Prevalence and factors associated with thoracic alterations in infants born prematurely

Josy Davidson[1], Kessey Maria B. Garcia[2], Liu C. Yi[3], Ana Lucia Goulart[4], Amelia Miyashiro N. dos Santos[5]

[1] PhD, Physiotherapist, Department of Pediatrics, Neonatal Division of Medicine, Universidade Federal de São Paulo (UNIFESP), SP, São Paulo, SP, Brazil
[2] MSc, Physiotherapist, Department of Pediatrics, Neonatal Division of Medicine, UNIFESP, São Paulo, SP, Brazil
[3] PhD, Physiotherapist, Professor of Musculoskeletal Physiotherapy Section, UNIFESP, São Paulo, SP, Brazil
[4] Adjunct Professor, Department of Pediatrics, Neonatal Division of Medicine, UNIFESP, São Paulo, SP, Brazil
[5] Associate Professor, Department of Pediatrics, Neonatal Division of Medicine, UNIFESP, São Paulo, SP, Brazil

Summary

Objective: To determine the prevalence of thoracic musculoskeletal alterations and associated factors in infants born prematurely. **Methods:** This was a cross sectional study with infants in the first year of age, born prematurely with birth weight < 2,000 g, who were followed up at the Premature Clinic from February, 2007 to December, 2008. Exclusion criteria were: major congenital malformations as defined by the Centers for Disease Control and Prevention (CDC), grade III/IV intraventricular hemorrhage, or periventricular leucomalacia. Physical examinations performed independently by two physiotherapists were used to assess shoulder elevation and thoracic retractions. Comparisons between groups were performed using the chi-squared test or Fisher's exact test for categorical variables, and Mann-Whitney's test or Student's t-test were used for continuous variables. Inter-observer reliability between the two physiotherapists was assessed by the kappa coefficient. Variables associated with these thoracic musculoskeletal alterations were studied by univariate and multiple logistic analyses. Statistical differences were considered significant when $p < 0.05$. This study was approved by the ethical committee of the institution, and parents/guardians signed an informed consent. **Results:** 121 infants with a gestational age of 31.1 ± 2.8 weeks and birth weight of 1,400 ± 338 g were included. Thoracic alterations were detected by Physiotherapist 1 in 81 (66.9%) infants, and in 83 (68.6%) by Physiotherapist 2 (kappa coefficient = 0.77). By multivariate logistic regression analysis, factors associated with thoracic musculoskeletal alterations were: respiratory distress syndrome (odds ratio [OR] = 3.246, 95% confidence interval [CI]: 1.237-8.732), bronchopulmonary dysplasia (OR = 11.138, 95% CI: 1.339-92.621), and low length/age ratio (OR = 4.571, 95% CI: 1.371-15.242). **Conclusion:** The prevalence of thoracic alterations was high in infants born prematurely, and was associated with pulmonary disease and low length/age ratio.

Keywords: Child; physiotherapy; infant; premature; posture; chest.

Resumo

Prevalência e fatores associados às alterações torácicas em lactentes nascidos prematuros

Objetivo: Determinar a prevalência e os fatores associados às alterações torácicas musculoesqueléticas em lactentes nascidos prematuros. **Métodos:** Estudo transversal com lactentes no primeiro ano de vida, nascidos prematuros com peso < 2000 g e acompanhados em um ambulatório de seguimento de prematuros, de fevereiro/2007 a dezembro/2008. Foram excluídas crianças com malformações maiores definidas pelo CDC ou com hemorragia peri-intraventricular grau III/IV ou leucomalácia periventricular. Duas fisioterapeutas realizaram o exame físico, avaliando, de modo independente, a elevação de ombros e as retrações da caixa torácica. O estudo foi aprovado pelo Comitê de Ética em Pesquisa da Instituição, sendo solicitada assinatura do Termo de Consentimento pelos pais. As variáveis numéricas foram comparadas pelo teste t ou Mann-Whitney. O grau de concordância entre as avaliações das fisioterapeutas foi obtido pelo coeficiente kappa e as variáveis associadas às alterações torácicas foram estudadas por regressão logística univariada e múltipla. Considerou-se significante p < 0,05. **Resultados:** Foram estudados 121 lactentes com idade gestacional de 31,1 ± 2,8 semanas e peso ao nascer de 1400 ± 338 g. A fisioterapeuta 1 detectou alterações torácicas em 81 (66,9%) lactentes e a fisioterapeuta 2 em 83 (68,6%) (coeficiente kappa = 0,77). Os fatores associados às alterações musculoesqueléticas foram: síndrome do desconforto respiratório no período neonatal (OR=3,246; IC 95%: 1,237-8,732), ter apresentado displasia broncopulmonar (OR=11,138; IC 95%: 1,339-92,621) e relação comprimento para a idade alterada (OR=4,571; IC 95%: 1,371-15,242). **Conclusão:** A prevalência de alterações torácicas foi alta em lactentes nascidos prematuros e associou-se a doença pulmonar no período neonatal e baixa relação comprimento/idade.

Unitermos: Criança; fisioterapia; prematuro; postura; caixa torácica.

Introduction

Immaturity of the lungs, rib cage, and central nervous system frequently require prolonged mechanical ventilation and oxygen therapy in preterm infants. These therapies may be associated with lung injuries such as bronchopulmonary dysplasia, increasing morbidity and prolonging hospitalization[1,2].

Recent studies have demonstrated that airway trapping in infants with bronchopulmonary dysplasia persists until adulthood[3]. This could increase the effort required to breathe, thus causing biomechanical alterations during childhood and adulthood, suggesting that preterm infants should be routinely examined until adulthood.

To the authors' knowledge, there are no studies on the prevalence of thoracic musculoskeletal abnormalities stemming from premature birth and associated factors in preterm infants after discharge from neonatal intensive care units (NICUs).

Thus, the purpose of this study was to assess the frequency and the factors associated with such abnormalities during the first year of life in infants born prematurely.

Methods

This is a cross-sectional study with infants aged 1 to 12 months, born before 37 weeks of gestation, and with a birth weight < 2,000g who were regularly examined at the Premature Clinic between February, 2007 and December, 2008. The study was approved by the ethics committee of the institution, and the parents signed an informed consent.

Preterm infants included in the study received routine care from a team of physiotherapists who performed daily bronchial hygiene, positioning, and stretching during their NICU stay. After discharge from the NICU, and before inclusion in the study, the parents received routine general recommendations regarding stimulation of their children's motor development.

Exclusion criteria for this study were major congenital malformations identified according to the Center for Diseases Control and Prevention (2012)[4] guideline, grade III/IV intraventricular hemorrhage or periventricular leukomalacia diagnosed by cranial ultrasound and/or magnetic resonance[5,6], or presence of acute respiratory tract infections in the previous two weeks.

Infants in the study underwent physical examination followed by a review of their medical charts for birth conditions and clinical evolution. Since physical examination is a subjective tool for detecting thoracic abnormalities, it was independently performed by two physiotherapists, in order to improve reliability (Physiotherapist 1 had ten years of experience in evaluating premature infants, Physiotherapist 2 had four years of experience). All infants were placed in the supine position, without clothes. Based on

the established frequencies of clinical alterations observed in adults and children with chronic pulmonary disease, two abnormalities were specifically evaluated:

– Fixed elevation of the shoulders (positioning of the rib cage in the inhalation phase when the child was in the exhalation phase), or muscle tension in the neck and shoulders at rest.
– Retraction in the rib cage (anterolateral region of the thorax between the inframamillary region and lower anterior ribs) was recorded when there was a local depression during inhalation and exhalation.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows (v. 17.0 – Chicago, IL, USA). Comparisons between groups were performed with the chi-squared test or Fisher's exact test for categorical variables, and Student's *t*-test for continuous variables. Inter-observer reliability between the two physiotherapists was assessed by the kappa coefficient. Univariate analysis identified independent clinical factors associated with the presence of thoracic alterations (dependent variable). Significant clinical and statistical variables identified in the univariate analysis were further included in a multivariate logistic regression model (backward stepwise). Differences were considered significant when p-values were < 0.05.

Results

During the study period, 162 infants aged 1 to 12 months were examined at the Premature Clinic. Of these, 27 (16.7%) were excluded: 17 with major malformations, five with grade III/IV intraventricular hemorrhage and/or periventricular leukomalacia, and five due to parental refusal. Of the 135 infants who met the eligibility criteria, 14 (10.4%) missed evaluation appointments. 121 (89.6%) infants were included, with a mean gestational age at birth of 31.1 ± 2.8 weeks (25.0-36.9 weeks), birth weight of 1,400 ± 338 g (715-1,990g), median first minute Apgar score of 8 (range: 2-9), and median fifth minute Apgar score of 9 (range: 6-10). Fifty-seven (47.1%) of the selected infants were males. On enrollment, the infants had a mean age of 5.3 ± 2.4 months (median of 5.3, range: 0.6 days to 11.7 months). The post-conceptual age at study entry was of 3.3 ± 2.4 months (median of 3, range: -0.7 to 10.3 months).

On physical examination, Physiotherapist 1 identified 81 (66.9%) infants with musculoskeletal alterations: 22 (18.2%) with elevated shoulders, 32 (26.4%) with thoracic retraction, and 27 (22.3%) with both abnormalities. Physiotherapist 2 identified 83 (68.6%) infants with musculoskeletal abnormalities: 16 (13.2%) with elevated shoulders, 43 (35.5%) with thoracic retraction, and 24 (19.8%) with

both abnormalities. There was agreement between the two observers in 109 cases (90.1%) with elevated shoulders and/or thoracic retraction, in 106 cases (87.6%) with elevated shoulders, and in 109 cases (90.1%) with thoracic retraction. This corresponds to kappa coefficients of 0.77 (standard error = 0.06), 0.74 (standard error = 0.06), and 0.80 (standard error = 0.05), respectively.

Analysis of the prevalence of thoracic alterations and associated factors was performed on the physical examination results reported by Physiotherapist 1, because of her greater professional experience.

Demographic and clinical characteristics of the studied infants are shown in Table 1. Regardless of the presence of thoracic alterations, infants in the study exhibited similar nutritional status (weight/age ratio, length/age ratio, weight/length ratio, and body mass index, according to the World Health Organization [WHO] Child Growth Standards)[7], frequency of bronchiolitis and/or pneumonia (18.5% *versus* 10.3%, p = 0.30), sibilance (18.5% *versus* 12.8%, p = 0.43), and need for hospitalization after discharge from the neonatal unit (14.8% *versus* 7.5%, p = 0.38). Likelihood ratios of the independent variables for the occurrence of thoracic alterations studied by univariate analysis are shown in Table 2.

The following statistically significant variables derived from the univariate analysis were included in the multivariate model: gestational age, presence of respiratory distress syndrome, patent ductus arteriosus (with clinical signs and symptoms and/or echocardiography alterations), bronchopulmonary dysplasia (stated as a need for supplemental oxygen therapy after 28 days of life), clinical sepsis, number of days on mechanical ventilation, length of NICU stay, and low length/age ratio. After adjustment for variables included in the model, the multivariate logistic regression analysis demonstrated that the chance of presenting thoracic alterations was higher in infants who developed respiratory distress syndrome and/or bronchopulmonary dysplasia during their NICU stay and in infants with a low length/age ratio in the first year of life (Table 3).

DISCUSSION

To the authors' knowledge, this is the first study assessing thoracic musculoskeletal abnormalities in infants born prematurely. Although there are no data for comparison, the prevalence of thoracic abnormalities found in this study appears to be high, especially considering that the infants included in this study received routine physiotherapy in the neonatal unit for the prevention or rehabilitation of cardiopulmonary impairment.

In premature infants, some factors could explain the high prevalence of musculoskeletal alterations found in this study. The immaturity of the lungs and rib cage favors an increase in the effort required to breathe, in case of acute respiratory illness. Under these conditions, accessory respiratory muscles, such as the trapezius and sternocleidomastoid, are recruited, thus increasing thoracoabdominal asynchronism. Successive increases in respiratory work during the neonatal period can alter respiratory muscles and, in the long-term, rib cage configuration.

Table 1 – Demographic and clinical characteristics of the studied infants, according to the presence of thoracic musculoskeletal abnormalities, expressed by mean ± SD, median (variation) or number (%)

Variables	With clinical abnormalities (n = 81)	Without clinical abnormalities (n = 40)	p-value
Gestational age (weeks)	30.7 ± 2.9	32.2 ± 2.9	0.001
Birth weight (g)	1335 ± 358	1533 ± 252	0.001
1st minute Apgar score	8 (2-9)	8 (3-9)	0.059
5th minute Apgar score	9 (4-10)	9 (7-10)	0.027
Small for gestational age n (%)	28 (34.6%)	13 (32.5%)	0.821
Respiratory distress syndrome n (%)	48 (59.3%)	8 (20.0%)	< 0.001
Patent ductus arteriosus n (%)	23 (28.3%)	2 (5.0%)	0.002
Clinical sepsis [n (%)]	30 (37.0%)	8 (20.0%)	0.064
Intraventricular hemorrhage (I/II) [n (%)]	44 (54.3%)	14 (35.0%)	0.045
Bronchopulmonary dysplasia [n (%)]	29 (35.8%)	4 (10.0%)	0.003
Days on mechanical ventilation	7 ± 13	1 ± 2	< 0.001
Days on oxygen therapy	25 ± 29	6 ± 9	< 0.001
Days of NICU stay	55 ± 39	30 ± 16	< 0.001

p-value, comparison between infants with and without thoracic musculoskeletal abnormalities by Student's *t*-test or Mann-Whitney's test for continuous variables and chi-squared or Fisher's exact test for categorical variables; NICU, neonatal intensive care unit; SD, standard deviation.

Table 2 – Univariate logistic regression analysis with demographic and clinical variables associated with thoracic alterations expressed by OR; 95% CI

Variables	OR	95% CI	p-value
Gestational age (one-week decrease)	1.259	1.075-1.479	0.005
Gestational age < 30 weeks	3.771	1.494-9.519	0.005
Birth weight (one-gram decrease)	1.002	1.001-1.003	0.003
1st minute Apgar score < 7	2.145	0.737-6.246	0.162
Small for gestational age	1.097	0.491-2.453	0.821
Respiratory distress syndrome	5.818	2.383-14.204	< 0.001
Patent ductus arteriosus	7.534	1.678-33.824	0.008
Clinical sepsis	2.353	0.960-5.767	0.061
Bronchopulmonary dysplasia	10.596	2.238-47.143	0.002
Mechanical ventilation	5.335	2.115-13.453	< 0.001
Days on mechanical ventilation	1.273	1.065-1.521	0.008
Days of NICU stay	5.057	2.226-11.489	< 0.001
Sibilance[a]	1.545	0.518-4.612	0.432
Bronchiolitis and/or pneumonia[a]	1.989	0.613-6.450	0.252
Low weight/age ratio[b]	1.832	0.740-4.535	0.191
Low length/age ratio[b]	4.375	1.409-13.583	0.011
Low weight/length ratio[b]	3.040	0.353-26.168	0.311
Low body mass index[b]	1.094	0.315-3.799	0.888

[a]Presence of at least one episode after discharge from NICU; [b]variables measured at the inclusion in the study; NICU, neonatal intensive care unit; OR, odds ratio; CI, confidence interval.

Table 3 – Final model of multivariate logistic regression analysis: factors associated with thoracic musculoskeletal abnormalities in infants born premature

Variables	OR	95% CI	p-value
Respiratory distress syndrome	3.246	1.237-8.732	0.020
Bronchopulmonary dysplasia	11.138	1.339-92.621	0.026
Low length/age ratio	4.571	1.371-15.242	0.013

p = 0.004, Hosmer and Lemershow test: 0.609; OR, odds ratio; CI, confidence interval.

Studies evaluating chest radiographs of children with bronchopulmonary dysplasia showed that these patients have significantly flatter chests than children without any respiratory diseases[2].

Studies of adolescents with asthma also indicate that the increased respiratory work that is caused by airway obstruction could permanently alter the rib cage configuration[8]. In patients with chronic obstructive pulmonary disease, the hyperinflation caused by parenchymal destruction could increase the rib cage diameter. The resulting altered diaphragm position, and reduced muscle contraction and tidal volume, cause the recruitment of accessory muscles of the neck and upper rib cage in order to to maintain ventilatory demand, thereby causing typical postural abnormalities in the long-term[9,10].

The thoracic alterations observed in this study could be explained by physiological and anatomical factors. The development of shoulder elevation reflects the use of neck and upper thorax muscles, such as the trapezius, sternocleidomastoid, and pectoral muscles, as imposed by increased respiratory effort. Thoracic retraction occurs due to thoracoabdominal asynchronism, causing depression of the rib and sternum[11].

According to the univariate analysis, every one-week decrease in gestational age increased the probability of having such abnormalities by 1.3-fold, and every 10g decrease in birth weight increased such a chance by 10-fold. This suggests that lower gestational age and lower birth weight represent a greater probability of morbidity and need for life support, particularly, mechanical

ventilation and oxygen therapy. Further, the univariate analysis demonstrated that all variables related to respiratory illness and the need for life support increased the probability of thoracic abnormalities in the first year of life (Table 2). Respiratory distress syndrome, patent ductus arteriosus, and bronchopulmonary dysplasia are inter-related and significantly contribute to the occurrence of thoracic musculoskeletal alterations. The presence of patent ductus arteriosus is known to contribute to the development of bronchopulmonary dysplasia[12], whose clinical consequences may persist into adolescence[13]. Similarly, the length of stay in the NICU represents the extent of clinical evolution during the neonatal period, and thus showed an association with thoracic abnormalities. The final model of the multivariate logistic regression analysis indicated that the presence of respiratory distress syndrome, bronchopulmonary dysplasia, and impaired growth as measured by length/age ratio were associated with thoracic abnormalities. This reinforces the hypothesis that thoracic alterations detected in the first year of life could be related to neonatal lung diseases.

Bronchopulmonary dysplasia may be followed by obstructive impaired lung function in the first years of life[11,13], and may cause biomechanical alterations and recruitment of all respiratory muscles, including the accessory muscles, over a long period, leading to thoracic alterations. Data shown in the present study corroborates this hypothesis.

The association between thoracic alterations and low length/age ratio found in the univariate and multivariate regression analysis appears to be a consequence of the high caloric consumption caused by increased respiratory effort, rather than a true cause of thoracic abnormality. Factors such as intensive care intervention, poor nutrition, increased respiratory effort, and infections during the neonatal period appear to contribute to impaired growth. Children with bronchopulmonary dysplasia showed smaller weight and length increments than children born prematurely who did not have any respiratory diseases during the first year of life[14,15]. This minimal gain in weight and height may persist until adulthood[16].

It would be expected that the occurrence of bronchiolitis and pneumonia after discharge from the neonatal unit would increase the chance of thoracic alterations[17,18]. However, the number of infants with bronchiolitis or pneumonia in this study did not provide the necessary statistical power to demonstrate this association.

A limitation of this study was that the prevalence of observed musculoskeletal alterations might have been affected by the fact that approximately 10% of the eligible infants were not included. A physical examination is a qualitative and subjective tool, and is dependent on the examiner's experience[19]; this could also be mentioned as a limitation of this study. However, in the present study,

physical examinations were performed by skilled professionals and showed good inter-rater reliability, thereby justifying its use as a reference standard for the assessment of musculoskeletal alterations. Moreover, in a recent study describing a new objective tool for the detection of thoracic abnormalities based on photogrammetry, the researchers found a good correlation between shoulder elevation detected by physical examination and the measurement of the manubrium/acromion/trapezius angle (intraclass correlation coefficient > 0.9), and between thoracic retraction and measurement of the deep thoracic retraction (intraclass correlation coefficient > 0.8)[20].

As the presence of thoracic alterations was found to be associated with neonatal pulmonary diseases, a new study assessing pulmonary function in infants born prematurely is already underway in this institution to investigate whether these alterations are truly related to impaired pulmonary function, as has been previously described[21,22].

CONCLUSIONS

The prevalence of thoracic alterations was high in infants born prematurely, and may also have compromised the growth rate of these infants during the first year of life. If evidence of thoracic musculoskeletal alterations in infants born prematurely is confirmed by new studies, it will have implications for follow-up protocols after NICU discharge.

REFERENCES

1. Gappa M, Pillow JJ, Allen J, Mayer O, Stocks J. Lung function tests in neonates and infants with chronic lung disease: lung and chest-wall mechanics. Pediatr Pulmonol. 2006;41:291-317.
2. de Boeck K, Smith J, Van Lierde S, Van Gijsel D, Devlieger H. Flat chest in survivors of bronchopulmonary dysplasia. Pediatr Pulmonol. 1994;18:104-7.
3. Narang I, Rosenthal M, Cremonesini D, Silverman M, Bush A. Longitudinal evaluation of airway function 21 years after preterm birth. Am J Respir Crit Care Med. 2008;178:74-80.
4. CDC. Center for Diseases Control and Prevention Classification of Diseases, Functioning, and Disability. International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). [cited 2012 may 23]. Available from: http://www.cdc.gov/nchs/icd/icd10cm.htm#10update.
5. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500g. J Pediatr. 1978;92:529-34.
6. Deng W, Pleasure J, Pleasure D. Progress in periventricular leukomalacia. Arch Neurol. 2008;65:1291-5.
7. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Llength/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Geneva: World Health Organization; 2006. [cited 2012 may 23]. Available from: http://www.who.int/childgrowth/standards/Technical_report.pdf.
8. Lopes EA, Fanelli-Galvani A, Prisco CC, Gonçalves RC, Jacob CM, Cabral AL, et al. Assessment of muscle shortening and static posture in children with persistent asthma. Eur J Pediatr. 2007;166:715-21.
9. Zanchet RC, Chagas AM, Melo JS, Watanabe PY, Simões-Barbosa A, Feijo G. Influence of the technique of re-educating thoracic and abdominal muscles on respiratory muscle strength in patients with cystic fibrosis. J Bras Pneumol. 2006;32:123-9.
10. McKenzie DK, Butler JE, Gandevia SC. Respiratory muscle function and activation in chronic obstructive pulmonary disease (COPD). J Appl Physiol. 2009;107:621-9.
11. Warren RH, Horan SM, Robertson PK. Chest wall motion in preterm infants using respiratory inductive plethysmography. Eur Respir J. 1997;10:2295-300.
12. Madan JC, Kendrick D, Hagadorn JI, Frantz ID 3rd; National Institute of Child Health and Human Development Neonatal Research Network. Patent ductus arteriosus therapy: impact on neonatal and 18-month outcome. Pediatrics. 2009;123:674-81.

13. Hennessy EM, Bracewell MA, Wood N, et al. EPICure Study Group. Respiratory health in pre-school and school age children following extremely preterm birth. Arch Dis Child. 2008;93:1037-43.

14. Huysman WA, de Ridder M, de Bruin NC, van Helmond G, Terpstra N, Van Goudoever JB, et al. Growth and body composition in preterm infants with bronchopulmonary dysplasia. Arch Dis Child Fetal Neonatal Ed. 2003;88:F46-F51.

15. Westerberg AC, Henriksen C, Ellingvåg A, Veierød MB, Júlíusson PB, Nakstad B, et al. First year growth among very low birth weight infants. Acta Paediatr. 2010;99:556-62.

16. Hack M, Schluchter M, Cartar L, Rahman M, Cuttler L, Borawski E. Growth of very low birth weight infants to age 20 years. Pediatrics. 2003;112:e30-8.

17. Broughton S, Roberts A, Fox G, Pollina E, Zuckerman M, Chaudhry S, et al. Prospective study of health care utilization and respiratory morbidity due to RSV infection in prematurely born infants. Thorax. 2005;60:1039-44.

18. Greenough A. Long-term pulmonary outcome in the preterm infant. Neonatology. 2008;93:324-7.

19. Ferreira EA, Duarte M, Maldonado EP, Burke TN, Marques AP. Postural assessment software (PAS/SAPO): validation and reliability. Clinics. 2010;65:675-81.

20. Davidson J, dos Santos AM, Garcia KM, Yi LC, João PC, Miyoshi MM, et al. Photogrammetry: an accurate and reliable tool to detect thoracic musculoskeletal abnormalities in preterm infants. Physiotherapy. 2012;98:243-9.

21. Aukland SM, Rosendahl K, Owens CM, Fosse KR, Eide GE, Halvorsen T. Neonatal bronchopulmonary dysplasia predicts abnormal pulmonary HRCT scans in long-term survivors of extreme preterm birth. Thorax. 2009;64:405-10.

22. Brostrom EB, Thunqvist Per, Adenfelt G, Borling E, Katz-Salamon M. Obstructive lung disease in children with mild to severe BPD. Respir Med. 2010;104:362-70.