REVIEW ARTICLE

MEDICAL PROGRESS

Management and Outcomes of Very Low Birth Weight

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N Engl J Med 2008;358:1700-11.

Approximately 12.5% of births in the United States are preterm (occurring before 37 weeks of gestation). Preterm infants with "very low" birth weight are those who weigh 1500 g or less; those with "extremely low" birth weight weigh 1000 g or less. Although they account for only 1.5% and 0.7% of live births, respectively, these infants contribute disproportionately to neonatal morbidity and to health care costs. For example, in the United States approximately 40% of the estimated 6600 cases of cerebral palsy that are diagnosed each year occur in children with a very low birth weight.[1] In 2003, preterm infants accounted for approximately $18.1 billion in health care costs, or half of total hospital charges, for newborn care in the United States.[1]

The often complicated medical outcomes in extremely premature infants have generated discussion of the ethics of investing medical and financial resources in those infants who are on the border of viability. This article reviews recent progress in the understanding, management, and outcomes of some of the most common conditions affecting infants with very low birth weight (Table 1). We emphasize the care of extremely-low-birth-weight infants and provide a perspective on the determinants of the long-term outcome.

OUTCOMES OF VERY LOW BIRTH WEIGHT

Approximately 85% of infants with a very low birth weight survive to be discharged from the hospital.[2] Within 2 years after discharge, 2 to 5% die from medical complications related to their preterm birth. During the past decade, survival has improved, particularly in infants with extremely low birth weight (Fig. 1A).[2,3] Extremely premature infants born in perinatal centers for high-risk infants, especially those with a high volume of such infants,[4,5] have better short-term outcomes than infants transferred to such centers after birth.[6] The incidence of most short-term major medical complications associated with prematurity (Table 1) has remained relatively stable (Tables 2 and 3), despite improvements in survival (Fig. 1A).[2,3]

Infants born at the threshold of viability (those with a gestational age of 23 to 25 weeks, a birth weight of less than 500 g, or both) are at the greatest risk for a poor outcome (Fig. 1B), although it is uncertain what proportion of these infants are resuscitated and given intensive care. For example, in the Vermont Oxford Network (a voluntary network for data collection in more than 650 neonatal intensive care units in the United States and abroad), among infants born between 1996 and 2000 with a birth weight of 401 to 500 g and a mean gestational age of 23.2 weeks, mortality was 83%, and survivors often had serious short-term medical complications.[7] The EPICure study reported outcomes for all infants born at a gestational age of 20 to 25 weeks over a 10-month period in 1995 in the United Kingdom and Ireland.[8] Only 811 of the 4004 infants (20%) received intensive care, and 39% of those survived to discharge. Of the survivors, 16.5% had ultrasonographic evidence

Table 1. Major Short- and Long-Term Problems in Very-Low-Birth-Weight Infants.

Affected Organ or System	Short-Term Problems	Long-Term Problems
Pulmonary	Respiratory distress syndrome, air leak, bronchopulmonary dysplasia, apnea of prematurity	Bronchopulmonary dysplasia, reactive airway disease, asthma
Gastrointestinal or nutritional	Hyperbilirubinemia, feeding intolerance, necrotizing enterocolitis, growth failure	Failure to thrive, short-bowel syndrome, cholestasis
Immunologic	Hospital-acquired infection, immune deficiency, perinatal infection	Respiratory syncytial virus infection, bronchiolitis
Central nervous system	Intraventricular hemorrhage, periventricular white-matter injury, hydrocephalus	Cerebral palsy, hydrocephalus, cerebral atrophy, neurodevelopmental delay, hearing loss
Ophthalmologic	Retinopathy of prematurity	Blindness, retinal detachment, myopia, strabismus
Cardiovascular	Hypotension, patent ductus arteriosus, pulmonary hypertension	Pulmonary hypertension, hypertension in adulthood
Renal	Water and electrolyte imbalance, acid–base disturbances	Hypertension in adulthood
Hematologic	Iatrogenic anemia, need for frequent transfusions, anemia of prematurity	
Endocrine	Hypoglycemia, transiently low thyroxine levels, cortisol deficiency	Impaired glucose regulation, increased insulin resistance

of severe brain injury, and 74% needed supplemental oxygen at 36 weeks' postmenstrual age.[8]

Decisions about which infants will be considered candidates for resuscitation and intensive care are generally based on the anticipated gestational age at birth. However, the likelihood of survival without serious sequelae may be influenced by factors in addition to gestational age. Elsewhere in this issue of the *Journal*, Tyson et al. present an analysis of these factors in a prospective cohort of infants born at a gestational age of 22 to 25 weeks who were provided intensive care at the National Institute of Child Health and Human Development Neonatal Research Network sites between 1998 and 2003.[9] In a multivariate analysis, exposure to antenatal corticosteroids, female sex, singleton gestation, and higher birth weight (in 100-g increments) were each associated with a decrease in the risk of death or of survival with neurodevelopmental impairment; the reduced risk was similar to the risk for infants with an additional week of gestational age.[9]

Accurate assessment of longer-term outcomes, especially at school age or in adulthood, is difficult because most studies are not population-based, and patients are often lost to follow-up. In most studies, a large proportion of extremely-low-birth-weight infants assessed in early childhood (18 to 30 months of age) have neurosensory disability or cerebral palsy (Fig. 2).[10-12] Of the surviving infants from the EPICure study who were evaluated at 30 months of age, half had a motor, cognitive, or neurosensory disability; in approximately one quarter of the children, the disability was considered severe.[11] The prevalence of neurosensory disability in childhood appears to have decreased in the case of infants with a birth weight of 1000 to 1499 g who were born after 1990.[14] However, data are inconsistent about whether the improved survival among infants with extremely low birth weight has been accompanied by an increase or a decrease in disability.[15,16]

Severe disability in early childhood generally persists at school age. In the EPICure study, 86% of infants with severe disability at 30 months had moderate-to-severe disability at 6 years of age.[11] In a study by Hack et al.,[17] children who had been born between 1992 and 1995 were evaluated at 8 to 9 years of age. Of every 100 children studied, 24 more children with an extremely low birth weight had an IQ of less than 85, 38 more received special medical or educational services, and 43 more had some functional limitation, as compared with children with a normal birth weight.[17] However, approximately one third of the children with an extremely low weight at birth and no neurosensory abnormalities at discharge had an IQ of less than 85, learn-

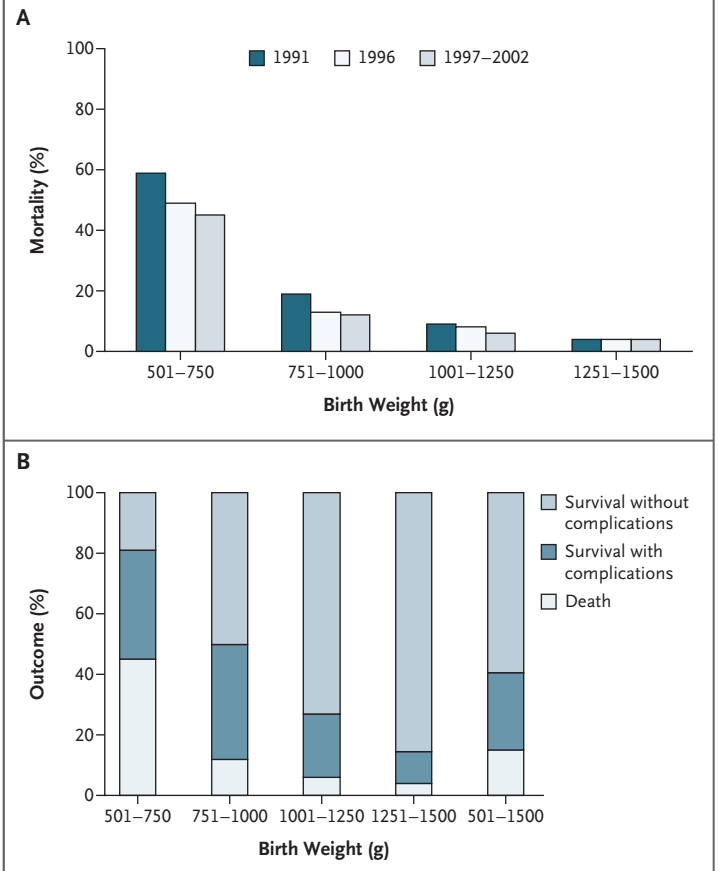

Figure 1. Short-Term Outcomes of Very Low Birth Weight According to Birth-Weight Group.

Panel A shows mortality for the period from 1991 through 2002 at the National Institute of Child Health and Human Development Neonatal Research Network sites. Data are from Fanaroff et al.[2] and Lemons et al.[3] Panel B shows the proportion of very-low-birth-weight infants who died and the proportion who survived with short-term complications (bronchopulmonary dysplasia, severe intraventricular hemorrhage, necrotizing enterocolitis, or a combination of these disorders) or with no complications for the period from 1997 through 2002 at the National Institute of Child Health and Human Development Neonatal Research Network sites. Data are from Fanaroff et al.[2]

ing problems, or poor motor skills, and two thirds had behavioral problems — a proportion that was two to three times as high as that of controls (Fig. 3). Other studies show similar rates of neurosensory and motor disability at school age for children with an extremely low birth weight.[10,12,13,18,19]

Few studies have examined outcomes of very low birth weight in adolescence or adulthood.[20-23] In two cohort studies of young adults, subjects with a very low birth weight, who were assessed at an average age of 20 years,[20] and those with an extremely low birth weight, who were assessed at an average age of 23 years,[21] were more likely to have medical, functional, and neurodevelopmental problems than controls with a normal birth weight. However, many of those with a very low or extremely low birth weight were functional as young adults in terms of educational attainment, employment, and independent living, suggesting that early functional and cognitive impairments can be overcome. The development of hypertension, insulin resistance, and impaired glucose tolerance in adulthood has also been associated with very low birth weight.[24]

COMPLICATIONS OF VERY LOW BIRTH WEIGHT

Complications of very low birth weight, especially if several are present, are associated with a poor neurocognitive outcome. For example, in a large study of indomethacin prophylaxis in infants with extremely low birth weight, the rates of disability at 18 months of age were 42% among infants with bronchopulmonary dysplasia, ultrasonographic evidence of brain injury, or severe retinopathy of prematurity; 62% among infants with two of these diagnoses; and 88% among those with all three.[25] In contrast, only 18% of children without these conditions had disability at 18 months.

Most research on management strategies for infants with very low birth weight has focused on prevention of the complications of prematurity. Since these complications are strongly associated with later neurodevelopmental disability, a reduction in their number and severity would be expected to improve long-term outcomes. However, the best practices for avoiding short-term complications of prematurity are uncertain, and both short-term and long-term outcomes for very-low-birth-weight infants vary substantially among centers.[26]

BRONCHOPULMONARY DYSPLASIA

Bronchopulmonary dysplasia, also known as chronic lung disease of prematurity and typically defined as the need for supplemental oxygen at 36 weeks' postmenstrual age, affects approximately 10% and 40% of very-low-birth-weight and extremely-low-birth-weight infants, respectively, who survive to discharge.[2] Nearly two thirds of in-

fants in whom bronchopulmonary dysplasia develops had an extremely low birth weight and were born before a gestational age of 28 weeks.[27] Affected infants are more likely to have long-term pulmonary problems, to be rehospitalized during the first year of life, and to have delayed neurodevelopment.[27,28]

Inflammation of the lung resulting from ventilator-induced mechanical injury, oxidant stress, and prenatal or postnatal infection contributes to the pathogenesis of bronchopulmonary dysplasia.[29-33] Nutritional deficiencies, genetic factors, and abnormal growth factor signaling also may play a role. Histologic chorioamnionitis and funisitis affect 80% of spontaneously delivered preterm infants and are associated with an increased risk of bronchopulmonary dysplasia. Elevated inflammatory markers (interleukin-8, tumor necrosis factor α, interleukin-6, and leukotrienes) in amniotic fluid, cord blood, and tracheal secretions of infants undergoing mechanical ventilation have also been linked to the development of bronchopulmonary dysplasia.[30,33]

Bronchopulmonary dysplasia is the most common and most extensively studied complication of prematurity.[27] Rates vary widely among institutions even after risk adjustment, suggesting that differences in management influence the incidence of this condition.[34-37] The best-studied strategies to prevent bronchopulmonary dysplasia include using pharmacologic approaches, such as administration of postnatal corticosteroids and inhaled nitric oxide, and limiting mechanical injury from assisted ventilation.

Table 2. Survival and Selected Complications in Very-Low-Birth-Weight Infants Born in NICHD Neonatal Research Network Sites, 1995–1996 vs. 1997–2002.*

Outcome	1995–1996 (N=4438)	1997–2002 (N=18,153)
	percent of infants	
Survival	84	85
Survival without complications	70	70
Bronchopulmonary dysplasia	23	22
Need for supplemental oxygen at home	15	11
Necrotizing enterocolitis	7	7
Severe intraventricular hemorrhage	12	12
Periventricular white-matter injury	5	3
Late-onset sepsis	24	22

* Very low birth weight was defined as a weight of 500 to 1500 g. Data for 1995–1996 are from Lemons et al.[3] Data for 1997–2002 are from Fanaroff et al.[2] NICHD denotes National Institute of Child Health and Human Development.

Ventilatory Strategies to Prevent Bronchopulmonary Dysplasia

Because of a deficiency in the amount of surfactant in the lung, inadequate respiratory drive, or both, the majority of infants with extremely low birth weight need supplemental oxygen and assisted ventilation soon after birth to achieve adequate gas exchange. Surfactant therapy has reduced mortality from the acute respiratory distress syndrome but has not reduced the incidence of bronchopulmonary dysplasia, most likely because of the increased survival among more immature infants, who are at the greatest risk for the disease.

Table 3. Overall Survival and Survival with Selected Complications among Very-Low-Birth-Weight Infants in the NICHD Neonatal Research Network, 1997–2002.*

Outcome	Birth Weight			
	501–750 g (N=4046)	751–1000 g (N=4266)	1001–1250 g (N=4557)	1251–1500 g (N=5284)
	percent of infants			
Overall survival	55	88	94	96
Survival with complications	65	43	22	11
Bronchopulmonary dysplasia alone	42	25	11	4
Severe intraventricular hemorrhage alone	5	6	5	4
Necrotizing enterocolitis alone	3	3	3	2
Bronchopulmonary dysplasia and severe intraventricular hemorrhage	10	4	2	<1

* Data are from Fanaroff et al.[2] NICHD denotes National Institute of Child Health and Human Development.

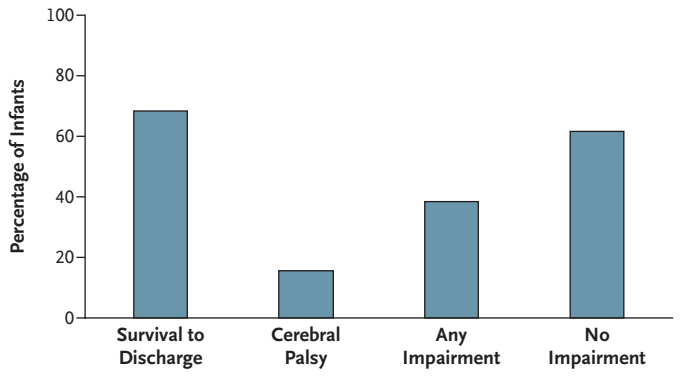

Figure 2. Outcomes of Extremely Low Birth Weight among 2539 Infants Evaluated at 18 to 22 Months of Corrected Age.

Data are for surviving infants born between 1997 and 1998 at National Institute of Child Health and Human Development Neonatal Research Network sites for whom complete follow-up data were available (18% of infants who were alive at discharge had no or incomplete follow-up or died after discharge). Any impairment was defined as one or more of the following: moderate-to-severe cerebral palsy, a score on the Mental Developmental Index or the Psychomotor Developmental Index of less than 70 (2 SD below the mean), blindness in both eyes, or hearing loss requiring amplification in both ears. Data are from Vohr et al.[13]

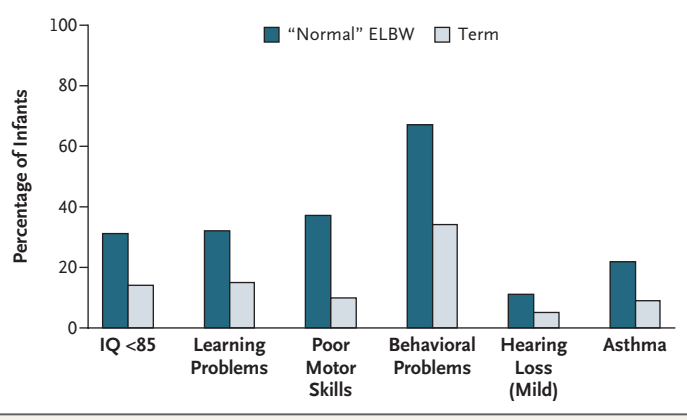

Figure 3. Selected Neurodevelopmental and Medical Complications at 8 to 9 Years of Age in Children with Extremely Low Birth Weight (ELBW) but No Apparent Neurosensory Abnormalities at Initial Hospital Discharge (termed "normal" ELBW), as Compared with Term Controls.

Data are from Hack et al.[17]

Practices that limit excessive exposure to oxygen or high tidal volumes from mechanical ventilation may minimize lung injury. Targeting lower oxygen saturation in infants who are receiving supplemental oxygen may protect the lung from oxidative injury. For example, in a randomized trial of routine as compared with lower targets for oxygen saturation in very-low-birth-weight infants who continued to require supplemental oxygen at 32 weeks' postmenstrual age, the incidence of bronchopulmonary dysplasia and the need for home oxygen therapy were reduced in the group with a lower target for oxygen saturation (91 to 94%) as compared with the group with a routine target (95 to 98%).[38] In addition, application of nasal continuous positive airway pressure (CPAP) soon after birth instead of early endotracheal intubation and mechanical ventilation is associated with a lower incidence of bronchopulmonary dysplasia.[34,36] Routine use of CPAP immediately after delivery may obviate the need for intubation in infants with a gestational age of 24 weeks or more, and increasing experience with this approach has been shown to improve its success.[39,40] According to one report, mechanical ventilation was avoided in approximately one third of infants with a gestational age of 25 weeks or less and in nearly 80% of infants with a gestational age of 28 weeks or more.[39]

Another approach to assisted ventilation is early administration of surfactant and mechanical ventilation for 1 or 2 days followed by extubation and application of CPAP. Studies have shown that with the use of this approach, approximately one quarter of infants born before a gestational age of 27 weeks do not require a subsequent course of mechanical ventilation and are less likely to have bronchopulmonary dysplasia.[41,42] Different approaches to ventilatory support in the delivery room were compared in a prospective, randomized trial.[43] In this study, infants with a gestational age of 25 to 28 weeks who were breathing but required ventilatory assistance at 5 minutes after birth were randomly assigned to treatment with nasal CPAP or to intubation and mechanical ventilation. In the infants who were assigned to treatment with CPAP, 56% did not require intubation, and surfactant use was halved. Although respiratory outcomes at 36 weeks' postmenstrual age and complications of prematurity were equivalent in the two study groups, a greater number of the infants who were assigned to initial treatment with CPAP had pneumothorax (9% vs. 3%). Two similar multicenter trials are in progress.

Hypocapnia in mechanically ventilated infants often indicates that tidal volumes are excessive, and this condition has been associated with an

increased incidence of subsequent bronchopulmonary dysplasia.[44] Because of its biologic plausibility, "minimal ventilation," also known as permissive hypercapnia, which targets levels of the partial pressure of carbon dioxide ($PaCO_2$) that are higher than physiologic levels as a proxy for more gentle ventilation, is widely used, although the acceptable range of hypercapnia is not known. In a large trial of this strategy, 220 infants with extremely low birth weight were randomly assigned to minimal ventilation (target $PaCO_2$ value, 52 mm Hg or higher) or routine ventilation (target $PaCO_2$ value, 48 mm Hg or lower).[45] The combined rate of bronchopulmonary dysplasia or death and other short-term complications did not differ between the two groups, although fewer infants in the hypercapnia group required mechanical ventilation at 36 weeks' postmenstrual age. However, in a smaller study in which the target $PaCO_2$ range in the hypercapnia group was higher (55 to 65 mm Hg), neurodevelopmental impairment or death at 18 to 22 months of corrected age (the chronologic age the infant would be if the pregnancy had gone to term) was higher than that in the control group, with no difference in the incidence of bronchopulmonary dysplasia.[46] Because high $PaCO_2$ levels may impair autoregulation of cerebral blood flow, the safety of this strategy requires additional study.

Conventional mechanical ventilation, which is typically time-cycled, pressure-limited, and synchronized with the infant's spontaneous breathing rate, is the most widely used technique for respiratory support in preterm infants. Other types of ventilation may minimize lung injury by avoiding overdistention of the airways and airspaces or avoiding repetitive inflation and collapse of the lung, or both, although this advantage has not been proved. High-frequency ventilation, a technique of rapid ventilation using very small tidal volumes, is the alternative that has been studied most extensively. A meta-analysis of 17 randomized trials with a total of 3776 enrolled infants showed no benefit of high-frequency ventilation as compared with conventional mechanical ventilation in the composite outcome of death or bronchopulmonary dysplasia, although the risk of air leak was unexpectedly higher among the infants treated with high-frequency ventilation.[47] Other techniques, such as noninvasive synchronized nasal ventilation[48] and volume-targeted ventilation,[49,50] may reduce the duration of mechanical ventilation and limit complications such as pneumothorax, as compared with conventional ventilation, although the effect with respect to the long-term pulmonary outcome and other complications has not been adequately addressed.[51]

Pharmacologic Prevention of Bronchopulmonary Dysplasia

Pharmacologic approaches to the prevention of bronchopulmonary dysplasia that have been evaluated include the use of corticosteroids, inhaled nitric oxide, vitamin A supplements, and other antioxidants.

Corticosteroids. The association of bronchopulmonary dysplasia with low baseline serum cortisol concentrations and with a blunted response to stimulation with a synthetic adrenocorticotropic hormone (cosyntropin) in infants with very low birth weight suggests that an exaggerated inflammatory response to lung injury may contribute to the development of bronchopulmonary dysplasia and that corticosteroid administration might treat or prevent this condition.[52] Dexamethasone given in the first few days after birth, at 1 to 2 weeks of age, or to infants with a prolonged need for assisted ventilation improves lung function, facilitates extubation, and lowers the incidence of bronchopulmonary dysplasia.[53] However, the association of early dexamethasone treatment with intestinal perforation (especially when the dexamethasone is used in combination with indomethacin),[54] as well as with neurodevelopmental impairment and cerebral palsy has diminished enthusiasm for this treatment and has led to a marked decrease in its use over the past decade.[55,56] The possible role of postnatal corticosteroids in the prevention of bronchopulmonary dysplasia in selected infants, such as those exposed to chorioamnionitis, was suggested by a trial of early treatment with hydrocortisone.[57] The risk of impaired neurodevelopment may be lower with hydrocortisone than with dexamethasone therapy,[58,59] although comparative trials are unlikely to be undertaken, owing to safety and ethical considerations.

Inhaled Nitric Oxide. Inhaled nitric oxide may improve the pulmonary outcome in some infants with very low birth weight, through mechanisms that are thought to involve decreased pulmonary vascular resistance or improved ventilation–perfusion matching,[60] bronchodilatation, antiin-

flammatory effects, promotion of lung remodeling in response to injury, or normalized surfactant function.[61-63] Inhaled nitric oxide used as an early rescue therapy for very-low-birth-weight infants with severe hypoxic respiratory failure does not improve the pulmonary outcome or survival and may be associated with increased mortality or an increased incidence of intraventricular hemorrhage.[64] Results of trials involving premature infants with less severe lung disease who were at risk for bronchopulmonary dysplasia are mixed.[65-67] In a multicenter trial involving ventilator-dependent infants with a birth weight of 500 to 1250 g, treatment with inhaled nitric oxide started at 7 to 14 days of age and continued for an average of 23 days increased survival without bronchopulmonary dysplasia, as compared with placebo.[65] In a single-center trial involving infants with a gestational age of less than 34 weeks and a weight of less than 2 kg at birth, nitric oxide treatment started before 24 hours of age and continued for 7 days, as compared with placebo, also increased survival without bronchopulmonary dysplasia.[67] In the latter study, treated infants also were less likely to have ultrasonographic evidence of brain injury and had a better neurodevelopmental outcome at 2 years of age than those who received placebo.[67,68] In contrast, in a multicenter trial of nitric oxide treatment started before 48 hours of age and continued for 21 days in infants with a birth weight of 500 to 1250 g who continued to require mechanical ventilation, only nitric oxide–treated infants with a birth weight of greater than 1000 g had a pulmonary benefit.[66] Treated infants in this study were also less likely to have ultrasonographic evidence of brain injury than control infants.[66] Routine use of this therapy awaits long-term follow-up of pulmonary and neurodevelopmental outcomes. Additional studies are also required to identify the infants who are most likely to benefit from this therapy and to determine the optimal dose, time to initiate treatment, and duration of treatment.

Other Pharmacologic Therapies. Multiple strategies may be needed to prevent bronchopulmonary dysplasia because its cause is multifactorial.[69] Vitamin A contributes to lung growth, response to lung injury, and protection from infection, and a deficiency of vitamin A, which is a common condition in extremely-low-birth-weight infants, is associated with an increased risk of bronchopulmonary dysplasia. Supplementation with vitamin A in infants with extremely low birth weight has been shown to reduce biochemical evidence of vitamin A deficiency and decrease the incidence of bronchopulmonary dysplasia by approximately 12%.[70] In a trial involving infants with a birth weight of 500 to 1250 g, the initiation of treatment with caffeine citrate in the first 10 days after birth decreased the rate of bronchopulmonary dysplasia (a secondary outcome), as compared with placebo (36% vs. 47%), without adverse effects.[71] Caffeine also reduced the composite primary outcome of death, cerebral palsy, cognitive delay, deafness, or blindness at 18 to 22 months of age.[72] Other drugs in early stages of investigation include antioxidants (superoxide dismutase, *N*-acetylcysteine), antiproteinases (alpha-1 proteinase inhibitor), and targeted cytokine and anticytokine therapies.[69]

PATENT DUCTUS ARTERIOSUS

Spontaneous closure of the ductus arteriosus is delayed in approximately 65% of infants with very low birth weight, especially those with respiratory disease. Bronchopulmonary dysplasia occurs more often in infants in whom symptomatic patent ductus arteriosus develops.[73] The association of these two conditions is thought to be due to the excessive pulmonary blood flow caused by left-to-right shunting of blood through the persistent vessel, leading to an increased need for supplemental oxygen and ventilator support. Cyclooxygenase inhibitors (indomethacin or ibuprofen) close a persistent patent ductus approximately 80% of the time.[73] In randomized trials, indomethacin as prophylaxis or treatment for symptomatic patent ductus arteriosus did not reduce the incidence of bronchopulmonary dysplasia, as compared with placebo, although the fact that treatment with pharmacologic or surgical closure was used in the control groups limits the interpretation of this finding.[74,75]

In the largest trial reported, prophylactic indomethacin reduced the incidence of patent ductus arteriosus and the rate of surgical ligation but did not change the incidence of bronchopulmonary dysplasia.[74] Although the rate of severe intraventricular hemorrhage was lower in the indomethacin group, the neurodevelopmental outcome at a corrected age of 18 to 22 months was not different from that in the control group.[74] However, in a post hoc analysis, the incidence of

bronchopulmonary dysplasia among infants in whom the ductus closed spontaneously was higher among those who received indomethacin than among those who received placebo (43% vs. 30%), suggesting a possible adverse and independent negative effect of indomethacin treatment.[75]

Surgical ligation of the ductus is typically performed when pharmacologic closure is unsuccessful. This surgical procedure is associated with an increased risk of bronchopulmonary dysplasia and a poor neurodevelopmental outcome.[76] Whether surgery is responsible for the increased risk of a poor outcome or merely identifies a group of infants who are at increased risk is unclear.[76] Further research is needed to identify which infants might benefit from ductal closure and what effect current surgical approaches have on the incidence of bronchopulmonary dysplasia and impaired neurodevelopment.

GASTROINTESTINAL IMMATURITY AND NECROTIZING ENTEROCOLITIS

Optimal early nutrition is essential for growth and neurodevelopment and may influence health through adulthood. Despite aggressive early nutrition, many very-low-birth-weight infants have growth failure at the time of discharge. The most immature infants receive nutrients in specially formulated parenteral nutrition solutions, which are often delivered through a central venous catheter; enteral feeding of expressed human milk or of special formulas for premature infants is provided through an orogastric tube. Decisions regarding the initiation of feeding depend in part on the balance between the risk of complications, such as sepsis or thrombosis, that are associated with the use of central catheters and the risk of necrotizing enterocolitis, which is associated with enteral feeding.

Necrotizing enterocolitis, a syndrome of inflammation and necrosis of the small and large intestines, develops in approximately 5 to 10% of very-low-birth-weight infants.[2] The incidence of this syndrome varies widely among centers.[2] Fifteen to 30% of infants with necrotizing enterocolitis do not survive, and survivors have greater neurodevelopmental impairment than unaffected infants.[77-79] The disease primarily affects infants who have received enteral feedings. Most infants have a response to medical management, which consists of bowel rest and administration of systemic antibiotics; however, 20 to 40% require surgery for bowel necrosis and perforation.[2] Mortality among infants who require surgery is as high as 50% and is highest among the least mature infants. Extensive surgery may also lead to nutritional deficiencies and a failure to thrive, owing to the short-bowel syndrome.

The pathogenesis of necrotizing enterocolitis is poorly understood.[80] One of the factors thought to contribute to this syndrome is immaturity of gastrointestinal function (which includes immature gastrointestinal motility, digestive ability, intestinal barrier function, and innate immunity).[80] In addition, commensal bacteria in the gut may modulate the intestinal inflammatory response.[80] Frequent treatment with broad-spectrum antibiotics and exposure to nosocomial flora modify bacterial colonization of the gut. Abnormal bacterial colonization after birth may induce a hyperactive inflammatory response to challenges to intestinal integrity and contribute to the development of necrotizing enterocolitis.

Treatment with antenatal corticosteroids and feeding of expressed breast milk reduce the rate of necrotizing enterocolitis.[81] H_2-receptor antagonists appear to increase the risk of this disorder, perhaps by changing the intestinal pH and influencing bacterial colonization.[82] Studies of strategies to prevent necrotizing enterocolitis have focused primarily on the effect of the initiation and advancement of enteral feedings. A Cochrane review indicates that early minimal enteral (trophic) feeding, as compared with delayed feeding, reduces the number of days needed to achieve full feeding, feeding intolerance, and length of stay in the hospital, with no increase in the risk of necrotizing enterocolitis.[83] However, the studies included in this review were small, had methodologic limitations, and did not focus on infants with extremely low birth weight. Implementation of a standardized feeding regimen for very-low-birth-weight infants reduces variations in practice among practitioners and may enhance early recognition of feeding intolerance and reduce the rate of necrotizing enterocolitis by as much as 87%.[84]

A promising approach to the prevention of necrotizing enterocolitis is to modify bacterial colonization of the gut.[85] In small trials involving infants with very low birth weight, enteral administration of probiotic supplements, including lactobacilli, bifidobacteria, and saccharomyces, reduced the incidence and severity of nec-

rotizing enterocolitis, although it is not known whether this treatment altered intestinal flora.[86,87] Because probiotic bacterial colonization may lead to invasive disease in newborns,[88] further study is needed to ensure the safety of this approach.

An alternative approach is the use of "prebiotics," nondigestible dietary supplements such as long-chain carbohydrates and mucins that promote intestinal growth of normal commensal organisms. Prebiotics given to preterm infants who are fed formula decrease colonization of the intestines with pathogenic bacteria, although the effect of this approach on the incidence of necrotizing enterocolitis is not known.[89]

Surgical intervention in infants with necrotizing enterocolitis in whom bowel perforation occurs consists of either laparotomy for excision of necrotic or compromised bowel or percutaneous placement of a peritoneal drain. In a randomized trial of these approaches, mortality and the proportion of infants who still needed parenteral nutrition 90 days postoperatively were similar in the two treatment groups.[90] In a prospective cohort study comparing these strategies, almost three quarters of the infants died or had neurologic impairment at 18 to 22 months of corrected age.[91] In a risk-adjusted analysis, the rate of death or impairment was lower with laparotomy than with drain placement.[91]

NEUROSENSORY COMPLICATIONS

The major neurosensory complications of premature birth are intraventricular hemorrhage, periventricular white-matter injury, and retinopathy of prematurity. Although the incidence of severe intraventricular hemorrhage has fallen with improvements in management and increased antenatal corticosteroid use, it remains a major cause of brain injury with consequent abnormal neurodevelopment. Pharmacologic approaches to the prevention of intraventricular hemorrhage after birth have been generally unsuccessful. Prophylactic treatment with indomethacin reduces the incidence of severe intraventricular hemorrhage but does not improve long-term neurodevelopment.[74]

Periventricular white-matter injury is the predominant form of brain injury in extremely preterm infants and correlates strongly with the development of cerebral palsy. Its pathogenesis is poorly understood, and no specific neuroprotective strategy is known. In some infants, cerebral blood flow and oxygen delivery, as measured with near-infrared spectroscopy, vary during fluctuations in blood pressure that are considered to be in the normal range, and this lack of autoregulation of cerebral blood flow may lead to ischemic white-matter injury.[92] Whether aggressive treatment of hypotension in extremely-low-birth-weight infants prevents or leads to subsequent brain injury is unclear, probably because blood pressure, which is easily measured, does not correlate well with systemic or cerebral blood flow.[93,94] Maternal or neonatal infection or elevated levels of proinflammatory cytokines in amniotic fluid or cord blood increase the risk of white-matter injury, suggesting that inflammation plays a role in its pathogenesis.[95] Advanced techniques of magnetic resonance imaging in infants with white-matter injury show disturbances in cerebral growth, with a reduced volume of both gray and white matter.[96] These observations may explain the motor and cognitive dysfunction that is often seen in infants with white-matter injury.

Retinopathy of prematurity, a vascular proliferative disorder that affects the incompletely vascularized retina in preterm infants, is a major cause of blindness in these children. Severe retinopathy is 18 times as likely to develop in infants delivered before a gestational age of 25 weeks as in those born at a gestational age of more than 28 weeks. Periods of hyperoxia due to exposure to an excessive concentration of inspired oxygen contribute to its development.[97,98] However, the optimal target range of oxygen saturation is not known. Because the hemoglobin–oxygen saturation curve of fetal hemoglobin is shifed to the left, oxygen saturation exceeding 95% may be associated with arterial oxygen tension greater than 80 mm Hg, which may be excessive in an infant with extremely low birth weight. Conversely, oxygen saturation that is too low may increase the risk of injury to the brain or other end organs.[99]

Adjusting the concentration of inspired oxygen to achieve a lower oxygen saturation in extremely preterm infants may decrease the rate of severe retinopathy. In a prospective observational study, extremely-low-birth-weight infants who were treated in centers with a "restrictive" approach to oxygen delivery (maximum oxygen saturation, 70 to 90%), as compared with those treated in units with a "liberal" approach (88 to 98%), were less likely to have retinopathy requir-

ing cryotherapy (6.3% vs. 27.7%); the neurodevelopmental outcome at 1 year of age was similar with the two approaches.[100] In two studies involving infants with a gestational age of 28 weeks or less and historical controls, the incidence of severe retinopathy decreased after oxygen saturation limits were lowered from a range of 87 to 97% to a range of 85 to 93% until the infants reached 32 weeks' postmenstrual age.[101,102]

In two ongoing randomized trials, babies born before 28 weeks of gestational age are randomly assigned to a "high" target for oxygen saturation (91 to 95%) or a "low" target (85 to 89%).[97] The samples in these studies are sufficiently large to determine whether lower targets for oxygen saturation affect the incidence of retinopathy, bronchopulmonary dysplasia, and long-term disability and should help determine the appropriate approach to management with supplemental oxygen.

CONCLUSIONS

Progress in medical care has contributed to improved survival among all but the most immature infants. Neurosensory disability remains a major problem associated with preterm birth, although its incidence may be decreasing with greater use of antenatal corticosteroids, decreased use of postnatal corticosteroids, and improved intensive care. However, approaches to care and outcomes vary widely among centers. Future research to improve the understanding of disease mechanisms and their management should reduce unexplained variation and improve long-term outcomes.

No potential conflict of interest relevant to this article was reported.

We thank Ms. Allison Brooks for her assistance in the preparation of the manuscript and Dr. Lu-Ann Papile for her critical review of the manuscript.

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