ARTICLE

Developmental Sequelae in Preterm Infants Having a Diagnosis of Bronchopulmonary Dysplasia

Analysis Using a Severity-Based Classification System

Elizabeth J. Short, PhD; H. Lester Kirchner, PhD; George R. Asaad, BA; Sarah E. Fulton, MA, CCC-SLP; Barbara A. Lewis, PhD; Nancy Klein, PhD; Sheri Eisengart, PhD; Jill Baley, MD; Carolyn Kercsmar, MD; Meeyoung O. Min, PhD; Lynn T. Singer, PhD

Objective: To investigate the relationship between the severity-based definition of bronchopulmonary dysplasia (BPD), choice of treatment, and neurocognitive outcomes at age 3 and 8 years.

Design: This is a secondary analysis of data collected from a prospective, longitudinal sample of 99 children with a history of BPD.

Setting: Children born with BPD admitted to 3 hospitals from February 1, 1989, to November 31, 1991.

Participants: Ninety-nine children with BPD were longitudinally assessed at age 3 and 8 years. Three severity groups (mild, moderate, and severe) were formed based on gestational age and need for supplemental oxygen therapy.

Main Exposures: Supplemental oxygen therapy for 28 days or longer, birth weight less than 1500 g, and radiographic evidence of lung disease.

Main Outcome Measures: Neurologic and medical outcomes; type of medical management; and language, achievement, and cognitive functioning were compared among the 3 severity groups.

Results: Severity classification of BPD was associated with poorer outcomes. Compared with children with mild or moderate BPD, children with severe BPD performed more poorly on IQ tests (Mental Development Index, 90 vs 76.4; and Psychomotor Development Index, 92.5 vs 73.9) and language measures (total, 95 vs 82) at age 3 years and performance IQ (86 vs 75) and perceptual organization (86 vs 76) at age 8 years. Severity of BPD was not associated with choice of medical management but was related to educational interventions. Children with severe BPD received more special education services (69% vs 44%) than did children with mild BPD.

Conclusions: The severity-based classification clarifies the relationship between BPD and developmental sequelae. Children with severe BPD required more interventions at age 8 years than did children with mild or moderate BPD.

Arch Pediatr Adolesc Med. 2007;161(11):1082-1087

Author Affiliations:
Departments of Psychology (Dr Short and Mr Asaad) and Pediatrics (Drs Kirchner, Lewis, Eisengart, Baley, Kercsmar, Min, and Singer and Ms Fulton), Case Western Reserve University; and Department of Education, Cleveland State University (Dr Klein), Cleveland, Ohio.

BRONCHOPULMONARY DYSPLASIA (BPD) continues to be the leading chronic lung disease in infants in the United States.[1-3] Previously, the most widely used definition of BPD was requirement of oxygen therapy for at least 28 days and radiographic evidence of lung disorders.[3] Until recently, most researchers used this definition of BPD, which was dichotomous and did not allow for examination of how severity of BPD might affect outcomes. More recently, a new definition of BPD was advanced that attempted to quantify severity of disease based on the National Institute of Child Health and Human Development (NICHD)/National Heart, Lung, and Blood Institute (NHLBI) Workshop criteria.[2] Three levels of disease severity were proposed for preterm infants whose gestational age was younger than 32 weeks: (1) mild BPD, defined as requiring at least 28 days of supplemental oxygen therapy and discharge or termination of supplemental oxygen therapy by 36 weeks; (2) moderate BPD, defined as requiring at least 28 days of supplemental oxygen therapy with less than 30% oxygen at 36 weeks' postmenstruation age; and (3) severe BPD, defined as requiring at least 28 days of supplemental oxygen therapy with 30% oxygen or greater at 36 weeks' postmenstruation age. Although the consensus group strongly advocated for a change in the definition of BPD, to our knowledge, only 1 study has examined the validity of this severity-based definition using childhood outcomes.[4]

Ehrenkranz et al[4] found in a sample of preterm infants weighing less than 1000 g

that severity of BPD was related to adverse neurodevelopmental outcomes and seemed to be related to medical care. Children with severe BPD were more likely to experience chronic hypoxia,[5] were rehospitalized because of pulmonary disorders, and were administered more pulmonary medications compared with children with mild BPD. Severity of BPD was also related to intraventricular hemorrhage, sepsis, and postnatal steroid therapy. In addition, development of neurodevelopmental problems increased as a function of severity of BPD through age 22 months, with greater likelihood of mental and physical impairments and cerebral palsy in the group with severe BPD. The present study extends the findings of Ehrenkranz et al[4] in 2 ways: it includes infants weighing more than 1000 g but less than 1500 g and it provides follow-up on the effect of the severity of BPD through age 8 years. This is a secondary analysis using the NICHD/NHLBI classification of BPD in a cohort of children who had BPD as infants and were enrolled in a prospective, longitudinal study.[6,7] The analyses examined whether the severity of BPD was related to medical treatment, demographic findings, and cognitive outcomes at age 3 and 8 years.

METHODS

PARTICIPANTS

The children with BPD in the present study were part of a larger prospective study of children with very low birth weight and healthy term infants (control group).[6,7] All preterm infants with BPD admitted to the neonatal intensive care units of hospitals in the region of Cleveland, Ohio, from February 1, 1989, to November 31, 1991, were eligible for the study and were prospectively recruited. All preterm infants with BPD from a 4-county region were cared for in the level 3 neonatal intensive care units of the 3 participating hospitals. Infants with BPD were defined as having weighed less than 1500 g at birth, required supplemental oxygen therapy for more than 28 days, and exhibited radiographic evidence of lung disease.[8] The BPD definition of Northway et al,[8] which relies on the 28-day cutoff, was in use at the time of recruitment and has been shown to yield comparable results in assessments of outcomes using the Mental Development Index and Psychomotor Development Index of the Bayley Scales of Infant Development when compared with later definitions of BPD (oxygen dependence at 36 weeks).[9] A partial stratification sampling strategy was adopted to enroll adequate numbers of participants without socioeconomic disadvantage or severe neurologic risk. Infants having a diagnosis of BPD who were free of neurologic problems other than grades I or II intraventricular hemorrhage and who were not socially disadvantaged (ie, Hollingshead classification IV or V) were exhaustively recruited.[10] The remainder were randomly recruited by approaching the family of the next available infant having a diagnosis of BPD who could be accommodated in the follow-up schedule, regardless of neurologic risk status. This sampling strategy enabled an examination of the effect of neurologic risk on BPD severity.

One hundred twenty-two infants with BPD were enrolled in the prospective longitudinal study. Seven died after enrollment, leaving 115 children with BPD available for study at follow-up visits. Outcome data were available for 105 of these children at 3 or 8 years or both. Six of these children could not be classified according to the BPD severity index because of incomplete hospital records, leaving 99 children with BPD available for analysis. Eighty-nine of these children had data available at 3 years, 91 children had data available at 8 years, and 81 children had data available at both follow-up visits. Comparisons between included and excluded participants were performed for those demographic indices given in **Table 1** and proved to be nonsignificant.

All neonatal medical and demographic information was obtained from the hospital records and parent or guardian interviews. Cranial ultrasound studies were performed and reviewed by board-certified radiologists, typically at 3, 10, and 28 days and before hospital discharge. A system for rating the severity of intraventricular hemorrhage was used based on the extent of the lesion. A score of 0 was used to indicate no hemorrhage. Identifiable lesions were graded on a scale of 1 to 4, based on the criteria of Papile et al.[11] At least 1 ultrasound study was available for all premature infants, with ratings based on the most severe lesion diagnosed. In addition to 4 levels of intraventricular hemorrhage, coded 1 (least severe) through 4 (most severe), the following neurologic abnormalities were coded: seizures, meningitis, echodense lesions, porencephaly, hydrocephalus, neurologic malformations, ventriculoperitoneal shunt, and periventricular leukomalacia. Presence of a neurologic abnormality was coded as 1, and absence as zero. A total neurologic risk score was calculated based on the sum of these 8 abnormalities and the 4 grades of intraventricular hemorrhage, with the total neurologic risk score ranging from 0 to 12. The validity of the summary score has been demonstrated in its significant relationship to IQ at 3 years of age in a previous study.[9]

In addition to the medical and demographic data obtained from hospital records and parent or guardian interviews, the severity of BPD was recorded according to the criteria defined in the 2001 consensus workshop conducted by the NICHD/NHLBI.[2] Gestational age (<32 or ≥ 32 weeks) and supplemental oxygen therapy (none, $<30\%$ oxygen, or $\geq 30\%$ oxygen) both factored into whether a child was classified as having mild, moderate, or severe BPD. Also, the neonatal medical treatment used to manage BPD was abstracted and classified into 1 of 4 types: steroid therapy only, surfactant therapy only, a combination of both steroid and surfactant therapy, or neither steroid nor surfactant therapy.

PROCEDURES

All children with BPD who were recruited at birth were invited to participate in the 3- and 8-year follow-up visits. Assessments were completed in the behavioral laboratory of the Department of Pediatrics, Case Western Reserve University, Cleveland, Ohio, by examiners (one of whom was S.E.F.) uninformed about neonatal history including BPD severity. Families were reimbursed for transportation when needed or requested and were given a stipend of $100. The institutional review board of the hospital approved this study, and informed consent from parents or guardians and children's assent were obtained for all participants.

The measures used in this study were designed to assess the following 4 general areas of functioning: cognitive, psychomotor, academic, and language. School outcomes were obtained from multiple sources including teacher and parent ratings and school records. Parent and teacher surveys were used to obtain information about school placements, grade retention, and enrollment in special education services. Demographic information such as race/ethnicity and maternal educational achievement level was obtained through maternal interview and was used to ensure comparability across groups.

OUTCOME MEASURES AT AGE 3 AND 8 YEARS

The Bayley Scales of Infant Development, Second Edition,[12] were administered to assess general cognitive and physical development at age 3 years. Standard scores were obtained for the Mental Development Index and Psychomotor Development Index.

Table 1. Neonatal Characteristics in BPD Severity–Based Groups

Characteristic	Severity of BPD, Median (Interquartile Range)				*P* Value
	Mild (n = 53)	Moderate (n = 13)	Severe (n = 33)	Total (n = 99)	
Birth weight, g	998 (835-1132)	851 (766-980)	949 (722-1124)	959 (780-1170)	.19
Gestational age, wk	27 (26-29)	27 (25-28)	27 (26-29)	27 (26-29)	.43
Total oxygen therapy, d	44 (34-54)	92 (76-109)	117 (84-150)	63 (42-104)	<.001[a,b]
Assisted ventilation, d	24 (12-36)	31 (14-38)	43 (30-72)	32 (14-46)	<.001[b]
Head circumference, cm	25 (24-27)	26 (23-26)	25 (23-27)	25 (24-27)	.75
Neurologic risk	1.0 (0-2)	0.0 (0-3)	0.0 (0-3)	0.0 (0-2)	.90
White race	32 (60)	5 (38)	19 (58)	56 (57)	.38
Male sex	26 (49)	8 (62)	21 (64)	55 (56)	.40
Socioeconomic status low	27 (51)	7 (54)	21 (64)	54 (55)	.52
Singleton birth	36 (68)	13 (100)	27 (82)	76 (77)	.03[a]
Septicemia	25 (47)	8 (62)	15 (45)	48 (48)	.64
Periventricular leukomalacia	4 (8)	1 (8)	3 (9)	8 (8)	>.99
Cerebral palsy	6 (13)	1 (8)	4 (13)	11 (11)	.83
Intraventricular hemorrhage[c]					
Grade I	14 (26)	1 (8)	3 (9)	18 (18)	.29
Grade II	7 (13)	1 (8)	3 (9)	11 (11)	
Grade III	3 (6)	2 (15)	6 (18)	11 (11)	
Grade IV	2 (4)	1 (8)	1 (3)	4 (4)	
Neurologic risk score >1	28 (53)	5 (39)	14 (49)	47 (48)	.64
Medical management					
None	27 (51)	8 (62)	20 (61)	55 (56)	
Steroid therapy	13 (27)	2 (15)	13 (41)	28 (30)	.20
Surfactant therapy	22 (46)	7 (54)	15 (47)	44 (47)	.87

Abbreviation: BPD, bronchopulmonary dysplasia.
[a] Mild differed from moderate.
[b] Mild differed from severe.
[c] In grade I, bleeding occurs only in a small area of the ventricles; in grade II, bleeding also occurs inside the ventricles; in grade III, the ventricles are enlarged by blood; and in grade IV, bleeding occurs into the brain tissues around the ventricles.

The Communication domain from the Battelle Developmental Inventory[13] was administered to assess language skills at age 3 years. Standard scores were obtained for Receptive Language, Expressive Language, and the Total Language composite.

The Wechsler Intelligence Scale for Children, Third Edition (WISC-III),[14] was used to assess general cognitive development at age 8 years. Standard scores were obtained for Verbal, Performance, and Full-Scale IQ, and subscores for Perceptual Organization and Verbal Composites.

The Woodcock-Johnson Tests of Achievement, Revised,[15] was used at age 8 years to ascertain current academic achievement in Reading Recognition and Comprehension, and Calculation and Applied Problems. These 4 standard scores were used for data analyses.

The Clinical Evaluation of Language Fundamentals, Third Edition,[16] was also administered to assess language functioning at age 8 years. This is a standardized, normative language assessment comprised of Receptive, Expressive, and Total Language standard scores.

The Home Observation for Measurement of the Environment (HOME)[17] obtained from the 3-year assessment battery was used to assess the quality of the home environment. This measure assesses the areas of Responsivity, Acceptance, Organization, Play Materials, Involvement, and Variety gathered through observation, structured interview of the primary caregiver, or both. The total composite score from the HOME was used to control for environmental differences between the groups.

STATISTICAL ANALYSIS

Data were summarized as median and interquartile range, mean (SD), or frequency and percentage, as appropriate, for continuous and categorical data, respectively. The interquartile range is defined by the interval between the 25th and 75th percentiles of the distribution. The Kruskal-Wallis rank sum and Fisher exact tests were used to compare severity groups for infant and maternal demographic and medical characteristics at birth. The relationships between BPD severity and cognitive, psychomotor, language, and achievement outcomes for children with BPD were analyzed using analysis of covariance (ANCOVA). In an attempt to address problems of prematurity and environmental differences, birth weight and the HOME score were used as covariates in the multivariate analysis of covariance (MANCOVA) and ANCOVA models. The MANCOVA model was conducted for measures lacking global composite scores, including IQ on the Bayley Scales of Infant Development at age 3 years and achievement on the Woodcock-Johnson Tests of Achievement at age 8 years. The ANCOVAs were conducted on the total composite scores for the Battelle Developmental Inventory at age 3 years and the WISC-III at age 8 years, with significant effects enabling further examination of the subscale scores.

Percentages of children meeting clinical criteria for developmental disabilities, scoring 2 SDs below the mean on the WISC-III and Woodcock-Johnson Tests of Achievement, were computed for the severity groups also. Logistic regression was used to assess group differences controlling for the same covariates listed. Owing to the small sample sizes of our severity groups, a significance level of 20% was chosen to perform post hoc pairwise testing. In addition, for the continuous outcomes, any pairwise difference of 10 points or more was considered clinically significant and is presented and discussed in the text and tables. Statistical significance was defined as $P<.05$ (2-sided).

Table 2. Cognitive and Linguistic Outcomes for Study Sample at Age 3 and 8 Years as a Function of BPD Classification

Test	Severity of BPD, Mean (SD)				*P* Value
	Mild	Moderate	Severe	Total	
Bayley	n = 47	n = 12	n = 30	n = 89	
MDI	89.5 (22.5)	90.8 (24.7)	76.4 (22.6)	85.2 (23.4)	.02[a,b]
PDI	91.2 (26.3)	94.0 (24.5)	73.9 (29.2)	85.7 (28.1)	.01[a,b]
Battelle	n = 42	n = 12	n = 29	n = 83	
Receptive	89.5 (18.1)	88.2 (23.8)	78.9 (13.0)	85.6 (18.0)	.04[a]
Expressive	99.7 (22.2)	96.9 (23.8)	86.1 (19.8)	94.6 (22.3)	.02[a,b]
Total	96.0 (22.1)	94.2 (23.2)	82.2 (17.1)	90.9 (21.4)	.01[a,b]
WISC-III	n = 49	n = 12	n = 30	n = 91	
Verbal	89.6 (19.4)	92.9 (19.4)	83.9 (18.4)	88.1 (19.1)	.06[b]
Performance	84.0 (18.3)	88.1 (17.8)	75.7 (17.2)	81.8 (18.3)	.04[a,b]
Full Scale	85.4 (19.7)	89.5 (19.3)	78.0 (17.4)	83.5 (19.1)	.04[b]
Verbal composite	90.8 (18.8)	93.9 (19.0)	85.2 (18.0)	89.4 (18.6)	.047[b]
Perceptual organization	84.7 (18.2)	88.4 (17.2)	76.0 (16.6)	82.3 (17.9)	.03[a,b]
CELF-3	n = 48	n = 12	n = 29	n = 89	
Receptive	92.9 (19.4)	90.0 (18.4)	81.2 (18.6)	88.7 (19.6)	.01[a]
Expressive	92.7 (20.1)	94.2 (18.0)	86.5 (17.8)	90.9 (19.1)	.08[b]
Total	92.2 (19.2)	91.4 (17.6)	82.7 (18.4)	89.0 (19.1)	.02[a,b]
WJ-R	n = 49	n = 12	n = 29	n = 90	
Letter word identification	97.6 (24.5)	90.6 (19.5)	86.8 (18.1)	93.2 (22.3)	.049[a]
Passage comprehension	99.8 (24.6)	96.2 (22.8)	87.0 (20.0)	95.2 (23.5)	.01[a,b]
Calculations	88.2 (22.0)	92.0 (21.6)	79.1 (22.6)	85.8 (22.4)	.03[b]
Applied problems	95.2 (24.2)	95.8 (23.6)	88.2 (20.2)	93.0 (22.9)	.19[b]

Abbreviations: Battelle, Battelle Developmental Inventory; Bayley, Bayley Scales of Infant Development; BPD, bronchopulmonary dysplasia; CELF-3, Clinical Evaluation of Language Fundamentals, Third Edition; HOME, Home Observation for Measurement of the Environment; MDI, Mental Development Index; PDI, Psychomotor Development Index; WISC-III, Wechsler Intelligence Scales for Children, Third Edition; WJ-R, Woodcock-Johnson Tests of Achievement, Revised.
[a] Mild differed from severe.
[b] Moderate differed from severe.

RESULTS

DEMOGRAPHIC DATA

Demographic Data at Birth

Sixty-one percent of the infants' mothers were married, 55% were of low socioeconomic status, and mean educational attainment was 13 years. Birth characteristics and socioeconomic status were not different across severity groups (Table 1).

Infant Demographic and Medical Characteristics at Birth

The 3 severity groups of infants with BPD did not differ significantly in neonatal characteristics except for singleton status, total days of supplemental oxygen therapy, and total days of assisted mechanical ventilation (Table 1). As expected, children with mild BPD received less supplemental oxygen therapy and required assisted mechanical ventilation for a shorter time than did children with severe BPD. The group with moderate BPD also required fewer days of supplemental oxygen therapy compared with those with severe BPD and were more likely to be a singleton than were children with mild BPD. The BPD severity classification was not significantly associated with postnatal steroid therapy ($P=.20$) or surfactant therapy ($P=.88$), nor was it related to our neurologic risk summary score. As is shown in Table 1, severity groups did not differ in neurologic risk summary score ($P>.64$), with approximately 50% of children in all 3 groups earning a risk score of less than 1.

Cognitive, Motor, and Language Outcomes at Age 3 and 8 Years

Cognitive and Motor Outcomes. The MANCOVA for the Bayley Scales of Infant Development scores revealed a significant severity effect ($F_{4,160}$ ratio=2.47; $P<.047$). The ANCOVAs of the Mental Development Index and the Psychomotor Development Index yielded significant effects for severity of BPD ($P=.02$ and $P=.01$, respectively). Children with mild or moderate BPD performed better on the Mental Development Index and the Psychomotor Development Index than did those with severe BPD (**Table 2**).

Language Outcomes. The language outcomes yielded a similar pattern of findings, with significant effects noted for all language scores ($P<.05$). Children with mild BPD performed significantly better on all language measures than did those with severe BPD. Children with moderate BPD had significantly better Total and Expressive language scores compared with those with severe BPD (Table 2).

Cognitive, Language, Achievement, and School Outcomes at Age 8 Years

Cognitive Outcomes. The BPD severity groups scored significantly different on Performance IQ and Percep-

Table 3. Educational Outcomes for Study Sample at Age 3 and 8 Years as a Function of BPD Severity

Variable	Severity of BPD, No. (%) of Patients				*P* Value
	Mild	Moderate	Severe	Total	
Special education	20 (44)	6 (50)	20 (69)	**46** (53)	.03[a,b]
Repeat grade	7 (16)	1 (8)	5 (17)	**13** (15)	.71
Physical therapy	19 (39)	7 (58)	19 (63)	**45** (49)	.11[a]
Occupational therapy	18 (37)	8 (67)	20 (67)	**46** (51)	.02[a]
Speech therapy	20 (41)	5 (42)	21 (70)	**46** (51)	.01[a]
Bayley score <85					
MDI	13 (27)	4 (33)	16 (53)	**33** (37)	.045[a]
PDI	12 (26)	2 (17)	15 (50)	**29** (33)	.03[a]
WISC-III score <85					
Verbal	18 (37)	4 (33)	17 (57)	**39** (43)	<.001[a,b]
Performance	21 (43)	3 (25)	20 (67)	**44** (48)	.009[a,b]
Full Scale	18 (37)	4 (33)	22 (73)	**44** (48)	.001[a,b]

Abbreviations: Bayley, Bayley Scales of Infant Development; BPD, bronchopulmonary dysplasia; MDI, Mental Development Index; PDI, Psychomotor Development Index; WISC-III, Wechsler Intelligence Scales for Children, Third Edition.
[a] Mild differed from severe.
[b] Moderate differed from severe.

tual Organization on the WISC-III. Children with severe BPD performed more poorly on Performance IQ and Perceptual Organization than did children with either moderate or mild BPD ($P = .04$ and $P = .03$, respectively). In addition, using the 10-point discrepancy rule, children with moderate BPD performed better than those with severe BPD on the Full-Scale IQ test (Table 2).

Language Outcomes. Although the overall analyses for the language outcomes revealed no significant severity effects, a 10-point discrepancy was obtained for Receptive Language. Children with mild BPD performed better than children with severe BPD in Receptive Language (Table 2).

Achievement Outcomes. The MANCOVA for achievement revealed a significant severity effect ($F_{8, 152}$ ratio = 2.19; $P = .03$). Although the separate ANCOVAs for the achievement outcomes revealed nonsignificant severity effects, 10-point discrepancies for Passage Comprehension and Calculations were noted. Examinations of the adjusted means suggest that children with mild BPD performed better on reading recognition and comprehension measures than those with severe BPD. In addition, children with moderate BPD performed better on both the reading comprehension and calculation subtests than did children with severe BPD (Table 2).

Categorical Analyses of Educational Outcomes. Therapy and educational outcomes at age 8 years are given in **Table 3**. As expected, many of the children with BPD (53%), regardless of severity, were receiving some form of special education. Significant severity effects were obtained for occupational and speech therapy. Children with severe BPD required more educational interventions than did children with mild BPD. Severity of BPD significantly affected IQ performance at age 3 years; children with mild BPD differed from those with severe BPD in both cognitive and psychomotor development. Severity of BPD affected IQ performance at age 8 years as well; more children with severe BPD achieved Full-Scale, Verbal, and Performance IQ scores more than 1 SD below the mean compared with children with mild or moderate BPD.

COMMENT

FINDINGS AND IMPLICATIONS

This study presents a secondary, retrospective analysis using the NICHD/NHLBI definition of BPD in a cohort of children who had a diagnosis of BPD as infants and were enrolled in a prospective longitudinal study. This study assessed the preschool and school-age consequences of the severity of BPD. As a group, children with BPD performed at the lower end of the average range on cognitive, psychomotor, linguistic, and achievement tests at both 3 and 8 years of age. In addition, children with severe BPD performed more poorly than children with mild BPD on cognitive and linguistic measures at both follow-up visits. Using the NICHD/NHLBI severity classification, we were able to identify a subgroup of children with BPD who seem to be at high risk for developmental problems. In this cohort of infants with BPD born from February 1, 1989, to November 31, 1991, we were not able to detect an association between neonatal medical management (ie, steroid or surfactant therapy), as defined in this study, and BPD severity.

These findings support and extend those of Ehrenkranz et al, who contended that a severity-based definition of BPD has the potential for identifying a "spectrum of risk for adverse pulmonary and neurodevelopmental outcomes."[4(p1358)] Adverse neurocognitive factors were associated with BPD in our sample.[6] Results of the present investigation suggest that the impairments increased as a function of severity of BPD in our sample and persisted in both the preschool and school-age periods. The effects of BPD severity persisted after controlling for birth weight and environment (HOME). These research findings, and previous findings from our laboratory,[5] underscore strongly the need for early and continued monitoring and intervention for the learning, behavior, and developmental prob-

lems in children with BPD. Our findings further suggest that comprehensive evaluation and monitoring of BPD is especially imperative in children with severe BPD because they seem most at risk for diagnosable school problems. Research should examine whether current intervention efforts (ie, speech therapy, occupational therapy, physical therapy, and special education) minimize the adverse effect of BPD severity on educational outcomes in children with BPD. Our findings suggest that although children with BPD seem to make some academic gains, identifying those children with BPD who are most at risk and individually tailoring interventions to their deficits might be a more effective and productive educational approach.

LIMITATIONS AND IMPLICATIONS

One of the strengths of this study is its prospective longitudinal nature. However, the sample size precluded noting statistically significant differences in some areas in which clinically meaningful differences emerged (>10-point differences in cognitive functioning and language). Using Cohen's *d* as a measure of the effect size,[18] this analysis yielded effect sizes ranging from 0.52 to 0.84 for those comparisons noted in the text. In addition, while BPD severity seemed to be related to the depth of neurologic sequelae, other inflammatory mediators or oxidative stress (ie, hypoxia) may be responsible for this association. Most deficits were found in the group with severe BPD. While, ideally, we had hoped to evaluate the 3-tiered NICHD/NHLBI system of BPD severity classification, the initial sampling strategy was designed to exhaustively recruit neurologically intact infants with BPD. Thus, severity groups were not evenly distributed across the sample. Adequate sample size emerged only for the groups with mild BPD (n=53) and severe BPD (n=33); the group with moderate BPD was quite small (n=13).

Although children with severe BPD demonstrated less optimal cognitive performance than did children with mild BPD, no definitive conclusion can be reached for the children with moderate BPD. Nevertheless, there was clear demarcation of the group with severe BPD in terms of outcomes, whereas the groups with moderate and mild BPD were not clinically different. This study is unique in that the entire cohort was born and treated during the era of surfactant therapy and postnatal steroid administration. However, careful examination of the roles of chronic hypoxia, supplemental use of oxygen therapy, and medical management strategies in infants having a diagnosis of BPD seems critical (E.J.S., unpublished data, 2007).[5]

Future research should use newer broad-based assessment instruments (eg, the Wechsler Intelligence Scale for Children, Fourth Edition) and narrow-band measures (eg, the Conners Continuous Performance Test) that may be helpful for identification of global areas of strengths and weaknesses and specific subskills that warrant further intervention. Despite these limitations, this study is important because it lends further evidence for the validity of a severity-based definition of BPD and its potential for identifying children with BPD who are most at risk for subsequent problems.

Accepted for Publication: May 2, 2007.
Correspondence: Elizabeth J. Short, PhD, Department of Psychology, Case Western Reserve University, Cleveland, OH 44106 (Elizabeth.Short@case.edu).
Author Contributions: *Study concept and design:* Short, Lewis, and Singer. *Acquisition of data:* Fulton, Baley, Kercsmar, and Singer. *Analysis and interpretation of data:* Short, Kirchner, Asaad, Lewis, Klein, Eisengart, Baley, Min, and Singer. *Drafting of the manuscript:* Short, Kirchner, Lewis, Eisengart, and Baley. *Critical revision of the manuscript for important intellectual content:* Short, Kirchner, Asaad, Fulton, Klein, Eisengart, Baley, Kercsmar, Min, and Singer. *Statistical analysis:* Kirchner, and Min. *Obtained funding:* Short, Lewis, Eisengart, and Singer. *Administrative, technical, and material support:* Short, Asaad, Fulton, Lewis, Kercsmar, and Singer. *Study supervision:* Short, Klein, Baley, and Singer.
Financial Disclosure: None reported.
Funding/Support: This study was supported by grants MCJ-390592, MC-00127, and MC-00334 from the Maternal and Child Health Program, Health Resources and Services Administration, Department of Health and Human Services, Rockville, Maryland (Dr Singer).
Additional Contributions: Terri Lotz-Ganley assisted on this project. We thank the families for their continued participation.

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