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Chronic Lung Disease and Developmental Delay at 2 Years of Age in Children Born Before 28 Weeks' Gestation

Matthew Laughon, MD, MPH^a, Michael T. O'Shea, MD, MPH^b, Elizabeth N. Allred, MS^{c,d,e}, Carl Bose, MD^a, Karl Kuban, MD^f, Linda J. Van Marter, MD, MPH^{g,h,i}, Richard A. Ehrenkranz, MD^j, and Alan Leviton, MD, MS^{c,e} for the ELGAN Study Investigators

^aDivision of Neonatal-Perinatal Medicine, School of Medicine, University of North Carolina, Chapel Hill, North Carolina

^bDivision of Neonatology, School of Medicine, Wake Forest University, Winston-Salem, North Carolina

^cDepartment of Neurology, Harvard Medical School, Boston, Massachusetts

^dDepartment of Biostatistics, Harvard School of Public Health, Boston, Massachusetts

^eDepartment of Neurology, Children's Hospital Boston, Boston, Massachusetts

^fDivision of Pediatric Neurology, Boston Medical Center, Boston, Massachusetts

^gDepartment of Pediatrics, Harvard Medical School, Boston, Massachusetts

^hDivision of Newborn Medicine, Children's Hospital Boston, Boston, Massachusetts

ⁱDivision of Newborn Medicine, Brigham and Women's Hospital, Boston, Massachusetts

^jDivision of Perinatal Medicine, School of Medicine, Yale University, New Haven, Connecticut

Abstract

Introduction—Extremely low gestational age newborns (ELGANs) are at increased risk of chronic lung disease (CLD) and of developmental delay. Some studies have suggested that CLD contributes to developmental delay.

Patients and Methods—We examined data collected prospectively on 915 infants born before the 28th week of gestation in 2002–2004 who were assessed at 24 months of age with the Bayley Scales of Infant Development-2nd Edition or the Vineland Adaptive Behavior Scales. We excluded infants who were not able to walk independently (Gross Motor Function Classification System score < 1) and, therefore, more likely to have functionally important fine motor impairments. We defined CLD as receipt of oxygen at 36 weeks' postmenstrual age and classified infants as either not receiving mechanical ventilation (MV) (CLD without MV) or receiving MV (CLD with MV).

Results—Forty-nine percent of ELGANs had CLD; of these, 14% were receiving MV at 36 weeks' postmenstrual age. ELGANs without CLD had the lowest risk of a Mental Developmental Index (MDI) or a Psychomotor Developmental Index (PDI) of <55, followed by ELGANs with CLD not receiving MV, and ELGANs with CLD receiving MV (9%, 12%, and 18% for the MDI and 7%, 10%, and 20% for the PDI, respectively). In time-oriented multivariate models, the risk of an MDI

Address correspondence to Matthew Laughon, MD, MPH, University of North Carolina Hospital, Division of Neonatal-Perinatal Medicine, CB#7596, Chapel Hill, NC 27599-7596. matt_laughon@med.unc.edu.

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of <55 was associated with the following variables: gestational age of <25 weeks; single mother; late bacteremia; pneumothorax; and necrotizing enterocolitis. The risk of a PDI of <55 was associated with variables such as single mother, a complete course of antenatal corticosteroids, early and persistent pulmonary dysfunction, pulmonary deterioration during the second postnatal week, pneumothorax, and pulmonary interstitial emphysema. CLD, without or with MV, was not associated with the risk of either a low MDI or a low PDI. However, CLD with MV approached, but did not achieve, nominal statistical significance (odds ratio: 1.9 [95% confidence interval: 0.97–3.9]) for the association with a PDI of <55.

Conclusions—Among children without severe gross motor delays, risk factors for CLD account for the association between CLD and developmental delay. Once those factors are considered in time-oriented risk models, CLD does not seem to increase the risk of either a low MDI or a low PDI. However, severe CLD might increase the risk of a low PDI.

Keywords

lung disease; prematurity; preterm infant; neurodevelopmental outcome

Chronic lung disease (CLD) (also known as bronchopulmonary dysplasia) seems to place an infant at increased risk of early developmental delays,^{1–3} cognitive impairment,^{4–6} language impairment,^{7,8} and poor academic performance.⁹ Predictors and correlates of CLD, such as prolonged mechanical ventilation (MV), are also associated with an increased risk of cognitive impairment.^{10–12}

CLD is associated with global dysfunction rather than specific neuropsychological impairments.¹³ The more severe the CLD, the greater the probability of developmental impairment.^{14–16} The putative causal pathways from antenatal events to the development of CLD involve multiple antecedents, effect modifiers, and confounders (chorioamnionitis, preterm birth, antenatal steroids, postnatal infection, patent ductus arteriosus [PDA], and fluid management, etc).^{17,18}

Although 2 randomized, controlled, clinical trials have shown that medications that reduce the risk of CLD also reduce the risk of neurodevelopmental impairment (eg, caffeine^{19,20} and vitamin A^{21,22}), the underlying mechanisms have not been identified.²³ Thus, we still do not know to what extent CLD, its antecedents, or comorbid conditions contribute to neurodevelopmental impairment.

The Extremely Low Gestational Age Newborn (ELGAN) study assessed measures of pulmonary dysfunction as well as prenatal, antenatal, and postnatal exposures and events.^{24, 25} The purpose of the analyses presented here was to explore to what extent CLD and its antecedents influence the risk of developmental delays at 24-months adjusted age, as assessed with the Bayley Scales of Infant Development-2nd Edition (BSID-II),²⁶ among infants without gross motor function impairments.

Patients and Methods

The ELGAN Study

The ELGAN study identified characteristics and exposures that increase the risk of structural and functional neurologic disorders in ELGANs. During the years 2002–2004, women delivering before 28 weeks' gestation at 1 of 14 participating institutions were asked to enroll in the study. The enrollment and consent processes were approved by the individual institutional review boards. We limited the sample to children who were assessed at 24 months of age with the BSID-II or the Vineland Adaptive Behavior Scales (VABS). Fine motor impairments, which interfere with the Mental developmental index (MDI) and the

Psychomotor developmental index (PDI) assessments, tend to accompany gross motor dysfunctions. To avoid attributing cognition and perception deficits to motor impairments, we limited our analyses to children who were able to walk independently (Gross Motor Function Classification System [GMFCS] < 1), and who, therefore, were unlikely to have functionally important fine motor impairments.

Demographic, Pregnancy, and Newborn Variables

The clinical circumstances that led to each maternal admission and ultimately to each preterm delivery were defined a priori.²⁷ The gestational age estimates were based on a hierarchy of the quality of available information.^{24,25} The birth weight *z* score is the number of SDs the infant's birth weight is above or below the median weight of infants at the same gestational age in a standard data set.²⁸ We collected the physiology, laboratory, and therapy data for the first 12 hours needed to calculate a Score for Neonatal Acute Physiology-II (SNAP-II).²⁹

During the first week, details about the newborn were collected daily, then weekly thereafter through the first month (days 7, 14, 21, and 28). Infants were classified by their respiratory characteristics during the first 2 postnatal weeks as “persistently low fraction of inspired oxygen [F_{IO_2}]” (F_{IO_2} consistently below 0.23 on all days between days 3 and 7 and $F_{IO_2} \leq 0.23$ on day 14), “pulmonary deterioration” (PD) ($F_{IO_2} < 0.23$ on any day between days 3 and 7 and $F_{IO_2} > 0.25$ on day 14), and “early and persistent pulmonary dysfunction” (EPPD) ($F_{IO_2} > 0.23$ on all days between days 3 and 7 and $F_{IO_2} > 0.25$ on day 14).²⁴ Late bacteremia was defined as recovery of an organism from blood drawn during postnatal weeks 2, 3, or 4.

Pneumothorax, pulmonary interstitial emphysema (PIE), pulmonary hemorrhage, and PDA (clinical and echocardiographic) were recorded. Ophthalmologists examined the eyes of the infants according to protocol and completed forms specifically for the ELGAN study. Definitions of retinopathy of prematurity (ROP) were those definitions endorsed by the International Committee for Classification of Retinopathy of Prematurity.³⁰

The diagnosis of CLD was made at 36 weeks' postmenstrual age (PMA). If an infant was receiving supplemental oxygen, the infant was classified as having CLD, and further classified on the level of respiratory support: CLD with MV (either conventional MV [CMV] or high-frequency ventilation) or CLD without MV. Necrotizing enterocolitis (NEC) was classified according to the modified Bell staging system.³¹

Protocol Ultrasound Scans

Cranial ultrasound scans were performed by technicians at all of the hospitals by using digitized high-frequency transducers (7.5 and 10 MHz) and included the standard views.³² The 3 sets of protocol scans were defined by the postnatal day on which they were obtained (days 1–4, 5–14, and ≥ 15). Reading procedures and efforts to reduce observer variability are presented elsewhere.³³

24-Month Developmental Assessment

The assessment at 24-months' corrected age included the BSID-II,²⁶ a neurologic examination,³⁴ an assessment of gross motor function by using the GMFCS³⁵ and, when necessary, a parent-reported assessment of adaptive development by using the VABS.³⁶ Seventy-seven percent of the children had developmental assessments within the range of 23.5 to 27.9 months; of the other children, about half were assessed before 23.5 months and about half after 27.9 months.

Certified examiners administered and scored the BSID-II. All examiners had previous experience with the BSID-II and attended a 1-day workshop at which the published guidelines for test administration and videotaped examinations were viewed and discussed. Examiners

were aware of the infant's enrollment in the ELGAN study but were not informed of any specifics of the child's medical history. Examiners were told the child's corrected age.

As suggested by the test manual, we defined a significant delay for the BSID-II Mental and Motor scales as a score <70, a score that is more than 2 SDs below the mean for the standardization sample. We also evaluated associations with MDIs and PDIs of <55, which are more than 3 SDs below the mean for the standardization sample. When a child's impairments precluded administration of the BSID-II, or >2 items were omitted or judged to be "unscorable," the child was classified as nontestable on that scale. The Adaptive Behavioral Composite of the VABS was obtained for 26 of 33 children who were considered nontestable with the BSID-II Mental scale. For these infants, the Adaptive Behavioral Composite was used as an approximation of the MDI. Among infants unscorable with the BSID-II Motor scale, 32 were assessed in the Motor Skills Domain of the VABS and that score was used as an approximation of the PDI.

Data Analysis

Data analysis was oriented to test the hypothesis that antecedents of CLD, and not CLD itself, contribute to suboptimal performance on the BSID-II. We assessed associations between antecedents (antenatal and postnatal variables and CLD) and low MDIs and PDIs.

Relationships were assessed with Pearson's χ^2 , and variables associated with both CLD and a low BSID-II at a P value of $\leq .30$ were considered candidates for logistic regression analyses.³⁷

Because postnatal phenomena, such as the need for ventilation, can be influenced by antepartum phenomena, we created logistic regression models in which risk factors were ordered in a temporal pattern, so that the earliest occurring predictors/covariates of an outcome (eg, MDI < 55) were entered first and were not displaced by later occurring covariates.^{11,38–42} For these time-oriented risk models (TORMs), we categorized sets of antecedents/covariates by the time they occurred or were identified. Each set is called an epoch. We used a step down procedure seeking a parsimonious solution without interaction terms. To account for the possibility that infants born at a particular hospital are more like each other than like infants born at other hospitals, a hospital cluster term was included in all models.⁴³

Results

The cohort comprised 915 children whose CLD status at 36 weeks was known and were able to walk independently (GMFCS < 1) at the 24-month follow-up assessment (Fig 1). Ninety-six infants had a GMFCS ≥ 1 and were excluded. The 450 children who were treated with oxygen at 36 weeks' PMA (ie, had CLD) were more likely than their 465 peers who were not oxygen dependent to have an MDI in the severely delayed range (<55: 13% vs 9%), although the 2 groups did not differ in the percentage of infants in the less severely delayed range (55–69: 10% vs 11%) (Table 1). MDIs in the 55 to 69 range tended to be modestly overrepresented among infants who had CLD with MV (15% vs 10% in the CLD without MV group versus 11% in the no CLD group). MDIs of <55 were more prominently overrepresented among children who had CLD with MV (18% vs 12% in the CLD without MV group versus 9% in the no CLD group).

Univariate Associations With CLD and BSID-II Scores

We chose to compare children with CLD to those children with no CLD without additional classification into CLD with or without MV because only 65 children were receiving MV at 36 weeks' PMA. A number of associations were observed for an increased risk of CLD and an increased risk of both an MDI and a PDI of <55, including lower birth weight z scores, higher

SNAP-IIs, and lower Pao₂ values (lowest quartiles) at the end of each of the first 2 weeks (Table 2). Children who had late bacteremia were at an increased risk of CLD, an MDI of <55, and a PDI between 55 and 69. Placental abruption was not associated with CLD, but was associated with a lower risk of an MDI and a PDI of <55.

Aggressive modes of ventilation on days 7, 14, 21, and 28 were associated with a greater risk of CLD, as well as a greater risk of an MDI of <55 and a PDI of <55 (Table 3). Treatment at 36 weeks' PMA with any form of respiratory support (continuous positive airway pressure [CPAP], CMV, or high-frequency ventilation) was associated with an increased risk of an MDI and a PDI of <55.

Receipt of a methylxanthine for more than 2 weeks was associated with a reduced risk of CLD, an MDI of <55, and a PDI of 55 to 69 (Table 4). Conversely, an increased risk of CLD and an increased risk of MDI and a PDI <55 were associated with receipt of hydrocortisone and with PDA ligation. Children who received an analgesic, a sedative, or multiple transfusions of packed red blood cells were at higher risk than others of CLD and a low MDI. Treatment with dexamethasone was associated with an increased risk of CLD, an MDI of <70, and a PDI of <70.

Pneumothorax, PIE, PD, EPPD, and higher stages of NEC and ROP were associated with an increased risk of CLD and a low MDI and a low PDI (Table 5). The diagnosis of PDA was associated with an increased risk of CLD, but not a low MDI or a low PDI. Ventriculomegaly and an echolucent lesion were not associated with an increased risk for CLD, but were minimally associated with a low MDI, and modestly with a low PDI.

Time-Oriented Risk Models

Because the associations between CLD categories (no CLD, CLD without MV, and CLD with MV) with both the MDI and the PDI were most evident for scores <55, we limited our models to these outcomes. We created 3 epoch models of the MDI and the PDI at <55. We grouped prenatal and birth characteristics and exposures into the antenatal epoch, all exposures and characteristics during the first 28 days into the neonatal epoch, and exposures and characteristics occurring or reported between 28 days and 36 weeks' PMA into the 36-weeks' PMA epoch.

In the antenatal epoch of the TORM for an MDI of <55, gestational age of 23 or 24 weeks, single mother, and the composite variable “preeclampsia or fetal indication” were associated with an increased risk of an MDI of <55 (Table 6). In the neonatal epoch, late bacteremia, pneumothorax, and NEC of Bell stage II or higher were also associated with an MDI of <55. Neither CLD without MV nor CLD with MV, added in the last epoch, achieved statistical significance for an MDI of <55 after we accounted for the antenatal and neonatal epoch variables.

In the antenatal epoch of the TORM for a PDI <55, single mother, a complete course of antenatal steroids, and the composite variable “preeclampsia or fetal indication” were associated with an increased risk of a PDI <55 (Table 7). In the neonatal epoch, pneumothorax, PIE, PD, and EPPD were also associated with a PDI <55. Neither CLD without MV nor CLD with MV achieved statistical significance for a PDI <55 after we accounted for the antenatal and neonatal epoch variables. However, CLD with MV approached, but did not achieve, nominal statistical significance (odds ratio [OR]: 1.9 [95% confidence interval (CI): 0.97–3.9]) for the association with a PDI <55.

Discussion

After adjusting for confounders and other antecedents, we found that CLD, even when adjusted for severity, was not associated with an increased risk of delayed development at 24-months adjusted age. On the other hand, antecedents of CLD seemed to be associated with impaired development. Several potential reasons might explain our observations: (1) brain injury occurs as a consequence of antecedents of CLD (eg, infection, pneumothorax, respiratory, and other therapies), rather than CLD itself; (2) brain injury is caused by CLD; however, this association was masked in the multivariate model by previous adjustment for factors in the causal chain leading to CLD; or (3) lung dysfunctions, and associated therapies, are indicators of maturation-associated vulnerabilities of lung and brain.

In reports of developmental delay identified with the BSID-II, study participants are often classified by whether their scores are <70, which according to the test developers indicates “significantly delayed performance.”²⁶ However, studies of extremely low birth weight infants indicate that an appreciable proportion of infants with an MDI of <70 do not have mental retardation when assessed at school age.^{44,45} By dichotomizing BSID-II scores at 55, we increased the positive predictive value of the definition of developmental delay used in this study. We also restricted our analyses to children who were free from moderate or severe gross, and presumably fine, motor function impairments, which were almost always because of cerebral palsy. The present study estimates the strength of association between CLD and developmental delay at 24 adjusted months only in children who do not have cerebral palsy. Significant fine motor impairment precludes valid assessment of cognitive functioning with the MDI portion of the BSID-II.

However, cerebral palsy is associated with mental retardation.⁴⁶ If CLD contributes causally to the outcome of cerebral palsy with mental retardation, then our exclusion of infants with cerebral palsy results in an understatement of the strength of the CLD/MDI < 55 relationship. On the other hand, this sample restriction provides a more informative analysis of the relationship of CLD to delayed cognitive and perceptual motor development.

Previous studies attribute much of the increased risk of delayed development to antecedents of CLD. For example, late bacteremia might prolong the need for MV, and prolonged MV is associated with developmental delay.⁴⁷ In another example, prolonged ventilation and hypocarbia, antecedents of CLD, are associated with ultrasonographically detectable cerebral white matter damage,⁴⁸ which is, in turn, associated with developmental delay.^{49,50} We also found that a number of our variables were highly correlated. For example, EPPD and PD predict a low PDI. It is possible that each of these variables conveys information about immaturity of the brain as well as the lung, along with information about exposures that might be in the causal chain leading to a low PDI. Our analyses suggest that it is not CLD, but rather risk factors for CLD, that are more closely linked to developmental delay at 24-months adjusted age. Once these risk factors are considered, CLD imparts no significant additional risk.

Traditionally, risk factors for both a low MDI and a low PDI have been considered together. In the analyses presented here, a low MDI and a low PDI shared antecedents, but some risk factors were antecedents of one but not of the other. This observation suggests that the pathogenesis of developmental delay differs for mental and motor domains.⁵⁰ Both late bacteremia⁵¹ and higher grade NEC^{52,53} have been identified as antecedents of a low MDI. What they have in common is a systemic inflammatory response that might lead to cerebral white matter injury,⁵⁴ which predicts low MDI and low PDI scores.⁵⁰ An inflammatory response, initiated in the intestinal compartment, may become systemic and lead to brain injury through a variety of inflammatory mediators such as tumor necrosis factor α , interleukin 6, and platelet activating factor.^{55,56} Interventions that have been associated with a lower risk of NEC,

such as probiotics⁵⁷ and human milk feeding⁵⁸ might improve developmental outcome, as observed in recent studies of human milk and developmental outcome.⁵⁹

Low PDI seems to be related to factors associated with pulmonary disease (eg, pneumothorax, PIE, PD, and EPPD). Two previous studies^{15,60} found that the association of CLD and developmental delay arises primarily from the group of infants with severe CLD. Pulmonary inflammation, either initiated or exacerbated by oxygen toxicity and injury from MV, plays a major role in the pathogenesis of CLD. Although lung inflammation may be confined within the lungs, under certain conditions, it may also be accompanied by a systemic inflammatory response.⁶¹ It is possible that a systemic inflammatory response associated with prolonged MV (ie, among infants with CLD with MV) might increase the likelihood of neonatal brain injury and subsequent disability. Our inability to demonstrate this relationship conclusively may have resulted from the relatively small number of infants with CLD with MV in our sample. Alternatively, the need for ventilator assistance and/or ventilator-associated lung injuries might be markers for immaturity-related brain vulnerability, and might not be causally related. It is also possible that by excluding infants with significantly impaired gross motor function, we may have understated the strength of association between severe CLD and development delay.

Compared with the infants of married mothers, infants of single mothers were at higher risk for delayed cognitive development. “Single mother” may be a variable that summarizes disadvantaged social class correlates. Social disadvantage has repeatedly been found as a predictor of impaired development in children born preterm.^{1–3,62–64} Explanations include potential contributions of genetics and limited access to resources that enhance development.

Delayed development was more frequent among children whose mothers were treated with antenatal steroids than among children not exposed in utero to exogenous steroids. An explanation for the apparent adverse effect of antenatal steroids is that antenatal steroids were not randomly assigned, so confounding by indication is likely to have occurred.⁶⁵ For example, deliveries in response to maternal and fetal indication tend to have higher rates of antenatal steroids than “spontaneous” deliveries. Another explanation is that exposure to antenatal steroids might have improved survival, which may come at the expense of greater risk of impairment.⁶⁶

Our study offers several advantages over previous studies. First, we selected infants on the basis of gestational age, not birth weight, to minimize confounding because of factors related to fetal growth restriction.⁶⁷ Second, examiners were not aware of the medical histories of the children they examined, thereby minimizing “diagnostic suspicion bias.”⁶⁸ Third, high quality ultrasonographic data describing brain damage were available to us as a result of rigorous efforts to minimize variability in sonologists' interpretations.³³

Conclusions

Antecedents and correlates of CLD are associated strongly with the risk of delayed mental and motor development. Infants with CLD who were receiving MV at 36 weeks' adjusted age might have an increased risk of neurodevelopmental impairment. This observation will inform future investigations of the biological mechanisms underlying the association between CLD and later neurodevelopmental impairments affecting former preterm infants.

- **What's Known on This Subject:** Some studies suggest that CLD in ELGANs is associated with neurodevelopmental impairments.

- **What This Study Adds:** Among children without severe gross motor delays, risk factors for CLD account for the association between CLD and developmental delay. However, severe CLD might increase the risk of lower motor scores.

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Abbreviations

CLD	chronic lung disease
MV	mechanical ventilation
PDA	patent ductus arteriosus
ELGAN	extremely low gestational age newborn
BSID-II	Bayley Scales of Infant Development-2nd Edition
VABS	Vineland Adaptive Behavioral Scales
MDI	Mental developmental index
PDI	Psychomotor developmental index
GMFCS	Gross Motor Function Classification System
SNAP-II	Score for Neonatal Acute Physiology-II
F _{io2}	fraction of inspired oxygen
PD	pulmonary deterioration
EPPD	early and persistent pulmonary dysfunction
PIE	pulmonary interstitial emphysema
ROP	retinopathy of prematurity
PMA	postmenstrual age
CMV	conventional mechanical ventilation
NEC	necrotizing enterocolitis
TORM	time-oriented risk model
CPAP	continuous positive airway pressure
OR	odds ratio
CI	confidence interval

FIGURE 1.
Description of the study sample.

TABLE 1

MDI and PDI Stratified According to Presence of CLD (Oxygen Dependence at 36 Weeks' PMA) and Severity of CLD (CLD Without MV [CMV or High Frequency] or CLD With MV)

	MDI, %		PDI, %		N
	<55	55–69	<55	55–69	
CLD					
No	9	11	7	14	465
Yes	13	10	12	17	450
Maximum <i>n</i>	103	99	86	143	915
Severity of CLD					
Without MV	12	10	10	17	385
With MV	18	15	20	18	65

TABLE 2
Selected Prenatal and Postnatal Factors Associated With CLD and MDI or PDI at 24 Months' Postterm Equivalent

Postnatal Factors	CLD, %	MDI, %		PDI, %		N
		<55	55–69	<55	55–69	
Marital status						
Single	47	16	14	12	16	375
Not single	50	8	9	8	16	540
Antenatal corticosteroid ^a						
Complete	47	12	11	12	15	588
Incomplete	54	9	12	6	17	234
None	48	11	9	4	15	93
Cesarean delivery						
Yes	49	10	10	9	15	611
No	49	13	12	10	16	304
Initiator of preterm delivery						
Preterm labor	46	9	11	8	18	411
Preterm, prolonged rupture of membranes	47	14	9	10	13	201
Preeclampsia	58	16	11	18	9	120
Abruptio	55	5	11	2	16	100
Cervical insufficiency	44	14	10	15	15	48
Fetal indication ^b	63	17	20	9	20	35
Gestational age, wk						
23	78	13	13	9	28	32
24	77	16	10	9	14	130
25	61	11	13	11	18	184
26	44	12	8	10	14	250
27	32	8	12	8	14	319
Birth weight z score						
Less than –1	71	17	13	16	18	174
–1 to 0	52	11	11	7	16	342
0 or higher	37	9	10	9	14	399

Postnatal Factors	CLD, %	MDI, %		PDI, %		N
		<55	55–69	<55	55–69	
SNAP-II						
<20	38	9	9	8	14	489
20–29	57	13	13	10	18	222
≥30	69	16	12	12	19	187
Pao ₂ week 1						
<42 (lowest quartile)	71	19	13	18	13	79
≥42	63	13	12	11	18	321
Missing	37	9	10	7	14	515
Pao ₂ week 2						
<41 (lowest quartile)	73	25	12	24	20	51
≥41	66	15	15	12	23	165
Missing	43	9	10	8	14	699
Early bacteremia, week 1						
None	47	9	10	10	16	532
Presumed	52	13	12	5	14	325
Definite	51	19	16	9	23	57
Late bacteremia, week 2–4						
None	44	9	10	8	14	549
Presumed	58	9	12	12	16	139
Definite	55	18	13	11	21	224
Maximum <i>n</i>	450	103	99	86	143	915

CLD included infants with and without MV (CMV or high-frequency ventilation).

^a A course of antenatal corticosteroids given to enhance fetal lung maturation was considered complete if the mother received 2 doses of betamethasone 24 hours apart or 4 doses of dexamethasone at 12-hour intervals and delivered at least 48 hours after the first dose.

^b Fetal indication includes nonreassuring fetal assessments, oligohydramnios, Doppler abnormalities of umbilical cord blood flow, and severe intrauterine growth restriction.

TABLE 3
Mode of Ventilation on Days 0, 7, 14, 21, and 28 and MDIs and PDI's at 24 Months' Postterm Equivalent

Mode of Ventilation	CLD, %	MDI, %		PDI, %		N
		<55	55-69	<55	55-69	
Day 0						
No support	0	0	0	0	0	0
Hood/cannula	50	0	50	0	0	2
CPAP	20	4	13	1	18	71
CMV	49	12	11	10	15	712
High frequency	66	12	11	13	20	130
Day 7						
No support	7	11	15	5	17	46
Hood/cannula	31	12	9	6	11	95
CPAP	26	6	8	8	17	236
CMV	68	12	13	9	14	437
High frequency	73	20	9	18	25	101
Day 14						
No support	7	11	11	9	13	46
Hood/cannula	25	9	7	5	15	135
CPAP	26	7	11	8	14	217
CMV	67	11	11	9	14	395
High frequency	75	23	14	18	25	119
Day 21						
No support	2	8	10	4	14	49
Hood/cannula	22	7	11	7	16	169
CPAP	29	19	11	9	14	130
CMV	68	11	12	9	15	422
High frequency	81	26	11	21	24	80
Day 28						
No support	2	8	11	6	15	62
Hood/cannula	26	7	12	8	12	216

Mode of Ventilation	CLD, %	MDI, %		PDL, %		N
		<55	55-69	<55	55-69	
CPAP	38	11	9	10	16	203
CMV	74	12	12	10	16	354
High frequency	84	25	8	16	27	63

CLD included infants with and without MV (CMV or high-frequency ventilation).

TABLE 4
Medication and Treatment Associated With CLD and MDIs and PDI at 24 Months' Postterm Equivalent

Medications and Therapies	CLD, %	MDI, %		PDI, %		N
		<55	55–69	<55	55–69	
Surfactant, first week						
Yes	53	11	11	10	16	809
No	24	11	11	7	12	106
Methylxanthine						
Yes	43	11	11	9	15	787
No	85	15	12	11	22	128
Hydrocortisone						
Yes	67	15	8	18	16	85
No	47	11	11	9	16	830
Dexamethasone						
Yes	71	4	21	8	25	24
No	49	11	11	9	15	821
Analgesics						
Yes	56	12	10	11	15	579
No	37	10	12	7	17	336
Sedative						
Yes	57	18	15	8	20	200
No	47	10	10	10	14	716
PDA treatment ^a						
Ligation	69	16	10	11	21	127
Indomethacin	53	10	12	11	15	349
Neither	46	11	13	8	10	130
PDA treatment ^b						
Yes	58	12	12	10	17	544
No	37	10	10	8	14	371
Transfusion ^c						

Medications and Therapies	CLD, %	MDI, %		PDI, %		N
		<55	55-69	<55	55-69	
Yes	52	12	11	8	16	842
No	14	8	11	10	11	72

CLD included infants with and without MV (CMV or high-frequency ventilation).

^a Among those with a clinical or echocardiographic PDA diagnosis.

^b Among all infants.

^c Packed red blood cells during 3 or 4 separate weeks in the first postnatal month.

TABLE 5
Diagnostic and Classification Entities Associated With MDIs and PDIs at 24 Months' Postterm Equivalent

Diagnosis	CLD, %	MDI, %		PDI, %		N
		<55	55-69	<55	55-69	
PDA						
No	38	11	8	8	16	309
Yes	55	11	12	10	15	606
Pneumothorax						
No	47	10	11	9	16	843
Yes	71	28	7	18	15	72
PIE						
No	45	10	11	8	14	782
Yes	77	19	12	16	26	133
Pulmonary hemorrhage						
No	49	11	11	9	16	889
Yes	50	19	8	12	12	26
Respiratory group classification						
Low Fio ₂	14	6	9	3	13	182
PD	49	13	10	11	16	341
EPPD	68	12	12	10	17	363
NEC						
None	47	9	10	9	14	569
Watch	48	13	14	10	20	147
Stage I	48	13	11	6	13	101
Stage II	68	19	14	8	17	36
Stage IIIa	60	10	10	10	20	10
Stage IIIb	62	28	10	17	31	29
Isolated perforation	70	22	4	17	9	23
ROP						
None	28	10	10	9	15	252
Stage I	40	6	12	7	12	204

Diagnosis	CLD, %	MDI, %		PDI, %		N
		<55	55-69	<55	55-69	
Stage 2	58	11	10	9	15	205
Stage 3	72	17	12	12	21	229
Stage 4/5	93	7	4	7	4	14
Ventriculomegaly						
No	49	11	11	15	9	844
Yes	50	14	11	21	14	70
Echolucent lesion						
No	49	11	11	9	15	871
Yes	53	14	14	19	21	43

CLD included infants with and without MV (CMV or high-frequency ventilation).

TABLE 6

ORs and 95% CIs Obtained With TORMs of MDI <55

Epoch	Epoch, OR (95% CI)		
	Antenatal	Neonatal (First 28 d)	36 wk PMA
Antenatal			
Gestational age 23–24 wk	1.7 (1.00–3.1)	1.4 (0.6–3.0)	1.3 (0.7–2.8)
Single mother	2.3 (1.5–3.5)	2.3 (1.5–3.5)	2.3 (1.5–3.6)
Preeclampsia or fetal indication	2.0 (1.01–3.8)	1.9 (0.96–3.8)	1.9 (0.9–3.8)
Neonatal (first 28 d)			
Late bacteremia	—	1.8 (1.3–2.5)	1.8 (1.3–2.5)
Pneumothorax	—	3.7 (2.6–5.4)	3.6 (2.5–5.4)
NEC $\geq$ stage II	—	2.2 (1.3–3.7)	2.1 (1.2–3.7)
36 wk PMA			
CLD without MV	—	—	1.1 (0.8–1.4)
CLD with MV	—	—	1.2 (0.7–2.3)

These analyses include only those children without a severe gross motor impairment (GMFCS score < 1). Antenatal epoch includes the following variables: gestational age of 23–24 weeks; gestational age of 25–26 weeks; single mother; complete course of antenatal steroids; cesarean delivery; and delivery for preeclampsia or fetal indications. Neonatal epoch includes the following variables: SNAP-II in the top quartile; MV or high-frequency ventilation at 7 days; late bacteremia; pneumothorax; PIE; Pao₂ in the lowest quartile (week 1); Pao₂ missing (week 1); transfusions (packed red blood cells); PD; EPPD; ventriculomegaly; echolucent lesion; echodense lesion; NEC stage II or worse; methylxanthine; PDA; and PDA ligation. Thirty-six weeks' PMA epoch includes the following variables: CLD without MV (CMV or high-frequency ventilation) at 36 weeks and CLD with MV.

TABLE 7

ORs and 95% CIs Obtained With TORMs of PDI <55

Epoch	Epoch, OR (95% CI)		
	Antenatal	Neonatal (First 28 d)	36 wk PMA
Antenatal			
Single mother	1.8 (1.02–3.0)	1.8 (0.95–3.5)	1.8 (0.9–3.5)
Complete antenatal corticosteroids	2.3 (1.5–3.5)	2.4 (1.5–3.9)	2.4 (1.5–3.8)
Preeclampsia or fetal indication	2.2 (1.5–3.1)	2.3 (1.7–3.3)	2.2 (1.5–3.2)
Neonatal (first 28 d)			
Pneumothorax	—	1.9 (1.1–3.5)	1.9 (1.1–3.3)
PIE	—	2.2 (1.04–4.7)	2.0 (0.99–4.2)
PD	—	3.6 (1.2–7.6)	2.7 (1.1–6.5)
EPPD	—	3.0 (1.2–7.6)	2.7 (1.1–6.5)
36 wk PMA			
CLD without MV	—	—	1.1 (0.6–2.0)
CLD with MV	—	—	1.9 (0.97–3.9)

These analyses include only those children without a severe gross motor impairment (GMFCS score < 1). Antenatal epoch includes the following variables: gestational age of 23–24 weeks; gestational age of 25–26 weeks; single mother; complete course of antenatal corticosteroids; cesarean delivery; and delivery for preeclampsia or fetal indications. Neonatal epoch includes the following variables: SNAP-II in the top quartile; MV or high-frequency ventilation at 7 days; late bacteremia; pneumothorax; PIE; Pao₂ in the lowest quartile (week 1); Pao₂ missing (week 1); transfusions (packed red blood cells); PD; EPPD; ventriculomegaly; echolucent lesion; echodense lesion; NEC stage II or worse; methylxanthine; PDA; and PDA ligation. Thirty-six weeks' PMA epoch includes the following variables: CLD without MV (CMV or high-frequency ventilation) at 36 weeks and CLD with MV.