CLINICAL SCIENCE

Respiratory outcomes and atopy in school-age children who were preterm at birth, with and without bronchopulmonary dysplasia

Hercília Guimarães,[I,II] Gustavo Rocha,[I] Susana Pissarra,[I] Maria Beatriz Guedes,[I] Teresa Nunes,[III] Bonito Vitor[III]

[I] Hospital de São João - Serviço de Neonatologia, Porto, Portugal. [II] Faculdade de Medicina do Porto, Porto, Portugal. [III] Hospital de São João - Serviço de Pediatria, Porto, Portugal.

OBJECTIVE: To assess pulmonary function and the prevalence of atopy in school-age children who were very low birth weight as infants and to compare those who had bronchopulmonary dysplasia to those who did not.

METHOD: We studied 85 (39 male and 46 female) at a mean age of 84 (range, 62 to 107) months who were very low birth weight infants. Bronchopulmonary dysplasia was defined as oxygen dependency at 36 weeks gestational age. We excluded 8 patients (4 for cerebral palsy and 4 for no collaboration). Detailed perinatal and clinical data were collected. Lung function was evaluated using conventional spirometry. Atopy (assessed by the allergy skin-prick test) was considered when at least one positive skin test occurred in a panel of the most common environmental allergens in the local region. Comparisons between the bronchopulmonary dysplasia and no bronchopulmonary dysplasia groups were performed using the Mann-Whitney, $\chi 2$ and Fisher's exact tests.

RESULTS: We compared the bronchopulmonary dysplasia (n = 13) and no bronchopulmonary dysplasia (n = 64) groups. Atopy was observed in 4 (30.8%) of the bronchopulmonary dysplasia patients and in 17 (26.6%) of the no bronchopulmonary dysplasia patients (p = 0.742). Two (15.4%) patients with bronchopulmonary dysplasia had a family history of atopy vs. 17 (26.6%) in the no bronchopulmonary dysplasia group (p = 0.5). Lung function tests showed airway obstruction in 2 (15.4%) of the bronchopulmonary dysplasia patients and in 10 (15.6%) of the no bronchopulmonary dysplasia patients (p = 1.0). Four (33.3%) of the bronchopulmonary dysplasia patients had small airway obstruction vs. 14 (22.2%) of the no bronchopulmonary dysplasia patients (p = 0.466).

CONCLUSION: Our data showed no significant differences in lung function between bronchopulmonary dysplasia and no bronchopulmonary dysplasia patients at school age and no evidence of an association between atopy and bronchopulmonary dysplasia.

KEYWORDS: .

Guimarães H, Rocha G, Pissarra S, Guedes MB, Nunes T, Vitor B. Respiratory outcomes and atopy in school-age children who were preterm at birth, with and without bronchopulmonary dysplasia. Clinics. 2011;66(3):425-430.

Received for publication on November 1, 2010; **First review completed on** November 1, 2010; **Accepted for publication on** November 25, 2010

E-mail: herciliaguimaraes@gmail.com

Tel.: +351 22 5512100

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a multifactorial, chronic respiratory disease that develops as a consequence of perinatal/neonatal lung injury. It is one of the most important sequelae of premature birth, and its prevalence varies widely.[1-9] In spite of receiving multifaceted treatment, affected infants can remain oxygen dependent for many months.[10,11] The gains in therapeutically reducing BPD have been modest.[9,12,13] Infants who require supplementary oxygen at home have increased healthcare utilization, even during preschool years, when they are no longer oxygen-dependent. Recurrent respiratory symptoms that require treatment are common in children who were born prematurely, especially those who had BPD.

More than 50% of BPD patients require rehospitalization in the first two years of life.[14] Premature children, especially those who had BPD, are more likely to suffer frequent, troublesome symptoms at school age and in adolescence than term-born controls.[11,15] Studies examining adolescents and adults have usually reported on patients who had ''classical'' BPD; that is, they often had had severe respiratory failure in the neonatal period with chronic pulmonary fibrosis and airway smooth muscle hypertrophy.[6,16,17]

In recent years, infants have been described as having ''new'' BPD, which involves developing chronic oxygen dependence despite initially minimal or even absent respiratory distress. However, affected patients have

reduced alveolarization and experience deterioration in lung function over the first year after birth. It is essential to determine if these patients' lung function can ''catch up'' and to identify which strategies impair and, most importantly, promote lung growth in this high-risk population.[8,18]

The most severely affected patients may remain symptomatic and have evidence of airway obstruction even as adults. Although lung function improves over time, abnormalities can be detected even in young adults who had severe BPD as infants.[14,19]

Because some children with BPD have recurrent wheezing, the question of whether there is a correlation between BPD and atopy arises. A family history of atopy is related to respiratory morbidity, and an atopic predisposition was found to be associated with the persistence of wheezing in preterm infants.[20, 21]

Nevertheless, recent studies suggest that children with BPD do not have an increased prevalence of atopy, as do those with asthma.[20,22]

The aim of this study was to assess the pulmonary function and prevalence of atopy in school-age children who were less than 1500 g (VLBW) as infants and to compare those who had BPD as infants to those who did not.

MATERIALS AND METHODS

Subjects

We studied 85 children (39 male and 46 female) at a mean age of 84 (range, 62 to 107) months who were VLBW infants. The children were born between January 1, 2002 and December 31, 2004. The total number of VLBW infants in our NICU over this period was 126. We excluded 8 (5 male and 3 female) patients (4 for cerebral palsy and 4 for no collaboration). All the children had been treated at our neonatal intensive care unit. Detailed perinatal and neonatal clinical data were collected, including the following: treatment with prenatal steroids, intrauterine growth restriction, gestational age at birth (GA), birth weight (BW), hyaline membrane disease, mechanical ventilation (MV), length of MV, oxygen therapy and length of oxygen therapy.

The diagnosis of PBD was based on dependence on supplementary oxygen at 36 weeks gestational age. We classified BPD as moderate or severe according to the consensus definition of the National Institutes of Health.[5]

Follow-up at school age

A questionnaire that included questions about personal history of allergic diseases, family history of atopy, past respiratory symptoms, frequency of airway infections and hospital respiratory readmissions during the previous year, medical treatments and school absenteeism was created and distributed.

A physical examination was conducted that included measurements of body weight and height. To evaluate the child's nutritional status, we calculated the body mass index (BMI) using charts from the National Institute of Child Health and Human Development.

An allergy skin-prick test and spirometry were conducted at the outpatient department.

None of the children had respiratory infections at the time of the lung function tests. If the child was receiving bronchodilator treatment due wheezing episodes, the bronchodilators were withdrawn 12 hours before the evaluation of pulmonary function.

Lung function was evaluated using conventional spirometry (Compact Vitalograph, Buchingham, U.K.). At least three acceptable flow-volume curves were obtained, following the reproducibility criteria of the European Respiratory Society.[23]

The forced vital capacity (FVC), forced expiratory volume at one second (FEV1), FEV1/FVC ratio (FEV%) and mid-expiratory flow at 25 to 75% of FVC (FEF 25-75%) were recorded. The values of Polgar were used as reference data.[24]

We defined airway obstruction and small airway obstruction as, respectively, maximal FEV1 and FEF 25-75% values of less than 80% of the predicted values in both determinations.

Atopy was assessed by the allergy skin-prick test for the most common environmental allergens in the local region: Dermatophagoides farinae, Dermatophagoides pteronyssinus, Lepidoglyphus destructor, dog, cat, Alternaria, gramineae, trees, egg white, fish and peanut. Histamine chloride (10 mg/ml) was the positive control and NaCl 0.9% was the negative control.

Atopy was defined as at least one positive skin-prick test (a weal with a diameter greater than or equal to the negative control).

The parents were fully informed of the purpose of the study and written informed consent was obtained. The study was approved by the local ethics committee (Hospital de São João).

Data Analysis

The BPD and no BDP groups were compared using the Mann-Whitney, $\chi 2$ and Fisher's exact tests.

RESULTS

Perinatal and neonatal data

Out of 77 children, 25 (32.5%) were extremely low birth weight infants.

Thirteen had BPD, of whom 12 were graded as moderate and 1 as severe BPD. The perinatal data are presented in Table I. The average BW and GA of the children with BPD were significantly lower than those of the children without BPD. The BPD risk factors were male gender, hyaline membrane disease, length of mechanical ventilation and oxygen therapy (Table I).

Health status and symptoms at school age

As shown in Table II, the children were observed at a mean age of 84 (range, 62 to 107) months in the BDP group and 92 (range, 69 to 105) months in the no BPD group ($p = 0.115$).

- Body mass index. In the school-age evaluation, there was no difference between the body mass indices of the children with and without BPD (Table II).

- Respiratory Outcomes. Wheezing was reported in 8 (61.5%) of the BPD patients and in 46 (71.9%) of the children without BPD ($p = 0.063$). Dyspnea was observed in 9 (69.2%) of the children with BPD and 55 (85.9%) of those without BPD ($p = 0.092$).

School absenteeism was reported in 5 (6.5%) and hospital admissions in 16 (20.7%) of our patients, and 22 (28.5%) needed medical treatment in the first two years of life, but

Table I - Clinical characteristics of the studied population and comparisons between patients who did and did not have BPD.

	BPD (n = 13)	No-BPD (n = 64)	p
Birth weight (grams,) median (range)	850 (565-1400)	1210 (655-1500)	0.01
X ± SD	900 ± 221	1162 ± 875	
Gestational age (weeks), median (range)	27 (23-30)	30 (26-35)	<0.0001
X ± SD	27 ± 1.9	29.9 ± 2.4	
Male sex, n (%)	10 (76.9)	24 (37.5)	0.013
Intrauterine growth restriction, n (%)	2 (15.4)	12 (18.2)	1.0
Prenatal corticosteroids, n (%)	12 (92.3)	60 (93.8)	1.0
Hyaline membrane disease, n (%)	13 (100)	35 (54.7)	0.01
Mechanical ventilation, n (%)	13 (100)	55 (85.9)	0.343
MV length (days), median (range)	58 (7-107)	10 (0-72)	<0.0001
X ± SD	54.5 ± 26.6	15.72 ± 16.6	
Oxygen therapy, n (%)	13 (100)	50 (78.1)	0.110
Oxygen therapy length (days), median (range)	53 (7-365)	5.5 (0-58)	<0.0001
X ± SD	106.3 ± 117.2	12.6 ± 15.4	

X ± SD = mean ± standard deviation

no significant differences were observed between the groups (Table II). In the school-age evaluation, none of the children were on systemic steroids, and 7 (9.9%) of them intermittently needed inhaled bronchodilators and/or steroids.

Table II - Comparisons of body mass index, respiratory symptoms, school absenteeism, hospital admissions and treatment at school age between patients who had BPD or did not have BPD.

	BPD (n = 13)	No BPD (n = 64)	p
Age (months), median (range)	84 (62-107)	92 (69-105)	0.115
X ± SD	91.0 ± 11.3	84.7 ± 13.2	
Body mass index (percentile)			
< 5	1 (7.7)	4 (6.3)	0.975
5-25	4 (30.8)	17 (26.6)	
25-50	5 (38.5)	30 (46.9)	
50-85	2 (15.4)	7 (10.6)	
> 85	1 (7.7)	6 (9.4)	
Wheezing*			0.063
No wheezing, n (%)	8 (61.5)	46 (71.9)	
Wheezing, n (%)	5 (38.5)	18 (28.1)	
Mild, n (%)	1 (7.7)	10 (15.6)	
Moderate, n (%)	1 (7.7)	6 (9.4)	
Severe, n (%)	3 (23.1)	2 (3.1)	
Dyspnea*		0.092	
No dyspnea, n (%)	9 (69.2%)	55 (85.9)	
Dyspnea, n (%)	4 (30.8)	9 (14.1)	
Mild, n (%)	1 (7.7)	5 (7.8)	
Moderate , n (%)	2 (15.4)	4 (6.3)	
Severe, n (%)	1 (7.7)	0 (0)	
Absenteeism, n (%)	1 (7.7)	4 (6.3)	1.0
Hospital respiratory admissions, n (%)	4 (30.8)	12 (18.8)	0.452
Medical treatment, n (%)	5 (38.5)	17 (26.5)	0.50

X ± SD = mean ± standard deviation
*Definitions of severity from GINA (Global Initiative for Asthma, WHO 2008)

Lung function tests (spirometry)

The majority of the children (74/77) performed the spirometry test without difficulty. Out of 77 children, 12 had airway obstruction; of these, 6 had moderate to severe airway obstruction.

No significant differences were seen in FVC, FEV1, FEV% and FEF 25-75% between the BPD and no BPD patients (Table III).

The lung function tests showed airway obstruction in 2 (15.4%) of the BPD patients and in 10 (15.6%) of the no-BPD patients (p = 1.0); 4 (33.3%) of the patients in the BPD group had small airway obstruction, versus 14 (22.2%) in the no-BPD group (p = 0.466) (Table III).

Atopy

Atopy was observed in 4 (30.8%) of the BPD patients and in 17 (26.6%) of the no BPD patients (p = 0.742); 2 (15.4%) of the patients in the BPD group had a family history of atopy versus 17 (26.6%) in the no BPD group (p = 0.5) (Table III). Of the 19 patients with a familiar history of atopy, 6 (32%) had positive skin-prick tests. Of the 21 children with allergies, 15 (71%) did not have a family history of atopy.

DISCUSSION

In this study, we did not find significant differences in lung function tests and atopy prevalence of school-age children who were VLBW infants, with and without BPD.

In spite of the increased morbidity during first years of life, our patients showed good respiratory outcomes by the time they were school age, a finding which has also been observed by others.[15,22,25]

Some controversy still exists over the relationship between prematurity, atopy and bronchopulmonary dysplasia, some aspects of which are discussed later in this article .[20,21,24,26-29,32] Also, the prevalence of atopy at school

Table III - Atopy and lung function comparison at school age between patients who had BPD or did not have BPD.

	BPD (n = 13)	No-BPD (n = 64)	p
Age (months), median (range)	84 (62-107)	92 (69-105)	0.115
X ± SD	91.0 ± 11.3	84.7 ± 13.2	
Allergy (positive skin-prick test), n (%)	4 (30.8)	17 (26.6)	0.742
Family atopy history, n (%)	2 (15.4)	17 (26.6)	0.5
Lung function			
Airway obstruction, n (%)	2 (15.4)	10 (15.6)	1.0
Small airway obstruction, n (%)	4 (33.3)	14 (22.2)	0.466
FVC, median (extremes) (% predict)	88 (58-111)	91 (56-117)	0.157
FEV1, median (extremes) (% predict)	79 (58-98)	89 (48-124)	0.172
FEV %, median (extremes) (% predict)	8.5 (1-17)	6 (1-43)	0.324
FEF 25-75 %, median (range) (% predict)	87 (48-148)	97 (5-223)	0.439

X ± SD = mean ± standard deviation

age in our patients was not significantly different from that of the general Portuguese school-age population.[33,34]

Perinatal and neonatal data

The following BPD risk factors were identified in our patients: birth weight, gestational age at birth , male gender, hyaline membrane disease, length of MV and length of oxygen therapy (Table I). We expected these results based on the findings of other authors.[6,16] No significant difference was seen in prenatal corticosteroid treatment (Table I).

Health status and symptoms at school age

The children were observed at school age: a mean age of 84 (range, 62 to 107) months in the BDP group and a mean age of 92 (range, 69 to 105) months in the no BPD group ($p = 0.11$) (Table II).

Out of 77 children, 13 had BPD; of these, only one had severe BPD.

- Body Mass Index. In spite of some evidence that BPD patients have increased morbidity, we did not find a significant difference in the body mass indices of the children with and without BPD (Table II). Our results are consistent with a recent study in which no significant differences were seen in weight or height at the time of evaluation.[22] This finding may be due to most of our children having had moderate BPD. Only one patient had severe BPD. Another reason might be that the BPD patients in our neonatal intensive care unit received a nutritional protocol with a high-calorie diet.

It has been demonstrated that greater linear growth, lean mass and bone mass occur in the enriched formula group, which suggests that infants with bronchopulmonary dysplasia achieve faster ''catch-up'' growth when fed higher intakes of protein, calcium, phosphorus, and zinc than are provided in standard proprietary formulas.[30] Korhonen and co-workers have shown that at 7 years of age, VLBW children are shorter than term controls independently of whether they had had BPD.[31]

- Respiratory Outcome. Wheezing was reported in 8 (61.5%) of the BPD patients and in 46 (71.9%) of the children without BPD ($p = 0.063$). Dyspnea was observed in 9 (69.2%) of the children with BPD and 55 (85.9%) of those without BPD ($p = 0.092$).

School absenteeism was reported in 5 (6.5%) and hospital admissions in 16 (20.7%) of our patients, and 22 (28.5%) needed medical treatment in the first years of life; no significant differences were observed between the groups, however (Table II). The BPD patients had more readmissions in the first years of life (30.8% vs. 18.8%), as has been shown by others.[11,19]

Longitudinal studies on children with BPD have identified significant airflow obstruction and a greater need for inhaled asthma medication at all ages.[8,19] None of the children in the study were on systemic steroids, and about 10% of them needed intermittently inhaled bronchodilators and/or steroids at school age.

Lung Function - Spirometry

The majority of the children performed the spirometry test without difficulty. Lung function values from a longitudinal study of healthy children and adolescents have been published by Hibbert and co-workers.[35] Our patients were younger, however, and we used the values from our Department of Pediatrics as references.[24]

The lung function tests showed airway obstruction in 15.4% of the BPD patients, a frequency not significantly different from the 15.6% observed in the no-BPD patients (Table III). Out of 77 children, 12 had airway obstruction; of these, 6 had moderate to severe airways obstruction.

Our study was not designed to evaluate whether the non-BPD preterm group differed from healthy children born at term. We only compared BPD and no-BPD VLBW children, and we did not find a significant difference.

Other studies have demonstrated early impairment of lung function at school age in BPD children,[22,36-41] and isolated prematurity has been shown to play an important role in children's respiratory pathology (the role being the impairment of lung function present in these children since the first years of life).[15,42] Depending on its severity, children with BPD may have reduced lung function through childhood and into early life.[11,14,19,43]

We speculate that our lung function results for PBD and no BPD VLBW infants can be explained by the following reasons. First, only 25 (32.5%) were extremely low birth weight infants, and preterm children of extremely low gestational age show greater impairment in lung function due to reduced alveolarization.[6,18] Second, most of our patients had moderate BPD, and only one child had severe BPD. Severe cases show the greatest impairment in lung function.[22]

Third, the four patients who were the most severely neurologically handicapped were excluded, along with four others who did not choose to collaborate. These patients did not have respiratory symptoms and had radiologically normal lungs. Eight of the children selected for this study could not collaborate. Nevertheless, this is not a valid reason because they had not had BPD. Fourth, our patients had good nutrition status, as evaluated by BMIs at school age that were not significantly different between the groups. Adequate nutrition is mandatory for preventing lung injury and allowing lung growth in preterm infants, particularly for those with BPD. Fifth, our good results probably correspond to the improvements in lung function observed at school age by others.[44]

Atopy

There is some controversy concerning the association between atopy, prematurity and BPD.[20,21,26-28,32]

In our study, no evidence of an association between atopy and BPD was found. Wheezing was observed in 61.5% of the children with BPD and 71.9% of those without BPD (Table II).

The prevalence of wheezing during infancy and early childhood among VLBW infants is high. Siltanen et al. has shown that preterm wheezers who still wheezed at age of 10 were atopic significantly more often than those who no longer wheezed (62% vs. 9%, $p = 0.006$). Although atopy is not associated with a lifetime prevalence of respiratory symptoms in prematurely born children, an atopic predisposition has been found to be associated with the persistence of wheezing.[20]

In a previous study, we found that respiratory symptoms were related to perinatal events (specifically, mechanical ventilation and oxygen therapy) and not to the existence of atopy.[32] These findings have not been confirmed by others; they have found that that chronic and recurrent episodes of wheezing are more directly related to atopy than to neonatal problems.[28]

We did not find that a family history of atopy was related to respiratory symptoms at school age, as has previously been reported.[21]

Of the 19 patients with a family history of atopy, 6 (32%) had positive skin-prick tests. Of 21 children with allergies, 15 (71%) had no familial history of atopy. These results are not significantly different from those of the general Portuguese population, in which the prevalence of asthma at school age is approximately 10 to 12% and in which atopy is approximately 2 to 2.5 times more prevalent that asthma.[33,34]

CONCLUSION

Our data show no significant differences in lung function between BPD and no BPD patients at school age and no evidence of an association between atopy and BPD.

In spite of greater morbidity in the early lives of children with BDP, our data point to good respiratory outcomes at school age, which is consistent with some studies that have shown an improvement in lung function with age.[45] In this very high-risk population, however, residual abnormalities may persist later in life, which supports careful follow-up of the clinical condition and lung function of these patients. The importance of these respiratory problems in adult life needs to be determined (whether BPD survivors have a greater risk of developing a chronic obstructive pulmonary disease-like phenotype with aging, for example). Only longitudinal lung function studies will answer such questions.

Further studies need to be performed with extremely low gestational age and extremely low birth weight infants because this population has a high risk of lung function impairment.

ACKNOWLEDGEMENTS

The authors thank the children and parents for their collaboration.

REFERENCES

1. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med. 1967;276:357-68, doi: 10.1056/NEJM196702162760701.
2. Bancalari E, Abdenour GE, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. J Pediatr. 1979;95):819-23.
3. Shennan AT, Dunn MS, Ohlsson A, Lennox K,Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics. 1988;82:527-32.
4. Walsh MC, Yao Q, Gettner P, Hale E, Collins M, Hensman A, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. Pediatrics. 2004;114:1305-11, doi: 10.1542/peds.2004-0204.
5. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics. 2005;116:1353-60, doi: 10.1542/peds.2005-0249.
6. Sosenko IRS, Bancalari E. New developments in the presentation, pathogenesis, epidemiology and prevention of bronchopulmonary dysplasia. In: The Newborn Lung Eduardo Bancalari. Consulting Ed: Richard A Polin. Saunders Elsevier. 2008:187-207, doi: 10.1016/B978-141603166-6.10009-9.
7. VLBW infants in Portugal. National Multicenter Study 1996-2000. Portuguese Neonatal Network. Bial Award of Clinical Medicine. 2002. ISBN. 972-99224-0-3.
8. Baraldi E, Carraro S, Filippone M. Bronchopulmonary dysplasia: definitions and long-term respiratory outcome. Early Hum Dev. 2009;85:S1-3, doi: 10.1016/j.earlhumdev.2009.08.002.
9. Tin W, Wiswell TE. Drug therapies in bronchopulmonary dysplasia: debunking the myths. Semin Fetal Neonatal Med. 2009;14:383-90, doi: 10.1016/j.siny.2009.08.003.
10. Moro M, Pérez-Rodriguez J, Figueras-Aloy J, Fernández C, Doménech E, Jiménez R, et al. Predischarge morbidities in extremely and very low-birth-weight infants in Spanish neonatal units. Am J Perinatol. 2009;26:335-43, doi: 10.1055/s-0028-1110083.
11. Greenough A. Long-term pulmonary outcome in the preterm infant. Neonatology. 2008;93:324-7, doi: 10.1159/000121459.
12. Gupta S, Sinha SK, Donn SM. Ventilatory management and broncho-pulmonary dysplasia in preterm infants. Semin Fetal Neonatal Med. 2009;14:367-73, doi: 10.1016/j.siny.2009.08.011.
13. Laughon MM, Smith PB, Bose C.Prevention of bronchopulmonary dysplasia. Semin Fetal Neonatal Med. 2009;14:374-82, doi: 10.1016/j.siny.2009.08.002.
14. Northway WH Jr, Moss RB, Carlisle KB, Parker BR, Popp RL, Pitlick PT, et al. Late pulmonary sequelae of bronchopulmonary dysplasia. N Engl J Med. 1990;323:1793-9, doi: 10.1056/NEJM199012273232603.
15. Pérez Pérez G, Navarro Merino M. Bronchopulmonary dysplasia and prematurity. Short-and long-term respiratory changes. An Pediatr. 2010;72:79.e1-16, doi: 10.1016/j.anpedi.2009.09.010.
16. Bancalari E, Claure N, Sosenko IR. Bronchopulmonary dysplasia: changes in pathogenesis, epidemiology and definition. Semin Neonatol. 2003;8:63-71, doi: 10.1016/S1084-2756(02)00192-6.
17. Hayes D Jr, Feola DJ, Murphy BS, Shook LA, Ballard HO. Pathogenesis of Bronchopulmonary Dysplasia. Respiration. 2009:25.
18. Merritt TA, Deming DD, Boynton BR. The 'new' bronchopulmonary dysplasia: challenges and commentary. Semin Fetal Neonatal Med. 2009;14:345-57, doi: 10.1016/j.siny.2009.08.009.
19. Greenough A. Late respiratory outcomes after preterm birth. Early Hum Dev. 2007;83:785-8, doi: 10.1016/j.earlhumdev.2007.09.006.
20. Siltanen M, Savilahti E, Pohjavuori M, Kajosaari M. Respiratory symptoms and lung function in relation to atopy in children born preterm. Pediatr Pulmonol. 2004;37:43-9, doi: 10.1002/ppul.10402.
21. Greenough A, Giffin FJ, Yüksel B, Dimitriou G. Respiratory morbidity in young school children born prematurely--chronic lung disease is not a risk factor? Eur J Pediatr. 1996;155:823-6.
22. Broström EB, Thunqvist P, Adenfelt G, Borling E, Katz-Salamon M. Obstructive lung disease in children with mild to severe BPD. Respir Med.2010;104:362-70, doi: 10.1016/j.rmed.2009.10.008.
23. Loeb JS, Blower WC, Feldstein JF, Koch BA, Munlin AL, Hardie WD. Acceptability and repeatability of spirometry in children using updated ATS/ERS criteria. Pediatr Pulmonol. 2008;43:1020-4, doi: 10.1002/ppul.20908.
24. Polgar G, Promadhat V. Pulmonary function testing in children: technics and standards. Philadelphia:WB Saunders; 1971.
25. Lundqvist P, Källén K, Hallström I, Westas LH. Trends in outcomes for very preterm infants in the southern region of Sweden over a 10-year period. Acta Paediatr. 2009;98:648-53, doi: 10.1111/j.1651-2227.2008.01155.x.
26. Siltanen M, Kajosaari M, Pohjavuori M, Savilahti E. Prematurity at birth reduces the long-term risk of atopy. J Allergy Clin Immunol. 2001;107:229-34, doi: 10.1067/mai.2001.112128.
27. Mai XM, Gäddlin PO, Nilsson L, Finnström O, Björkstén B, Jenmalm MC, et al. Asthma, lung function and allergy in 12-year-old children with very low birth weight: a prospective study. Pediatr Allergy Immunol. 2003;14:184-92 , doi: 10.1034/j.1399-3038.2003.00045.x.
28. Kwinta P, Tomasik T, Klimek M, Lis G, Cichocka-Jarosz E, Pietrzyk JJ. Wheezing in very low birth weight infants: sequence of early neonatal lung injury or increased susceptibility for allergic reactions? Follow-up study up to age of 5-7 years. Przegl Lek. 2007;64:118-21.
29. Halvorsen T, Skadberg BT, Roksund O, AksnesL, Oymar K. Characteristics of asthma and airway hyper-responsiveness after premature birth. Pediatr Allergy Immunol 2005;16:487-9, doi: 10.1111/j.1399-3038.2005.00314.x.
30. Brunton JA, Saigal S, Atkinson SA. Growth and body composition in infants with bronchopulmonary dysplasia up to 3 months corrected age: a randomized trial of a high-energy nutrient-enriched formula fed after hospital discharge. J Pediatr. 1998;133:340-5, doi: 10.1016/S0022-3476(98)70266-5.
31. Korhonen P, Hyodynmaa, Lenko HL, Tammela O. Growth and adrenal androgen status at 7 years in very low birth weight survivors with and without Bronchopulmonary dysplasia. Arch Dis Child. 2004;89:320-4, doi: 10.1136/adc.2002.022699.
32. Guimarães H, Pissarra S, Guedes MB, Vasconcellos G, Ramos JP, Bonito Vítor A. Atopy and respiratory status at 6 months of age in very low birthweight infants. Biology Neonate. 2005;88:337.
33. Wirl C, Puklova V. Prevalence of asthma and allergies in children. World Health Organization, 2007. www.euro.who.int
34. Falcão H, Ramos E, Marques A, Barros H. Prevalence of asthma and rhinitis in 13 year old adolescents in Porto, Portugal. Rev Port Pneumol. 2008; XIV:747-8.
35. Hibbert ME, Lannigan A, Landau LI, Phelan PD. Lung function values from a longitudinal study of healthy children and adolescents. Pediatr Pulmonol.1989;7:101-9, doi: 10.1002/ppul.1950070209.
36. Giacoia GP, Venkataraman PS, West-Wilson KI, Faulkner MJ. Follow-up of school-age children with bronchopulmonary dysplasia. J Pediatr. 1997;130:400-8, doi: 10.1016/S0022-3476(97)70231-2.
37. Vrijlandt EJ, Boezen HM, Gerritsen J, Stremmelaar EF, Duiverman EJ. Respiratory health in prematurely born preschool children with and without bronchopulmonary dysplasia. J Pediatr. 2007;150:256-61, doi: 10.1016/j.jpeds.2006.12.007.

38. Doyle LW, Anderson PJ. Long-term outcomes of bronchopulmonary dysplasia. Semin Fetal Neonatal Med. 2009;14:391-5, doi: 10.1016/j.siny.2009.08.004.
39. Palta M, Sadek-Badawi M, Sheehy M, Albanese A, Weinstein M, McGuinness G, Peters ME. Respiratory symptoms at age 8 years in a cohort of very low birth weight children. Am J Epidemiol. 2001;154:521-9, doi: 10.1093/aje/154.6.521.
40. Anand D, Stevenson CJ. West CR, Pharoah PO. Lung function and respiratory health in adolescents of very low birth weight. Arch Dis Child. 2003; 88:135-8, doi: 10.1136/adc.88.2.135.
41. Doyle LW. Respiratory function at age 8-9 years in extremely low birth weight/very preterm children born in Victoria in 1991-1992. Pediatr Pneumol. 2006;41:570-6.
42. Doyle LW, Faber B, Callanan C, Freezer N, Ford GW, Davis NM. Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. Pediatrics. 2006;118:108-13, doi: 10.1542/peds.2005-2522.
43. May C, Prendergast M, Salman S, Rafferty GF, Greenough A. Chest radiograph thoracic areas and lung volumes in infants developing bronchopulmonary dysplasia. Pediatr Pulmonol. 2009;44:80-5, doi: 10.1002/ppul.20952.
44. Blayney M, Keren E, Whyte H. Bronchopulmonary dysplasia: improvement in lung function between 7 and 10 years of age. J Pediatr 1991;118:201-6, doi: 10.1016/S0022-3476(05)80483-4.
45. Baraldi E, Filippone M. Chronic Lung Disease after Premature Birth. N Engl J Med. 2007;357:1946-55, doi: 10.1056/NEJMra067279.