Patterns of Respiratory Disease During the First 2 Postnatal Weeks in Extremely Premature Infants

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Abstract

Background—Pulmonary disease among infants of <28 weeks' gestation (extremely low gestational age newborns) often has the following pattern: the infant starts out with little need for supplemental oxygen and ventilatory support in the first postnatal week but then has pulmonary deterioration in the second postnatal week, with an increased need for supplemental oxygen and respiratory support. We evaluated the antecedents and correlates of patterns of early lung disease, with particular emphasis on pulmonary deterioration, in a large cohort study (the Extremely Low Gestational Age Newborn [ELGAN] study).

Patients and Methods—We examined data collected prospectively on 1340 infants born between 2002 and 2004 at 23 to 27 completed weeks of gestation and who survived to 14 days. Pulmonary deterioration was defined as receipt of fraction of inspired oxygen <0.23 on any day between days 3 and 7 and receipt of fraction of inspired oxygen ≥ 0.25 on day 14.

Results—One fifth (20%) of the infants had consistently low fraction of inspired oxygen, approximately two fifths (38%) had pulmonary deterioration, and the remaining approximately two fifths (43%) had consistently high fraction of inspired oxygen (early and persistent lung dysfunction). Compared with infants who had consistently low fraction of inspired oxygen, infants who experienced pulmonary deterioration had lower gestational ages and lower birth weights, had higher

What's Known on This Subject
ELGANs experience different patterns of respiratory disease in the first 2 postnatal weeks.

What This Study Adds
We examined the antecedents and modifiers of 3 a priori–defined patterns of respiratory disease in ELGANs.

scores for neonatal acute physiology, and received more intensive modes of respiratory support. Gender, multifetal pregnancy, cesarean delivery, antenatal steroids, chorioamnionitis, and funisitis were not associated with pulmonary deterioration. The incidence of chronic lung disease, defined as oxygen therapy at 36 weeks' postmenstrual age, was 17% in the consistently low fraction of inspired oxygen group, 51% in the pulmonary deterioration group, and 67% in the early and persistent pulmonary dysfunction group. The incidence of death in these 3 groups before 36 weeks' postmenstrual age was 1%, 3%, and 5%, respectively.

Conclusions—Nearly 40% of extremely low gestational age newborns experience pulmonary deterioration in the first 2 postnatal weeks, and half of these infants develop chronic lung disease. Indicators of developmental immaturity and illness severity were associated with both pulmonary deterioration and chronic lung disease. Studying the antecedents of pulmonary deterioration might provide new insights about chronic lung disease pathogenesis.

Keywords

lung disease; prematurity; preterm infant

Nearly all infants born before 28 weeks' gestation (extremely low gestational age newborns [ELGANs]) require ventilatory assistance immediately after birth; most often with mechanical ventilation and supplemental oxygen.[1] During the first 2 postnatal weeks, several distinct patterns of lung disease emerge.[2–6] Some ELGANs have relatively little lung disease and rapidly recover, whereas others have early and persistent pulmonary dysfunction (EPPD) characterized by the need for mechanical ventilation and high concentrations of supplemental oxygen during the weeks after birth. A third group has resolution of their initial lung disease during the first week when mechanical ventilation may no longer be necessary and the need for oxygen is markedly reduced, only to deteriorate during the second week resulting in the need for increased supplemental oxygen and resumption of mechanical ventilation. We describe this group as having pulmonary deterioration (PD).

Rarely do infants with PD die; however, approximately one half develop chronic lung disease (CLD), also known as bronchopulmonary dysplasia.[7] Therefore, PD seems to be an important early identifier of infants likely to develop CLD. The antecedents of PD have not yet been identified, although late surfactant deficiency might be a contributing factor.[8] Bacteremia, pneumonia, and patent ductus arteriosus (PDA) are sometimes suspected as the cause of PD, but most often no cause is identified. Because PD is associated with CLD, acquiring a better understanding of PD might provide important insights about CLD.

A major advantage to focusing on PD, rather than the more established outcome, CLD, is that PD can be identified early in life. The events that may confound our understanding of PD are fewer in number than those that occur between birth and the diagnosis of CLD at 36 weeks' postmenstrual age. Finally, it is possible that risk factors for PD might be modified or mitigated, and that reducing exposure to these risk factors might reduce the likelihood of CLD. Therefore, we sought to identify the antecedents and modifiers of 3 patterns of early lung disease, with particular emphasis on PD, in a large cohort of ELGANs.

Methods

The study population included infants enrolled in a multicenter epidemiologic study to identify characteristics and exposures that increase the risk of structural and functional neurologic disorders in ELGANs (the ELGAN Study).[9] From March 2002 to August 2004, women delivering before the 28th week of gestation at 1 of 14 participating institutions were asked to enroll in the study. Individual institutional review boards approved the enrollment and consent processes. Of 1506 infants enrolled, 1340 survived the first 2 postnatal weeks and were thus

eligible for the analyses presented here. Historical, demographic, and clinical data were abstracted from maternal and infant charts, and histologic and microbiologic studies of the placentas were performed to identify evidence of inflammation and infection.

ELGANs were classified into 3 mutually exclusive groups: those with consistently low fraction of inspired oxygen (F_{IO_2}) (an F_{IO_2} consistently <0.23 on all days between 3 and 7 postnatal days and receiving $F_{IO_2} \leq 0.25$ on day 14), those with PD (an $F_{IO_2} < 0.23$ on *any* days between 3 and 7 days and receiving $F_{IO_2} > 0.25$ on day 14), and those with EPPD (an F_{IO_2} consistently ≥ 0.23 on all days between 3 and 7 postnatal days and receiving $F_{IO_2} > 0.25$ on day 14). For individual infants, the F_{IO_2} assigned for each day of life was the mode F_{IO_2} for that day. Day 0 began at the time of birth and continued through 24 hours of age. Day 1 began at the end of the first 24 hours of age and ended at midnight of that calendar day. Thus, day 1 varies in length. After day 1, all days began and ended at midnight.

We examined candidate risk factors for each respiratory outcome defined above including gender, gestational age, birth weight *z* score (based on an external standard[10]), maternal race, receipt of antenatal steroids, chorioamnionitis, funisitis, pregnancy complications, and multifetal pregnancy. Gestational age was determined by an a priori hierarchy based in order of decreasing preference on: fetal ultrasound before 14 weeks (62%), ultrasound between 14 and 18 weeks (17%), ultrasound after 18 weeks with a consonant maternal report of the beginning of the last menstrual cycle (13%), maternal report of the beginning of the last menstrual cycle only (7%), and gestational age recorded in the log of the NICU (1%).

The presence of chorioamnionitis (defined by polymorphonuclear leukocytes in the chorion or chorioamnion) and funisitis (defined by polymorphonuclear leukocytes in the wall of a blood vessel in the umbilical cord or the chorionic plate) was determined by a pathologist at each institution who first engaged in training procedures to minimize interobserver variability, was masked to maternal history, and used predefined operational definitions.[10,11]

To further identify evidence of infection, we cultured chorion/decidua biopsies of the placenta. Immediately after delivery, the chorioamnionic membranes were removed from an area on the fetal surface of the placenta. Specimens of placenta were then collected under sterile conditions, flash-frozen, stored locally −80°C, and later shipped to a central laboratory where they were processed in a standardized manner.[12,13]

We examined bacteriologic information from the infant-placenta dyads according to mode of delivery, first, considering all deliveries, and second, limiting analyses to infants born by cesarean section. The latter approach has the disadvantage that it excludes a moderate number of deliveries initiated by factors associated with intrauterine infection (eg, preterm labor and rupture of membranes). On the other hand, it has the advantage of excluding placentas contaminated during passage through the vagina.

We examined the occurrence during the first 2 postnatal weeks of the following factors: Score for Neonatal Acute Physiology II (SNAP-II),[14] mode of ventilation, diagnosis and treatment of PDA, diagnosis of bacteremia, and medication use. Mode of ventilation was defined as the highest level of support on each day and ranged from no support, supplemental oxygen by hood or nasal cannula, nasal continuous positive airway pressure, and conventional mechanical ventilation to high frequency ventilation. We did not record the devices used. Presumed bacteremia was defined as an episode of suspected bacteremia during which the infants were treated with antibiotics for more than 72 hours, but the blood culture was negative. Confirmed bacteremia required a positive blood culture. The diagnosis of PDA was assigned by clinicians without uniformity of definition; echocardiographic confirmation was not required. CLD was defined as oxygen therapy at 36 weeks' adjusted gestation. Medications were recorded if given on any day during the first week and included surfactant, analgesics (ie, morphine, fentanyl,

or methadone), sedatives (ie, lorazepam, midazolam, or chloral hydrate), vitamin A, and steroids (ie, hydrocortisone and dexamethasone). We did not collect data about the dosages.

Infants in the EPPD and PD groups were compared in univariate analyses to those in the low F_{IO2} group to identify the characteristics that distinguished them. Characteristics that distinguished infants who developed PD from infants who remained in the low F_{IO2} group with a *P* value of ≤ .30 were then included in logistic regression analyses to assess the strength of association of each characteristic/exposure to the risk of PD, adjusted for other factors included in the regression. We also created separate logistic regression models of the risk of EPPD based on characteristics and exposures that distinguished children who developed EPPD from infants who remained in the low F_{IO2} group.

Gestational age and birth weight *z* score[15,16] were included in every multivariable model. Multivariate logistic regression models were developed using manual backward selection, dropping the least significant variable followed by rerunning the model with the remaining variables. A model was complete when all of the variables that remained were associated with the outcome at a level of *P* < .1. The dropped variables were individually reintroduced to see if they now contributed to the complete model.

Results

The cohort comprised 1340 infants: 249 (20%) infants had consistently low F_{IO2}, 484 (38%) infants had PD, and 576 (43%) infants had EPPD (Fig 1).

Univariate Analysis

Compared with the consistently low F_{IO2} group, infants in the PD group tended to have a lower gestational age, lower birth weight, and a higher SNAP-II (Table 1). Compared with the EPPD group, infants in the PD group had a higher gestational age, higher birth weight, and a lower SNAP-II. Gender, multifetal pregnancy, antenatal steroids, initiator of delivery, cesarean delivery, and histologic indicators of inflammation did not distinguish one group from another.

In samples from the entire cohort and from those delivered by cesarean section, no one organism was identified as having a statistically significant association with pulmonary outcomes. *Mycoplasma* species were recovered most frequently from the placentas of infants in the EPPD group, and least frequently from the placentas of infants in the consistently low F_{IO2} group (Table 2). No other species showed this gradient. Compared with infants whose placenta did not harbor a vaginal organism, infants whose placenta did harbor a vaginal organism were at modestly greater risk of PD (45% vs 36%).

With increasingly severe and persistent respiratory dysfunction (from the low F_{IO2} group, to the PD group, to the EPPD group), the frequency of undesirable characteristics/exposures increased, including high SNAP-IIs, presumed bacteremia, confirmed bacteremia, echocardiogram-documented PDA, medical and surgical treatment of PDA, and high frequency ventilation on days 0 and 7 (Table 3). The frequency of receipt of the following medications also increased: surfactant, hydrocortisone, analgesics, sedatives, and vitamin A (Table 3).

In addition, the incidence of CLD was 17% (41/243) among children in the low F_{IO2} group, 51% (238/469) among children in the PD group, and 67% (358/535) among children in the EPPD group. Among all infants with CLD, 37% had an antecedent history of PD. On day 0 through day 7, the frequency of mechanical ventilation was lowest in the low F_{IO2} group, and highest in the EPPD group (Fig 2).

Multivariate Analysis

In multivariate analysis comparing the PD group to the low F_{IO_2} group, low gestational age, low birth weight *z* score, and mode of ventilation on postnatal day 7 were associated with increase risk of PD (Table 4). The increased risk associated with a diagnosis of PDA approached, but did not reach, nominal statistical significance (*P* = .07).

When comparing the EPPD group to the low F_{IO_2} group, low gestational age, low birth weight *z* score, mechanical ventilation on day 7, confirmed bacteremia, receipt of vitamin A and surfactant, and treatment of PDA were associated with increased risk of EPPD (Table 5). The *P* value associated with a diagnosis of PDA nearly achieved nominal statistical significance (*P* = .06). Histologic chorioamnionitis and funisitis were not associated with PD or EPPD in these models (data not presented).

Discussion

The importance of EPPD and PD is that infants who have these respiratory patterns are at very high risk of CLD. Early descriptions of CLD noted its association with severe early lung disease that would be categorized as EPPD in our study. More recently, an additional pattern of early disease preceding CLD has been reported. Among infants who developed CLD, Charafeddine et al[2] observed 2 groups of infants who did not have antecedent EPPD. Infants in these groups were either well throughout the first week of life or had recovered from their acute lung disease by the end of the first postnatal week, but then developed an oxygen requirement during the second postnatal week. The authors were the first to describe this experience as "atypical CLD."[2] These infants experienced what we call PD.

Streubel et al[6] identified a group of infants who had an F_{IO_2} of <0.25 for 3 days after recovery from respiratory distress syndrome (RDS) and a subsequent increase in F_{IO_2} to at least 40%; these infants were classified as having atypical CLD. All infants in this atypical CLD group developed bronchopulmonary dysplasia (BPD). Compared with infants with no BPD, infants with atypical CLD were smaller, less mature, and had a higher rate of sepsis and pneumothorax. In a similar study, Panickar et al[3] reported that ~40% of all who developed BPD had an antecedent history of PD. We confirmed this relationship, finding that >50% of children with EPPD or PD developed CLD compared with <20% of children in the low F_{IO_2} group.

The terms in current use in the literature are confusing. We feel that our terms (PD and EPPD) describe a clinical pattern of respiratory disease, defined by F_{IO_2}, which may or may not develop into CLD. Previous authors identified patients as having CLD (usually at 36 weeks' adjusted gestation), and then looked retrospectively to identify the pattern of lung disease (eg, "atypical RDS"2). We do not believe that infants with PD or EPPD necessarily have RDS. The advantage of using our terms is threefold: first, we, and other investigators, will be able to relate events that occur after the pattern of lung disease to these patterns (eg, CLD and, in future studies, neurodevelopmental outcomes); second, a clinician is now able to distinguish these patterns by the 14th postnatal day and place infants into appropriate risk categories of morbidities associated with prematurity (namely, CLD); and third, therapeutic modalities designed to reduce the incidence of morbidities associated with prematurity (eg, CLD) can use these patterns as markers of risk.

In our cohort of ELGANs, PD occurred in 38% of infants, a prevalence similar to that of EPPD (43%). Only 19% of ELGANs were in the consistently low F_{IO_2} group, having little or no evidence of lung dysfunction throughout the first 2 postnatal weeks. We found that infants with PD had a risk factor profile that was intermediate between that of infants with consistently low F_{IO_2} and infants with EPPD. This risk factor profile included birth weight, gestational age, and a variety of treatments and complications that are associated with low gestational age, such as

higher SNAP-II values, treatment with mechanical ventilation, patent ductus arteriosus, treatment with hydrocortisone, and confirmed bacteremia.

To our knowledge, the entity of PD is unique to ELGANs. The peculiar predisposition of ELGANs to PD could be explained on the basis of processes that are developmentally regulated resulting in vulnerability by virtue of birth at extreme prematurity (eg, adrenal glucocorticoid synthesis and antioxidant production).[17–19] This possibility is supported by our observation of the association between PD and early gestational age.

ELGANs may also be vulnerable because of a unique environmental exposure that is distinct to this population. One possibility is an intrauterine exposure. The most common feature that distinguishes the intrauterine environment of ELGANs from more mature neonates is the far greater likelihood of intrauterine infection.[20] Although not a consistent finding, intrauterine infection has been associated with the development of CLD, either as a risk factor by itself[21] or when antenatal infection is associated with the need for prolonged mechanical ventilation.[22]

Neither EPPD nor PD had an increased frequency of histologic expressions of inflammation in the placenta as chorioamnionitis and funisitis. Therefore, we explored the possibility that placental infection with a specific organism might be associated with risk for PD. In previous work, postnatal recovery of *Ureaplasma urealyticum* from tracheal samples has been associated with the development of CLD.[23] Although not statistically significant, among our study subjects *Mycoplasma* species, including *Ureaplasma*, was detected more frequently among the placentas of infants who developed EPPD.

Besides gestational age and birth weight, the most consistent risk factor for PD was treatment with mechanical ventilation (conventional or high-frequency ventilation) on postnatal day 7. It is not clear whether this association reflects a causal link between ventilation mode and PD or whether ventilation mode identifies infants with more severe lung disease. Treatment with oxygen during the first week of life in the low F_{IO2} and PD groups was similar, as was the frequency of the diagnosis of apnea at any time during the study period.

Two neonatal events, confirmed bacteremia and persistent PDA, have been associated with adverse outcomes, including CLD.[24] However, prophylactic treatment of the PDA has not been demonstrated to reduce the risk of CLD.[25] We examined both of these antecedents in relation to patterns of early lung disease. Bacteremia was a risk factor for EPPD but not for PD. This finding suggests that the etiology of persistent, severe lung disease may be different from the etiology of PD. The relationship between EPPD and both intrauterine exposure to specific organisms and postnatal infection implicates an infectious/inflammatory exposure in the pathogenesis.[21]

The diagnosis of PDA at any time during the first 2 weeks of life may be a risk factor for both EPPD and PD as this association approached statistical significance for both entities. A cause-and-effect relationship between shunting through a PDA and lung disease has biological plausibility.[15,16] It is possible that our finding an association between PDA and both EPPD and PD is explained on the basis of an acquisition bias, in that infants with more severe lung disease were more likely to be clinically suspected of having a PDA and to be subjected to diagnostic testing (ie, echocardiography). Alternatively, PDA may be causally related to PD. Our data about indomethacin and/or ligation for PDA do not allow us to assess if these therapies reduced the risks of EPPD or PD. Determining the contribution of the PDA is important, because it may be a modifiable risk factor.

Conclusions

We examined the patterns of lung dysfunction in the first 2 weeks of life and the risk factors associated with these patterns in a large cohort of ELGANs. Infants with PD and EPPD tended to have lower gestational ages and lower birth weights than infants with consistently low F_{IO_2}. The only statistically significant potentially modifiable risk factor unique to infants in the PD group was receipt of mechanical ventilation (conventional or high-frequency ventilation) on postnatal day 7, although PDA might also be important. Future studies that characterize the inflammatory milieu of the lung by measuring biomarkers in tracheal fluid may suggest pathologic mechanisms for PD and strategies for prevention. Additional studies are also needed to characterize the relationship between these early patterns of lung dysfunction and subsequent health and development during infancy.

Acknowledgments

References

1. Finer NN, Carlo WA, Duara S, et al. Delivery room continuous positive airway pressure/positive end-expiratory pressure in extremely low birth weight infants: a feasibility trial. Pediatrics 2004;114(3): 651–657. [PubMed: 15342835]

2. Charafeddine L, D'Angio CT, Phelps DL. Atypical chronic lung disease patterns in neonates. Pediatrics 1999;103(4 pt 1):759–765. [PubMed: 10103299]

3. Panickar J, Scholefield H, Kumar Y, Pilling DW, Subhedar NV. Atypical chronic lung disease in preterm infants. J Perinat Med 2004;32(2):162–167. [PubMed: 15085893]

4. Choi CW, Kim BI, Koh YY, Choi JH, Choi JY. Clinical characteristics of chronic lung disease without preceding respiratory distress syndrome in preterm infants. Pediatr Int 2005;47(1):72–79. [PubMed: 15693871]

5. Choi CW, Kim BI, Park JD, Koh YY, Choi JH, Choi JY. Risk factors for the different types of chronic lung diseases of prematurity according to the preceding respiratory distress syndrome. Pediatr Int 2005;47(4):417–423. [PubMed: 16091080]

6. Streubel AH, Donohue PK, Aucott SW. The epidemiology of atypical chronic lung disease in extremely low birth weight infants. J Perinatol 2008;28(2):141–148. [PubMed: 18059466]

7. Kobaly K, Schluchter M, Minich N, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. Pediatrics 2008;121(1):73–81. [PubMed: 18166559]

8. Merrill JD, Ballard RA, Cnaan A, et al. Dysfunction of pulmonary surfactant in chronically ventilated premature infants. Pediatr Res 2004;56(6):918–926. [PubMed: 15496605]

9. Laughon M, Bose C, Allred E, et al. Factors associated with treatment for hypotension in extremely low gestational age newborns during the first postnatal week. Pediatrics 2007;119(2):273–280. [PubMed: 17272616]

10. Hecht J, Onderdonk A, Delaney M, et al. Characterization of chorioamnionitis in second trimester c-section placentas and correlation with microorganism recovery from sub-amniotic tissues. Pediatr Dev Pathol 2007;11(1):15–22. [PubMed: 18237241]

11. Hecht JL, Kliman HJ, Allred EN, et al. Reference weights for placentas delivered before the 28th week of gestation. Placenta 2007;28(10):987–990. [PubMed: 17573110]

12. Hecht JL, Onderdonk A, Delaney M, et al. Characterization of chorioamnionitis in 2nd-trimester c-section placentas and correlation with microorganism recovery from subamniotic tissues. Pediatr Dev Pathol 2008;11(1):15–22. [PubMed: 18237241]

13. Onderdonk AB, Delaney ML, DuBois AM, Allred EN, Leviton A. Detection of bacteria in placental tissues obtained from extremely low gestational age neonates. Am J Obstet Gynecol 2008;198(1): 110,e1–e7. [PubMed: 18166321]

14. Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: simplified newborn illness severity and mortality risk scores. J Pediatr 2001;138(1):92–100. [PubMed: 11148519]

15. Rojas MA, Gonzalez A, Bancalari E, Claure N, Poole C, Silva-Neto G. Changing trends in the epidemiology and pathogenesis of neonatal chronic lung disease. J Pediatr 1995;126(4):605–610. [PubMed: 7699543]

16. Marshall DD, Kotelchuck M, Young TE, Bose CL, Kruyer L, O'Shea TM. Risk factors for chronic lung disease in the surfactant era: a North Carolina population-based study of very low birth weight infants. North Carolina Neonatologists Association. Pediatrics 1999;104(6):1345–1350. [PubMed: 10585987]

17. Beresford MW, Shaw NJ. Detectable IL-8 and IL-10 in bronchoalveolar lavage fluid from preterm infants ventilated for respiratory distress syndrome. Pediatr Res 2002;52(6):973–978. [PubMed: 12438678]

18. Leviton A, Blair E, Dammann O, Allred E. The wealth of information conveyed by gestational age. J Pediatr 2005;146(1):123–127. [PubMed: 15644836]

19. Watterberg KL. Adrenocortical function and dysfunction in the fetus and neonate. Semin Neonatol 2004;9(1):13–21. [PubMed: 15013472]

20. Goldenberg RL, Andrews WW, Faye-Petersen OM, Goepfert AR, Cliver SP, Hauth JC. The Alabama Preterm Birth Study: intrauterine infection and placental histologic findings in preterm births of males and females less than 32 weeks. Am J Obstet Gynecol 2006;195(6):1533–1537. [PubMed: 16796981]

21. Kallapur SG, Jobe AH. Contribution of inflammation to lung injury and development. Arch Dis Child Fetal Neonatal Ed 2006;91(2):F132–F135. [PubMed: 16492951]

22. Van Marter LJ, Dammann O, Allred EN, et al. Chorioamnionitis, mechanical ventilation, and postnatal sepsis as modulators of chronic lung disease in preterm infants. J Pediatr 2002;140(2):171–176. [PubMed: 11865267]

23. Kotecha S, Hodge R, Schaber JA, Miralles R, Silverman M, Grant WD. Pulmonary Ureaplasma urealyticum is associated with the development of acute lung inflammation and chronic lung disease in preterm infants. Pediatr Res 2004;55(1):61–68. [PubMed: 14605250]

24. Clyman RI. Recommendations for the postnatal use of indomethacin: an analysis of four separate treatment strategies. J Pediatr 1996;128(5 pt 1):601–607. [PubMed: 8627430]

25. Fowlie PW, Davis PG. Prophylactic indomethacin for preterm infants: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2003;88(6):F464–F466. [PubMed: 14602691]

Abbreviations

PD	pulmonary deterioration
ELGAN	extremely low gestational age newborn
CLD	chronic lung disease
PDA	patent ductus arteriosus
EPPD	early and persistent pulmonary dysfunction
F_{IO_2}	fraction of inspired oxygen

SNAP-II   Score for Neonatal Acute Physiology II

RDS   respiratory distress syndrome

BPD   bronchopulmonary dysplasia
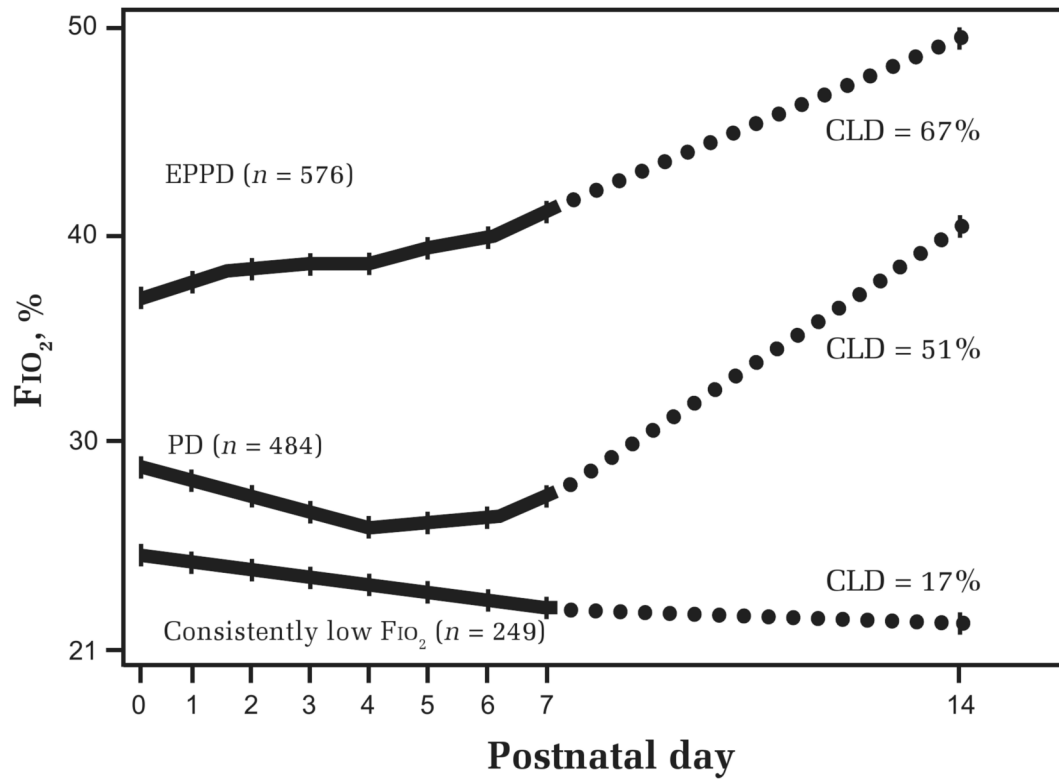
FIGURE 1.
Median of the mode F_{IO_2} on postnatal days 0 to 7 and on postnatal day 14 and frequency of CLD among 1340 ELGANs with 3 patterns of respiratory disease (low F_{IO_2}, PD, and EPPD) during the first 2 postnatal weeks.
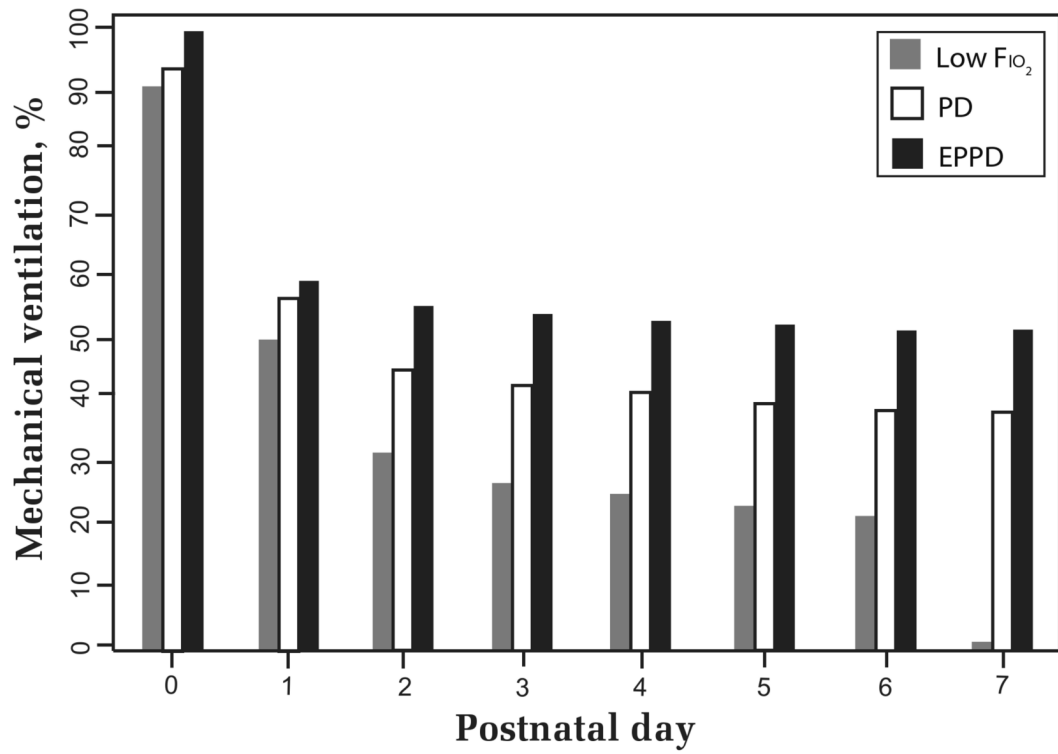
FIGURE 2.
Incidence of mechanical ventilation (conventional or high frequency) by postnatal days 0 to 7 and by group (low F_{IO_2}, PD, and EPPD).

TABLE 1

Characteristics and Antecedents Associated With Pulmonary Deterioration

Characteristic	Low F_{IO_2} (N = 249), Column %	Pulmonary Deterioration (N = 484), Column %	EPPD (N = 576), Column %	Row N	P
Gestational age, wk					
23	1	3	10	75	≤.0005
24	4	17	23	228	
25	11	21	25	272	
26	25	26	25	327	
27	59	34	17	407	
Birth weight, g					
≤750	14	37	54	527	≤.0005
751–1000	46	45	37	545	
1001–1250	37	16	9	216	
>1250	3	2	1	21	
Birth weight z score					
Less than −2	4	5	9	86	≤.0005
Less than −1	5	15	17	184	
−1 to 0	31	40	37	481	
≥0	60	40	37	558	
Male gender	50	53	55	696	.49
Multifetal pregnancy	32	33	30	412	.60
Any antenatal steroids	92	91	88	1177	.15
Initiator of delivery					
PTL	43	44	44	570	.45
pPROM	27	21	20	283	
Preeclampsia	10	14	15	180	
Abruption	10	11	11	139	
Cervical insufficiency	6	7	6	81	
Fetal indication	4	3	5	56	
Cesarean delivery	70	65	65	866	.39
Any chorioamnionitis	55	54	53	651	.89

Characteristic	Low F_{IO_2} (N = 249), Column %	Pulmonary Deterioration (N = 484), Column %	EPPD (N = 576), Column %	Row N	P
Any funisitis	40	33	32	396	.09

PTL indicates preterm labor; pPROM, preterm prolonged rupture of membranes.

TABLE 2

The Percentage of Infants Classified According to Their Pattern of Respiratory Assistance Whose Placenta Harbored the Organism or Group of Organisms Listed on the Left

Organisms	Low F_{IO_2}, Column %	Pulmonary Deterioration, Column %	EPPD, Column %	N	P
All deliveries					
Any organism					
Yes	20	35	45	588	.44
No	18	39	43	596	
Any anaerobe					
Yes	18	36	46	339	.56
No	20	37	43	845	
Any aerobe					
Yes	19	35	45	390	.77
No	19	38	43	794	
Any mycoplasma					
Yes	16	34	50	130	.34
No	20	37	43	1054	
No. organisms isolated					
0	18	39	43	596	.60
1	21	33	45	285	
≥2	18	37	45	303	
Skin organisms[a]					
Yes	21	37	43	248	.80
No	19	37	44	936	
Vaginal organisms[b]					
Yes	17	36	47	191	.61
No	20	37	43	993	
Maximum N	227	436	524	1184	
Cesarean delivery					
Any organism					
Yes	21	35	44	309	.82
No	20	37	43	465	

Organisms	Low F_{IO_2}, Column %	Pulmonary Deterioration, Column %	EPPD, Column %	N	P
Any anaerobe					
Yes	17	38	45	164	.55
No	21	35	43	611	
Any aerobe					
Yes	23	34	43	178	.52
No	19	37	44	596	
Any mycoplasma					
Yes	16	31	53	58	.30
No	21	37	43	716	
No. organisms isolated					
0	20	37	43	468	.91
1	20	36	44	198	
≥2	23	34	42	111	
Skin organisms[a]					
Yes	23	32	45	103	.52
No	20	37	43	671	
Vaginal organisms[b]					
Yes	14	45	42	74	.21
No	21	36	44	700	
Maximum N	156	282	336	774	

[a] *Corynebacterium* sp, *Propionebacterium* sp, *Staphylococcus* sp.

[b] *Prevotella bivia, Lactobacillus* sp, *Peptostrep magnus, Gardnerella vaginalis.*

TABLE 3

Postnatal Factors Associated With Pulmonary Deterioration

Postnatal Factor	Low FIO₂ (N = 249), Column %	Pulmonary Deterioration (N = 484), Column %	EPPD (N = 576), Column %	Row N	P
SNAP-II					
<20	70	54	40	658	≤.0005
20–29	18	27	27	326	
≥30	11	19	33	305	
Surfactant in the first week	78	89	97	1180	≤.0005
Bacteremia					
Confirmed	13	16	18	213	≤.0005
Presumed sepsis	27	34	41	465	
No	60	51	41	631	
Medications during the first 2 wk					
Methylxanthines	98	80	52	927	≤.0005
Hydrocortisone	2	11	16	151	≤.0005
Dexamethasone	2	1	4	31	.03
Analgesics	45	61	74	836	≤.0005
Sedatives	12	19	30	294	≤.0005
Vitamin A	20	25	36	382	≤.0005
PDA diagnosis					
Clinical	12	16	14	190	≤.0005
Echo	36	48	57	654	
None	52	36	28	465	
PDA treatment					
None	65	53	45	679	≤.0005
Indomethacin	31	41	46	540	
Ligation	4	6	9	90	
Highest level of ventilatory support on day 0					
No support	0	0	0	1	≤.0005
Hood	—	—	—	0	
Cannula	0.4	0.2	0	2	

Postnatal Factor	Low F$_{IO_2}$ (N = 249), Column %	Pulmonary Deterioration (N = 484), Column %	EPPD (N = 576), Column %	Row N	P
CPAP	19	6	1	84	≤.0005
Conventional	71	80	77	1008	
MV High frequency	10	14	22	214	
Highest level of ventilatory support on day 7					
No support	18	3	0	62	≤.0005
Hood	0	0.2	0	1	
Cannula	11	9	7	110	
CPAP	50	30	10	325	
Conventional	19	52	59	641	
MV High frequency	2	5	25	169	
CLD	17	51	67	620	≤.0005

MV indicates mechanical ventilation; CPAP, continuous positive airway pressure.

TABLE 4

Multivariate Analysis of ELGANs in the PD Group Versus the Low F_{IO_2} Group

Characteristic	Odds Ratio (95% Confidence Interval)	P
Gestational age, wk		
23	2.5 (0.5–12)	.25
24	3.6 (1.8–7.3)	≤.0005
25	2.4 (1.4–4.0)	.001
26	1.5 (1.0–2.3)	.04
27	1.0	
Birth weight *z* score		
Less than −1	2.8 (1.7–4.9)	≤.0005
−1 to 0	1.7 (1.2–2.5)	.003
≥0	1.0	
Mechanical ventilation, conventional or high frequency, on postnatal day 7	3.2 (2.4–4.8)	≤.0005
PDA diagnosis	1.4 (0.98–2.0)	.07

TABLE 5

Multivariate Analysis of ELGANs in the EPPD Group Versus the Low F_{IO_2} Group

Characteristic	Odds Ratio (95% Confidence Interval)	P
Gestational age, wk		
23	13 (2.7–59)	.001
24	4.2 (2.0–9.1)	≤.0005
25	3.8 (2.1–6.9)	≤.0005
26	2.8 (1.7–4.6)	≤.0005
27	1.0	
Birth weight *z* score		
Less than −1	3.1 (1.7–5.7)	≤.0005
−1 to 0	1.6 (1.0–2.6)	.04
≥0	1.0	
Mechanical ventilation, conventional or high frequency, on postnatal day 7	9.5 (6.1–15)	≤.0005
PDA diagnosis	1.4 (0.98–2.0)	.06
Confirmed bacteremia	1.7 (1.1–2.6)	.02
Hydrocortisone	2.4 (0.9–6.5)	.10
Vitamin A	1.8 (1.1–3.0)	.02
Surfactant	4.6 (2.2–9.5)	≤.0005