children in the United States.⁸⁸ The injury may occur in utero, at birth, or after birth up to about 3 years of age.^{88,89} Children born prematurely are at an increased risk and comprise about half of those affected. CP often is used as a marker for overall neurologic outcomes in association with prematurity.⁹⁰

Figure 12. Bayley developmental index. The Bayley score is a developmental test based on a play behavioral examination. The raw score is converted to a scale, which in turn can be referenced to normalized values. The pink shaded area represents the normal range (between 84 and 115). Scores below the red dashed line, at 70, indicate severe developmental disability, whereas scores above the green line indicate superior performance. When Bayley scores are used to quantify developmental outcomes, the point estimate, or effect size, is represented by the mean score $\pm$ standard deviation, or alternatively, the proportion of infants who score below a score of 70 can be used as the metric. Graphic drawn from data of Hack et al.²²

Observational studies from the 1980s through middle of the 1990s suggested that the occurrence of CP was increasing in association with increased survival of extremely premature babies. However, registry data from studies in Europe, Australia, and Canada^{91,92} indicate that since the late 1990s, the incidence of CP has decreased.^{91,92} Available pooled data from cohort studies^{14,20–43,82} used to examine survival suggest the risk of CP in this patient population is 10.4% (95% CI: 7.3%–13.4%); however, more recent data from 3 large international randomized controlled titrated oxygen therapy trials^{15–17} suggest that the risk is lower than 6% (95% CI: 6.7%–7.7%). In a study conducted by the NICHD, investigators noted that periventricular leukomalacia, severe IVH (grade 3–4), administration of postnatal steroids, and male sex were risk factors associated with the development of CP, whereas the use of antenatal steroids was associated with a decreased risk.⁸⁵

NEONATAL NEUROCRITICAL INTENSIVE CARE AND NEUROIMAGING

Neonatal neurocritical care has developed in response to goals of care for the preterm infant shifting from a single-minded focus on cardiopulmonary support to optimization of neurodevelopmental outcomes. Along with this focused brain care, advanced brain imaging has become the standard of care to facilitate diagnosis for both congenital and acquired conditions and to improve predicting prognosis.^{93,94} Ultrasound (US), magnetic resonance imaging, and CT are the 3 most commonly used imaging modalities.

Brain injury in preterm neonates admitted to a neurocritical care unit may present clinically as encephalopathy (8%), seizures (31%), or a precipitous decrease in hematocrit in the case of IVH (27%).⁹⁵ Although encephalopathy and seizures are common presenting signs, some neonates are asymptomatic. With the advent of improved imaging technology, unsuspected brain injury or developmental anomalies often are

Table 6. Neonatal Clinical Conditions That Present High Risk for Brain Injury or Developmental Anomalies and May Require Detailed Magnetic Resonance Brain Imaging to Determine Diagnosis and Prognosis

Suspected acute acquired brain injury
Encephalopathy
Seizures
Intracranial infection
Inborn error of metabolism
Abnormal ultrasound findings
High grade intraventricular hemorrhage
Suspected parenchymal injury
Ventriculomegaly or suspected malformation
Abnormal examination
Hypotonia or hypertonia
Multiple congenital defects or dysmorphic features
Microcephaly or macrocephaly
High risk for brain injury
Congenital heart defect, especially during and after corrective surgery
Postnatal cardiopulmonary arrest
Central nervous system vascular malformation
Symptomatic hypoglycemia
Extreme prematurity (<28 weeks' gestation at birth)
Need for extracorporeal membrane oxygenation (ECMO)

identified on routine imaging (Table 6), most commonly on screening US. In fact, US is recommended for all neonates at high risk (i.e., <30 weeks' gestational age)⁹⁶ to screen for intracranial pathologies (e.g., IVH, periventricular hemorrhagic infarct, ventriculomegaly, large cerebellar hemorrhages, and cystic white matter injury).⁹⁶⁻⁹⁸ Because it is readily performed at the bedside, US often is the initial diagnostic modality and is therefore easily performed urgently when critical neurosurgical conditions (e.g., posterior fossa bleed or hydrocephalus), are suspected, or when more definitive imaging by MRI must be delayed.⁸⁰ Of interest, US-detectable injury correlates with later development of CP.

MRI is more sensitive and specific than US for defining both qualitative and quantitative data about the developing and injured brain relevant for detecting subtle pathologies associated with cognitive impairment, including focal, noncystic white matter injury, diffuse white matter injury, and small cerebellar hemorrhages.⁹⁹⁻¹⁰⁶ On the basis of increasing evidence that MRI-detected injury may be more accurate than US for defining diagnosis and in estimating prognosis,^{107,108} some experts recommend imaging for all children born <28 weeks' gestation¹⁰⁹; however, routine use of MRI for all preterm neonates remains controversial.

MRI can be accomplished without sedation by feeding and swaddling and using a beanbag positioning device.¹¹⁰ However, despite careful preparation, at least 25% to 30% of newborns require sedation or general anesthesia to achieve high quality, motion-free images. Although it is recognized that anesthetizing these infants for imaging studies poses risks and challenges, the information often assists primary care takers and family members with management decisions.

CT requires a relatively high dose of radiation due to the high water content of the neonatal brain, especially the premature. Although some guidelines recommend CT in case of suspected intracranial hemorrhage,⁹⁷ many experts recommend avoiding the risks of radiation exposure, especially when MRI is available.¹¹¹

PROTECTING THE NEWBORN BRAIN

Prompt access to resuscitation and initiation of supportive care during the high-risk perinatal period (i.e., labor, birth, and postnatal) are essential for protecting the developing brain. Guidelines by the International Liaison Committee on Resuscitation and the Neonatal Resuscitation Program guide initial resuscitation.¹¹² Principles for maintaining normal cardiopulmonary function during the initial resuscitation are relevant to neonates at high risk for brain injury since hemodynamic stability is essential to prevent secondary brain injury (Table 7) and adverse postoperative outcomes.¹¹³

Inducing mild hypothermia (whole-body cooling to $33.5^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$, or selective head cooling) for 72 hours initiated within 6 hours of birth among term neonates with signs of perinatal asphyxia and encephalopathy has been reported to reduce brain injury,^{114,115} risk of death, and/or major developmental disability at age 18 (risk ratio 0.76; 95% CI: 0.69–0.84). Furthermore, hypothermia increases the rate of survival with normal neurological function (risk ratio: 1.63; 1.36–1.95).¹¹⁶ Current investigations are underway to examine the therapeutic effect of late-onset hypothermia (after 6 hours), of cooling preterm neonates (33–35 weeks' gestational age), and longer (120 hours) or deeper (32°C) cooling. In addition, a number of promising neuroprotective agents (erythropoietin and darbepoietin, melatonin, xenon, topiramate, allopurinol, magnesium sulfate, stem cells) are being investigated in animal models and clinical trials.

CONCLUSIONS

In conclusion, premature birth is a significant cause of infant and child morbidity and mortality. In the United States, the premature birth rate, which had steadily increased during the 1990s and early 2000s, has decreased annually for 7 years and is now approximately 11.39%. Human viability, defined as gestational age at which the chance of survival is 50%, is now approximately 23 to 24 weeks in developed countries. Infant girls, on average, have better outcomes than infant boys. A relatively uncomplicated course in the intensive care nursery for an extremely premature infant results in a discharge date close to the prenatal EDC. Despite technological advances and efforts of child health experts during the last generation, the extremely premature infant (less than 28 weeks gestation) and ELBW infant (<1000 g) remain at high risk for death and disability with 30% to 50% mortality and, in survivors, at least 20% to 50% risk of morbidity. The introduction of CPAP, mechanical ventilation, and exogenous surfactant increased survival and spurred the development of neonatal intensive care in the 1970s through the early 1990s. Routine administration of antenatal steroids during premature labor improved neonatal mortality and morbidity in the late 1990s. The recognition that chronic postnatal administration of steroids to infants should be avoided may have improved outcomes in the early 2000s. Evidence from recent trials attempting to define the appropriate target for oxygen saturation in preterm infants suggests that arterial oxygen saturation between 91% and 95% (compared with 85%–89%) avoids excess mortality. Final analyses of data from these trials have not been published, however, so definitive recommendations are still pending. The development of neonatal neurocritical intensive care units may improve neurocognitive outcomes in this high-risk group.

Table 7. Supportive Care for the At-Risk Developing Brain

Supportive care	Principles	Consequence of mismanagement
Oxygenation	Avoid hyperoxia	Oxygen toxicity during reperfusion Tissue damage from oxidative stress Cerebral proinflammatory responses
Ventilation	Avoid hypocapnea	Disrupted cerebral autoregulation and blood flow
Circulatory support	Maintain stable physiologic blood pressure	Hypoperfusion Risk of intraventricular hemorrhage in preterms with rapid shifts in blood pressure
Temperature control	Maintain normothermia	Hyperthermia can exacerbate underlying brain injury
Glucose management	Maintain Physiologic glucose levels	Hypoglycemia can cause de novo brain injury

Long-term follow-up to detect and address developmental, learning, behavioral, and social problems is critical for children born at these early gestational ages.

The striking similarities in response to extreme prematurity in the lung and brain imply that agents and techniques that benefit one organ are likely to also benefit the other. Finally, because therapy and supportive care continue to change, the outcomes of ELBW infants are ever evolving. Efforts to minimize injury, preserve growth, and identify interventions focused on antioxidant and anti-inflammatory pathways are now being evaluated. Thus, treating and preventing long-term deficits must be developed in the context of a “moving target.” ■■

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