Differences between Obliterative Bronchiolitis and Problematic Severe Asthma in a pediatric population

Teresa Bandeira, Filipa Negreiro, Marisa Salgueiro, Luísa Lobo, Pedro Aguiar, Jc Trindade

► To cite this version:

Teresa Bandeira, Filipa Negreiro, Marisa Salgueiro, Luísa Lobo, Pedro Aguiar, et al.. Differences between Obliterative Bronchiolitis and Problematic Severe Asthma in a pediatric population. *Pediatric Pulmonology*, 2011, 46 (6), pp.573. 10.1002/ppul.21405 . hal-00613788

HAL Id: hal-00613788

<https://hal.science/hal-00613788>

Submitted on 6 Aug 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Differences between Obliterative Bronchiolitis and Problematic Severe Asthma in a pediatric population

Journal:	<i>Pediatric Pulmonology</i>
Manuscript ID:	PPUL-10-0326.R1
Wiley - Manuscript type:	Original Article
Date Submitted by the Author:	06-Nov-2010
Complete List of Authors:	Bandeira, Teresa; University Hospital Santa Maria, Pediatric Department Negreiro, Filipa; Eurotrials, Biostatistics Department Salgueiro, Marisa; University Hospital Santa Maria, Pediatric Lung Function Laboratory Lobo, Luísa; University Hospital Santa Maria, Imaging Department Aguar, Pedro; Eurotrials, Biostatistics Department Trindade, JC; University Hospital Santa Maria, Pediatric Department
Keywords:	obliterative bronchiolitis, problematic asthma, children, overlap syndrome

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Title: Clinical, radiological and physiological differences between Obliterative Bronchiolitis and Problematic Severe Asthma in adolescents and young adults. The early origins of the overlap syndrome?

Short title: Discrimination between Obliterative Bronchiolitis and Problematic Severe Asthma in a pediatric population.

Authors: Teresa Bandeira¹, Filipa Negreiro², Marisa Salgueiro³, Luísa Lobo⁴, Pedro Aguiar⁵, J C Trindade⁶

Institutes and affiliations

- ¹ Pediatrician. Pediatric Department, Medical School at University of Lisbon, Hospital Santa Maria, Lisbon, Portugal
- ² Statistician. Biostatistics Department: Eurotrials, Portugal
- ³ Cardio-respiratory Technician. Pediatric Department, Medical School at University of Lisbon, Hospital Santa Maria, Lisbon, Portugal
- ⁴ Imaging Department, Medical School at University of Lisbon; Hospital Santa Maria, Lisbon, Portugal
- ⁵ Epidemiologist. Biostatistics Department: Eurotrials, Portugal
- ⁶ Professor of Pediatrics. Pediatric Department, Medical School at University of Lisbon, Hospital Santa Maria, Lisbon, Portugal

Corresponding author: Dr Teresa Bandeira

Respiratory Medicine Unit, Pediatric Department

Hospital Santa Maria (HSM). University of Lisbon

Av. Professor Egas Moniz - 1649-035

Lisbon, Portugal

Tel: + 35 964308314

Fax: + 35 217 805 623

email: teresa.bandeira@hsm.min-saude.pt

Short Title: 105 characters

Abstract: 245 words

Text Body: 3305 words

References: 43

Tables and Figures: 4

1 Online supplement

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abstract

PURPOSE: Few reports have compared chronic obstructive lung diseases (OLD) starting in childhood. AIMS: To describe functional, radiological and biological features of obliterative bronchiolitis (OB) and further discriminate to problematic severe asthma (PSA) or to diagnose a group with overlapping features. METHODS: data from 25 OB patients [median (range) age: 16.3(8.6-34.7)years] from a single center were compared with 15 PSA patients [median (range) age 14.2(8.3-24.9) years]. Lung function tests (LFT) included spirometry, determination of lung volumes and bronchodilation. High resolution CT (HRCT) images were scored for the presence and the extent of 21 findings. Blood samples for atopic and inflammatory parameters besides skin prick tests were performed. We used ROC curve to analyze the discriminative power of the variables and cluster analysis to look for a "3rd diagnostic group". RESULTS: Patients with OB showed a greater degree of obstructive lung defect and higher hyperinflation (p<0.001). The most frequent HRCT features (increased lung volume, inspiratory decreased attenuation, mosaic pattern and expiratory air trapping) showed significantly greater scores in OB patients. Patients with PSA have shown a higher frequency of atopy (p<0.05). ROC curve analysis demonstrated discriminative power for the LF variables, HRCT findings and for atopy between diagnoses. Further analysis released 5 final variables more accurate for the identification of a third diagnostic group (FVC%t, post-bronchodilator ΔFEV₁ in ml, HRCT mosaic pattern, SPT and *D.Pteronyssinus* specific IgE). CONCLUSIONS: We found that OB and PSA possess identifiable characteristic features but overlapping values may turn them undistinguishable.

Keywords: obliterative bronchiolitis, problematic asthma, children, computed tomography, lung function, atopy, overlap syndrome

For Peer Review

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Introduction

The far most common form of bronchiolitis obliterans in children follows a severe lower respiratory-tract infection[1,2]. Other causes include collagen vascular disease, toxic fume inhalation, aspiration syndromes, and Stevens-Johnson syndrome[3]. The patient typically has wheezing, tachypnea, dyspnea, and persistent cough for weeks or months after the initial infection. The disease may persist for years after its onset and may worsen due to exacerbations caused by viral infections. There are no epidemiological data available, but, for unclear reasons, OB seems to occur more frequently in the southern hemisphere (southern Brazil, Uruguay, Argentina, Chile, New Zealand, and Australia) generating a demand for hospital and clinic services similar to that observed in patients with cystic fibrosis[2,2,3] in other parts of the world.

OB is synonymous with the term “constrictive bronchiolitis” [4]. It has been shown that there are distinctive features of lung function (LF) and high-resolution CT (HRCT) that both characterizes the diagnosis and estimates the severity of attainment. LF results are usually characterized by fixed obstruction, minimum response to the administration of corticoids and normal total lung capacity [2].. HRCT most characteristic findings are segmental or lobular areas of hypoattenuation that are associated with narrowing of the caliber of the pulmonary vessels (mosaic perfusion). These abnormalities are

1
2
3 consistent with air trapping, and can be clearly demonstrated on CT
4 scans of the chest performed during expiration or on inspiratory or
5 lateral decubitus HRCT in the uncooperative pediatric patients [5-7].
6
7 Bronchiectasis are also recognized and associated with OB, and tend
8 to be peripheral and cylindrical in nature [4]. Most features presented
9 by OB patients parallel those of COPD [8].
10
11

12
13
14 In the last decade there is growing evidence for the overlap features
15 between obstructive lung diseases (OLD) in the adult patients [9]
16 drawing a *continuum* from the variable airflow obstruction (asthma)
17 to the incompletely reversible airflow limitation (COPD) with the
18 concomitant diagnosis of asthma, chronic bronchitis, or emphysema
19 being so common among OLD patients from the general population as
20 to account for as much as half of the OLD population who are aged
21 over 50 years [10].
22
23

24
25 In childhood the recognition of severe asthma is not an easy task
26 [11]. In 2000 the ATS Proceedings classified refractory asthma
27 mainly based on dose of corticosteroids prescribed [12]. Recently
28 Bush et al proposes the diagnosis of problematic severe asthma
29 (PSA) for the poor control asthma patients that will afterwards be
30 divided by the subspecialist in two subgroups either as difficult into
31 difficult-to-treat asthma or as severe therapy-resistant asthma
32 [13,14].
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

The purpose of our investigation was to describe the characteristic features and patterns distinctive for the diagnosis of OB and PSA through the analysis of the results of objective assessments consisting of conventional lung function tests, high resolution computed tomography (HRCT) and tests for atopy and inflammation. Our secondary goal was to determine the discriminative power of these variables for the diagnosis of OB or PSA or for the identification of an overlap syndrome. Studying overlap syndrome may shed light on the mechanisms of obstructive lung diseases development.

METHODS

Study design

A cross sectional observational study comparing two groups of patients with the diagnosis of OB and PSA was performed. The study was approved by the local research ethics committees and written informed parental or own consent was obtained prior to testing.

Subjects

OB patients were retrospectively identified in the computerized database of outpatients attending the pediatric respiratory clinic since 1975 at H. Santa Maria (HSM), using the following key diagnoses: OB, bronchiectasis, and post-adenoviral infection. The identified cases were checked to ascertain whether they met the following inclusion criteria[1-3]: initial episode of a severe respiratory infection ther relevant cause for OB in a previously healthy child followed by persistent cough, wheezing, retractions, crackles, abnormalities on chest radiograph for months or years, a high-resolution CT scan (HRCT) showing features consistent with the diagnosis: inspiratory decreased attenuation, expiratory air trapping and an attenuation mosaic pattern and lung function tests demonstrating persistent irreversible airflow limitation. Patients with the following diagnosis were excluded based on history or tests: cystic fibrosis, bronchopulmonary dysplasia, pulmonary tuberculosis, α 1-antitripsin deficiency,

Comment [TB1]: Text A

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

immunodeficiency, congenital heart disease and other major polimalformative syndromes.

The PSA group was selected from the Difficult Asthma Clinic at Pediatric Department of HSM based on the occurrence of persistent chronic symptoms of airways obstruction, frequent or severe exacerbations in last year despite multiple drug treatment associated with persistent airflow obstruction and variable obstructive pattern in LF tests sometimes with swings in lung function where the diagnosis of asthma was plausible and an appropriate work-up to exclude other diagnosis was done [14]. No attempt for discriminating between subgroups of PSA was done.

Routine OB management at our centre included 3-6 monthly reviews, and the prescription of inhaled steroids and long-acting beta-2-agonists and ipratropium or tiotropium. When bronchiectasis were present, chest physiotherapy was prescribed with advice to increase intensity when unwell, and antibiotics prescribed for exacerbations. General health measures such as optimizing domestic/social settings and financial support, immunizations, and exercise were strongly promoted. Two patients were submitted to lung resection, one with extensive unilateral MacLeod syndrome and medically uncontrollable bronchiectasis and another after collapse of a small bronchiectatic lung. Only one patient is on chronic home oxygenotherapy. PSA patients are maintained on medium to high dose ranges inhaled

steroids, long-acting beta-2-agonists and leukotriene antagonists as appropriate besides rhinitis associated treatment.

Lung function assessments

Spirometry was performed using a pneumotachometer in a Jaeger Masterscreen plethysmograph (Erich Jaeger AG, Würzburg, Germany) by skilled pediatric pulmonary function technicians who regularly work with children with obstructive lung diseases. The calibration of the plethysmograph was performed daily before each test. FEV₁ and forced vital capacity (FVC) were measured. The reproducibility and criteria of measurements were those recommended by the American Thoracic Society[15]. The residual volume (RV), and total lung capacity (TLC) were determined in the body plethysmograph [16]. Using the reference equations from www.growinglungs.org.uk [17], spirometric values were expressed as percent predicted and z-scores and lung volumes in % predicted in function to Zapletal or the ECCS according to age[18]. Weight and height z-scores were calculated after adjustment for age and sex. Z-score is calculated as (measured value - an value)/Population SD. It is a better way of expressing measurements than percent predicted, which now should be obsolete. For example, depending on the variance in the population, 80% predicted may be normal or abnormal, but a Z-score of -2.5 can be seen at once always to be

Comment [TB2]: Text D

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

abnormal [19]. Post-bronchodilator (BD) FEV₁ (Δ FEV₁) was measured 15 min after the administration of 400 mcg salbutamol using a metered dose inhaler and a large volume spacer. All results were reported from baseline tests.

High-resolution computed tomography (HRTC)

The HRTC studies were acquired at our institution between 2005 and September 2009 using four-rows CT scanner. Most of the studies (34/40) were performed between May 2008 and September 2009 (online supplement).

Atopy and inflammatory markers

Atopy was defined as either at least one positive specific immunoglobulin (Ig) E or one positive skin prick test to aeroallergens (cat, dog, house dust mite, grasses and fungi)[20]. Furthermore the presence of increased number of eosinophils ($>274\text{cel.mm}^{-3}$), and /or IgE higher than 2SD adjusted for the age was analyzed between groups [20]. Inflammation pattern was considered based on a high C-reactive protein (CRP) (mg/dl), sedimentation rate (SR) mm, fibrinogen (mg/dl), leukocytes ($>13\times10^9/\text{L}$) and alpha-1-antitrypsin (AAT) [21].

Statistical analysis

Descriptive statistics[22,23], including distribution of records, age, and gender, age at initial symptoms, hospital admission, mechanical ventilation history and clinical characteristics were completed using SPSS 16.0 (SPSS Inc., Chicago, IL). Results were considered statistically significant at $p < 0.05$.

To analyze the discriminative power of the variables LFT, HRCT, atopy and inflammation for the diagnosis of OB or PSA, Receiver Operating Characteristic (ROC) curves were used. For variables whose area under the ROC curve presented a good discriminating power (≥ 0.70) and shown to be statistically significant ($p < 0.05$) cut-offs (trim points) were identified with sensitivity and specificity equal to or greater than 75% (see online supplement for further details).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

RESULTS

Demographic and clinical characteristics of patients and comparison by group of diagnosis are shown in Tables 1 and 2. In both groups there was a male predominance. Patients from OB group were younger at acute episode, and 96% have been admitted to hospital for lower tract infection, more frequently than PSA patients ($p < 0.05$). Eight (32%) OB patients have been submitted to mechanical ventilation (MC) at this initial episode but from the 3 PSA patients on MV, one occurred at the neonatal period and two others were ventilated late at the course of disease because of severe asthma attack. In 15 (60%) of the OB patients a cause was identified, 93.3% were attributable to previous infection [8 (53.3%) to adenovirus, 2 (13.3%) to measles, 3 (20%) to *Mycoplasma pneumonia* one (6.7%) varicela; in one case positive for *M.pneumoniae*, Stevens-Johnson syndrome was diagnosed and in another (6.7%) near-drowning in soapy water had occurred]Afterwards the majority of patients in both groups had persistent symptoms but fine crackles were heard more frequently in OB (60%) than in PSA patients (6.7%) ($p < 0.001$).. In both groups a high prevalence of exposure to tobacco smoke was found ($p = 0.542$).

Lung function

There was no statistical difference between the two groups in age and height at lung function test (LFT) but patients with OB showed a reduced z-score for weight and BMI compared with PSA patients ($p < 0.05$) (table 2 of the online supplement). Patients with OB showed a significant decrease in FEV₁, FVC and FEV₁/FVC ratio. LFT of OB

Comment [TB3]: Text B

patients showed a range of values from 18.2 to 70.6%P for FEV₁ (z-scores -7.3 to -2.7), from 32.8 to 91% for FVC (z-scores -6.4 to -0.8), and from 46.8 to 92.6 for the FEV₁/FVC ratio (z-scores -4.7 to -1.0) compared to PSA patients ($p < 0.05$; table 3). The RV/TLC ratio was significantly increased in patients with OB (range 27.83 to 71) ($p < 0.001$), indicating higher hyperinflation compared with PSA patients (Table 3). Δ FEV₁ was greater than 12% in 12 (48.0%) OB patients and 8 (53.3%) of PSA patients, but only 8 (32%) OB patients had a 200 ml improvement after beta-2-agonist inhalation. Twelve (80%) PSA patients showed an improvement after bronchodilator greater than 200ml. The change of FEV₁ correlated significantly with baseline FVC and FEV₁ ($p < 0.01$) in PSA patients but not in OB patients (data not shown).

CT findings

Among OB patients, the most frequent HRCT features were increased lung volume, inspiratory decreased attenuation and mosaic pattern in all examinations, and expiratory air trapping in all of the 24 (100%) studies that included expiratory images. Bronchial wall thickening were observed in 23 (92%) and bronchiectasis in 22 (88%). Among PSA patients, the most frequent HRCT features were increased lung volume in 13 out of 14 (92.9%) where this could be classified, inspiratory decreased attenuation in 13 (86.7%) and mosaic pattern in 11 out of 14 (78.6%). Expiratory air trapping was present in 11/14

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

(78.6%) studies that included expiratory images. Bronchial wall thickening was observed in 8/14 (57.1%) and bronchiectasis in 4 (26.7%). When comparing groups of diagnosis, OB patients showed significantly higher scores for inspiratory decreased attenuation, mosaic pattern, expiratory air trapping and bronchiectasis than PSA (table 3 of the online supplement).

Atopy and inflammation

PSA patients had higher frequency of at least 1 positive allergen skin test ($p=0.002$), a greater mean number of positive skin tests per patient ($p=0.001$), significantly greater median serum IgE level ($p=0.007$), and mean peripheral blood eosinophil count ($p=0.004$) compared with patients with OB (table 4 of the online supplement). Overall 14 (93.3%) patients with PSA had at least one allergy marker positive versus 11 (44%) of the OB patients.

Inflammatory variables studied were in the normal range for both groups and there was no significant difference between the two groups (see table E0 on online supplement).

Variables with power to discriminate between groups of patients

ROC curve analysis demonstrated a good discriminative power (cut-off estimates higher than 75%) for LF variables (FVC%P, FEV₁%P, FEV₁/FVC%P, RV%TLC e Δ FEV₁ in ml) (Table 5 of the online

1
2
3
4 supplement), for HRCT findings (inspiratory decreased attenuation,
5
6 mosaic pattern, expiratory air trapping and bronchiectasis) (Table 6
7
8 of the online supplement) and for atopy (peripheral blood eosinophil
9
10 count, SPT, serum IgE level and *D.Pteronyssinus* specific IgE). No
11
12 inflammatory parameter showed enough discriminative power to be
13
14 included in further analysis. Cluster analysis for the identification of a
15
16 third group diagnosis showing overlap features determined that
17
18 FVC%P, Δ FEV₁ in ml, mosaic pattern, SPT and *D.Pteronyssinus*
19
20 specific IgE were the best variables (online supplement and Table 4).
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

DISCUSSION

To our knowledge, this is the first study to establish clinical, radiological and physiological differences between Obliterative Bronchiolitis (OB) and Problematic Severe Asthma (PSA) in the transition through pediatric to young adult ages. Our main results suggest that patients with OB start their symptoms early in life usually after a severe respiratory infection. Adenovirus is the most frequently identified etiological agent [24] although clinical studies frequently miss the identification of the causal agent as it occurred at this investigation [25,26]. In the second decade of life these patients still have persistent respiratory symptoms, poor nutrition and a significant airway obstruction and hyperinflation. Age and disease severity as shown by hospital admission and the need for ventilator support and persistent crackles distinguishes these from PSA patients. Moreover although persistent symptoms and an obstructive lung function pattern are found in PSA patients a significant less degree of compromise is evidenced. Advances in intensive therapy that have occurred over the last few years allowed many children to survive who, after being affected by serious respiratory infections, develop persistent and severe *sequelae* [2].

Furthermore the different extension of lung compromise between OB and PSA patients is also revealed through the HRCT findings.

Comment [TB4]: Text C

Technical improvements have turned HRCT in the imaging modality of choice for the morphological assessment of pulmonary parenchyma, even in children [27].

We found that LFT results of obstructive ventilatory defect were common in both OB and PSA patients. Bronchial reactivity after beta-2-agonist inhalation was also commonly seen in both conditions especially if % variation from baseline was accounted for. No significant differences were found in FEV₁/FVC ratio between OB and PSA. Severity of LF compromise expressed by the reduction of FEV₁, FEF₂₅₋₇₅ and FVC must be taken in account as they tend to be more severe in OB than in PSA otherwise being difficult to differentiate OB and PSA on the basis of the LF defect alone. FVC was reduced in OB patients and close to normal in the PSA patients and OB patients showed higher air-trapping pattern. . Furthermore FVC and Δ FEV₁ post-BD (ml) emerged as the better LF variables capable of identifying third group of diagnosis with overlapping features. We have recently demonstrated that results of bronchodilation are dependent on previous lung volumes [28] in OB patients as has been shown by others [29,30]. Casanova et al demonstrated that a 25% IC/TLC value had the best combined sensitivity, specificity, and positive and negative predictive values for mortality in COPD patients [29] and another study showed the same for the ratio RV/TLC[31]. Although we have not studied the IC because there are few reference

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

values determined in pediatrics [32] we found that FEV₁ and FVC are concomitantly decreased in OB patients determining that FEV₁/FVC ratio is only slightly decreased and so not far different the mean value found in PSA patients. It has been stated before that this pattern reflects failure of the patient to inhale or exhale completely. Another explanation, and that is our understanding, the patchy collapse of small airways early in exhalation may have a significant impact in the response to therapy[18,33]suggesting that the peripheral airway involvement is an established component of OB and PSA patients. Early on in the evolution of the disease and in less severe patients a simple test of gas distribution such as the traditional VC N₂ single breath washout test would be a valuable tool of diagnosing OB and in the future should be considered in the work-up for the diagnosis of these patients [34].

Regarding high-resolution CT, our findings were in agreement with previous studies which documented that no isolated features could accurately diagnose OB as increased lung volume, inspiratory decreased attenuation, expiratory air trapping and mosaic pattern were frequent both in OB and in PSA patients. However OB patients showed higher scores for these HRCT findings and bronchiectasis were by far more frequent in OB patients. In our study, mosaic pattern provided the best power to predict the emergence of a third group of diagnosis. The mosaic pattern of attenuation of lung tissue

on HRCT seems to be the key finding which may offer some confidence in suggesting a diagnosis of OB or overlap syndrome rather than asthma as has been shown before [35]. Colom and Teper demonstrated that a mosaic pattern on HRCT was strongly associated with the diagnosis of post-infectious OB [6]. Although there are different causes for the mosaic pattern of attenuation [36] we believe as Jensen [35] that the mosaic pattern seen in OB results from a combination of air-trapping due to small airways disease and associated oligoemia secondary to reflex vasoconstriction to the areas of underventilated lung tissue.

We found a great proportion of patients with atopic markers in both groups studied but variables from the atopic expression were more frequently is PSA than in OB patients. An interaction between atopy and induced viral wheezing is being increasingly described and a strong association between asthma and atopy comes from large epidemiologic studies [37,38].

Although the importance of atopy as a cause of asthma in individuals may have been overemphasized [39] and the available epidemiological evidence suggests that the population based proportion of asthma cases that are attributable to atopy is usually less than one half, another study on difficult asthma has shown increased proportion of atopy [40]. SPT and IgE for *D.Pteronyssinus* were identified as discriminative factors between OB and PSA. This is

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

in agreement with suggestion that quantitative measures of atopy especially cumulative titers of IgE specific for perennial inhalant allergens provide robust assessments of atopy-associated risk of current asthma and its severity [38]. Atopy has also been related to other respiratory diseases but the association between atopy and the development of obstructive lung diseases remains to be clarified [20].

The study does have a number of limitations. Patients were selected from a specialized clinic on a third care University Hospital and so the reduced number of patients over a large time span may turn difficult the generalization of findings. However both are rare diseases. This is the largest group of OB patients reported in Europe [41]. PSA constitutes a heterogeneous clinical diagnosis that only recently had their distinction clarified [14] so that the present study may add further discriminative features for severe obstructive diseases starting in pediatric ages and suggest a different pathophysiologic defect between them. We could have further studied peripheral airway measurements using different diagnostic tools [34,42]but mean values for FEF₂₅₋₇₅ and of expiratory lung attenuation described support the evidence of severe peripheral airway disease in both groups of patients although more severe in the OB group. No indirect acting stimulus to assess hyperreactivity was performed which could be more precise in discriminating between diseases [9].

1
2
3 In conclusion to our knowledge we have shown for the first time that
4
5 a large overlap exists between the spectrum of clinical, functional,
6
7 radiological and atopic features of patients with OB and those with
8
9 PSA. Practical implications in this debate are relevant because the
10
11 management for both diseases differ as that for asthma and COPD in
12
13 adult patients. However, a growing number of researchers and
14
15 clinicians consider that respiratory disease is a *continuum* from
16
17 childhood to adulthood [9], and only prospective studies can
18
19 determine the relationship between adult phenotypes of obstructive
20
21 lung disease and its pediatric origins [43].
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Reference List

1. del Pino M, Bauer G, González Pena H *et al.* Growth in post-viral chronic lung disease. *Eur J Pediatr* 2006;165:845-849.
2. Teper A, Fischer GB, Jones MH. Respiratory sequelae of viral diseases: from diagnosis to treatment. *Jornal de Pediatria* 2002;78(Suppl. 2):S187-S194.
3. Moonnumakal SP, Fan LL. Bronchiolitis obliterans in children. *Curr Opin Pediatr* 20, 272-278. 2008.
4. Chan A, Allen R. Bronchiolitis obliterans: an update. *Curr Opin Pulm Med* 10, 133-141. 2004.
5. Castro-Rodriguez JA, Daszenies C, Garcia M *et al.* Adenovirus pneumonia in infants and factors for developing bronchiolitis obliterans: A 5-year follow-up. *Pediatr Pulmonol* 2006;41:947-953.
6. Colom AJ, Teper AM. Clinical prediction rule to diagnose post-infectious bronchiolitis obliterans in children. *Pediatr Pulmonol* 2009;44:1065-1069.
7. Colom AJ, Teper AM, Vollmer WM *et al.* Risk factors for the development of bronchiolitis obliterans in children with bronchiolitis. *Thorax*2006;61:503-506.
8. Global Initiative for Chronic Obstructive Lung Disease. 2004. <http://www.goldcopd.com/> 2009;(Accessed Jan, 2010).
9. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax* 2009;64:728-735.
10. Soriano JB, Davis KJ, Coleman B *et al.* The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. *Chest* 2003;124:474-481.
11. Fleming L, Wilson N, Bush A. Difficult to Control Asthma in Children. *Curr Opin Allergy Clin Immunol* 2007;7:190-195.
12. Proceedings of the ATS Workshop on Refractory Asthma . Current Understanding, Recommendations, and Unanswered Questions. *Am J Respir Crit Care Med* 2000;162:2341-2351.
13. Bush A, Hedlin G, Carlsen KH *et al.* Severe childhood asthma: a common international approach? *Lancet*2008;372:1019-1021.

14. Hedlin G, Bush A, Lordrup Carlsen K *et al.* Problematic severe asthma in children, not one problem but many: a GA2LEN initiative. *Eur Respir J* 2010;36:196-201.
15. Miller MR, Hankinson J, Brusasco V *et al.* Standardisation of spirometry. *Eur Respir J* 2005;26:319-338.
16. Wanger J, Clausen JL, Coates A *et al.* Standardisation of the measurement of lung volumes. *Eur Respir J* 2005;26:511-522.
17. Stanojevic S, Wade A, Stocks J *et al.* Reference Ranges for Spirometry Across All Ages: A New Approach. *Am J Respir Crit Care Med* 2008;177:253-260.
18. Pellegrino R, Viegi G, Brusasco V *et al.* Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948-968.
19. Bush A. COPD: A Pediatric Disease. *Journal of Chronic Obstructive Pulmonary Disease* 2008;5:53-67.
20. Baldacci S, Omenaas E, Oryszczyn MP. Allergy markers in respiratory epidemiology. *Eur Respir J* 2001;17:773-790.
21. Cazzola M, Macnee W, Martinez FJ *et al.* Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* 2008;31:416-469.
22. Aguiar P. *Guia Prático de Estatística em Investigação Epidemiológica: SPSS*. Lisboa: Climepsi, 2007
23. Altman DG. *Practical statistics for medical research*. London: Chapman & Hall, 1991
24. Colom AJ, Teper AM. Postinfectious bronchiolitis obliterans. *Arch Argent Pediatr* 107, 160-167. 2009.
25. Hodges IG, Milner AD, Groggins RC *et al.* Causes and management of bronchiolitis with chronic obstructive features. *Arch Dis Child* 1982;57:495-499.
26. Zhang L, Irion K, Kozakewich H *et al.* Clinical course of postinfectious bronchiolitis obliterans. *Pediatr Pulmonol* 2000;29:341-350.
27. Rossi UG, Owens CM. The radiology of chronic lung disease in children. *Arch Dis Child* 2005;90:601-607.
28. Bandeira T, Almodovar T, Salgueiro M *et al.* FEV₁ response to bronchodilation in Pediatric Patients With Non-Transplant Obliterative Bronchiolitis and Asthma: Similarities to Adult Patients in the Discriminative Value For Diagnosis. *Chest Meeting Abstracts* 2009;136:38S-38c.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

29. Casanova C, Cote C, de Torres JP *et al.* Inspiratory-to-Total Lung Capacity Ratio Predicts Mortality in Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2005;171:591-597.

30. Verbanck S, Schuermans D, Vincken W. Small airways ventilation heterogeneity and hyperinflation in COPD: Response to tiotropium bromide. *Int J Chron Obstruct Pulmon Dis* 2007;2:625-634.

31. Nishimura K, Izumi T, Tsukino M *et al.* Dyspnea Is a Better Predictor of 5-Year Survival Than Airway Obstruction in Patients With COPD. *Chest* 2002;121:1434-1440.

32. Tomalak W, Radlinski J, Pogorzelski A *et al.* Reference values for forced inspiratory flows in children aged 7-15 years. *Pediatr Pulmonol* 2004;38:246-249.

33. Ferguson GT. Why Does the Lung Hyperinflate? *Proc Am Thorac Soc* 2006;3:176-179.

34. Robinson PD, Goldman MD, Gustafsson PM. Inert Gas Washout: Theoretical Background and Clinical Utility in Respiratory Disease. *Respiration* 2009;78:339-355.

35. Jensen SP, Lynch DA, Brown KK *et al.* High-resolution CT Features of Severe Asthma and Bronchiolitis Obliterans. *Clin Radiol* 2002;57:1078-1085.

36. Stern EJ, Swensen SJ, Hartman TE *et al.* CT mosaic pattern of lung attenuation: distinguishing different causes. *Am J Roentgenol* 1995;165:813-816.

37. Pinto-Mendes J. Infecção na modulação da asma. *Rev Port Pneumol* 2008;XIV:647-675.

38. Sly PD, Boner AL, Bjornsdottir US *et al.* Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 2008;372:1100-1106.

39. Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999;54:268-272.

40. Bossley CJ, Saglani S, Kavanagh C *et al.* Corticosteroid responsiveness and clinical characteristics in childhood difficult asthma. *Eur Respir J* 2009;34:1052-1059.

41. Cazzato S, Poletti V, Bernardi LL *et al.* Airway inflammation and lung function decline in childhood post-infectious bronchiolitis obliterans. *Pediatr Pulmonol* 2008;43:381-390.

42. Haruna A, Oga T, Muro S *et al.* Relationship between peripheral airway function and patient-reported outcomes in COPD: a cross-sectional study. *BMC Pulmonary Medicine* 2010;10:10.

- 1
2
3
4 43. Bush A, Menzies-Gow A. Phenotypic Differences between Pediatric and
5 Adult Asthma. *Proc Am Thorac Soc* 2009;6:712-719.
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

TABLES

Table 1 – Demographic characteristics and tobacco smoke exposure by group of diagnosis (OB, PA)

	Obliterative bronchiolitis	Problematic Asthma	p-value
	n=25	n=15	
Gender: male/ female, n (%)	15/10 (60/40)	11/4 (73.3/26.7)	0.392
Age at study *(years), median (min ; max)	16.3 (8.6 ; 34.7)	14.2 (8.3 ; 24.9)	0.250
Time of follow-up before the study (years), mean (SD) ^s	6.5 (2.6)	5.2 (1.74)	0.601
Gestational age (weeks), median (min ; max)	39 (32 ; 41)	40 (33 ; 42)	0.397
Birth weight (grams), mean (SD)	3004.1 (911.5) ^{a)}	3274.7 (588.9)	0.316
Duration of exclusive breastfeeding (weeks), mean (SD)	8.25 (7.4) ^{b)}	17.38 (18.0) ^{c)}	0.100
Age at acute injury / initial symptoms (months), median (min ; max)	13 (3 ; 81)	36 (2 ;144)	0.031

Admission to hospital, n (%)	24 (96)	8 (53.5)	0.001
Mechanical ventilation, n (%)	8 (32)	3 (20)	0.408
Hospital readmission, n (%)	15 (60)	5 (33.3)	0.108
Tobacco smoke exposure, n (%)	16 (64)	11 (73.3)	0.542

^{a)}n=23; ^{b)}n=22; ^{c)}n=13

*Age at lung function tests; § only time of follow-up with the performance of LF studies is considered

Table 2 – Clinical characteristics by group of diagnosis (OB, PSA)

	Obliterative bronchiolitis		Problematic Asthma		p-value
	n=25	%	n=15	%	
			Past history		
Eczema	3	12,0	3	20,0	0,654
AOM under 2 years-old	6 ^{b)}	25,0	9	60,0	0,029
AOM after 2 years-old	3 ^{b)}	12,5	2	13,3	>0,999
Food allergy	6	24,0	6	40,0	0,285
			Persistent symptoms		
Cough without colds or with exercise	18	72,0	10	66,7	0,722
Persistent cough	9 ^{a)}	39,1	7 ^{c)}	53,8	0,393

Dyspnea	20	80,0	13	86,7	0,691
Wheezing	22	88,0	15	100,0	0,279
Chest sounds					
Wheezes	11	44,0	7	46,7	0,870
Crackles	15	60,0	1	6,7	0,001
Reduced chest sounds	13	52,0	0	0,0	0,001

^{a)}n=23, ^{b)}n=24, ^{c)}n=13.

AOM	–	acute	otitis	media
-----	---	-------	--------	-------

Table 3 – Lung function results at test by group of diagnosis (OB, PSA)

	Obliterative bronchiolitis	Problematic Asthma	p-value
	n=25	n=15	
FVC% predicted			
Mean (SD)	64.7(16.5)	95.2 (19.8)	<0.001
Median (min; max)	63.8 (32.8 ; 91)	95.5 (46.9 ; 140)	
FVC z-score			
Mean (SD)	-3.3 (1.6)	-0.5 (1.9)	<0.001
Median (min; max)	-3.2 (-6.4 ; -0.8)	-0.4 (-5.1 ; 3.7)	
FEV₁% predicted			
Mean (SD)	44.1 (14.9)	77.3 (21.5)	<0.001
Median (min; max)	44.2 (18.2 ; 70.6)	81.6 (21.9 ; 112.4)	
FEV₁ z-score			
Mean (SD)	-4.9 (1.3)	-2.0 (1.9)	<0.001
Median (min; max)	-5.5 (-7.3 ; -2.7)	-1.6 (-6.9 ; 1.1)	
FEV₁/FVC% predicted			
Mean (SD)	67.4 (13.4)	79.6 (13.0)	0.008
Median (min; max)	66.5 (46.8 ; 92.6)	81.0 (46.4 ; 101.4)	

FEV₁/FVC z-score

Mean (SD)	-3.3 (1.0)	-2.2 (1.2)	0.009
Median (min; max)	-3.5 (-4.7 ; -1.0)	-2.1 (-4.7 ; 0.2)	

FEF₂₅₋₇₅%predicted

Mean (SD)	18.0 (13.2) ¹⁾	48.4 (21.2)	<0.001
Median (min; max)	14.1 (3.3 ; 54.6)	48.0 (5.6 ; 83.3)	

FEF₂₅₋₇₅ z-score

Mean (SD)	-5.3 (1.3) ¹⁾	-2.8 (1.5)	<0.001
Median (min; max)	-5.5 (-7.3 ; -2.3)	-2.6 (-6.4 ; -0.8)	

TLC% predicted

Mean (SD)	108.0 (21.1)	111.9 (10.6)	0.506
Median (min; max)	106.5 (68.7 ; 152.6)	109.7 (98.5 ; 138.3)	

RV%TLC

Mean (SD)	48.6 (11.6)	32.0 (8.1)	<0.001
Median (min; max)	46.4 (33.0 ; 68.6)	34.1 (18.4 ; 49.9)	

sRtot

Mean (SD)	2.7 (1.9)	1.3 (0.7)	0.002
Median (min; max)	2.0 (0.8 ; 8.9)	0.9 (0.6 ; 3.0)	

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

ΔFEV₁(%)			
Mean (SD)	13.6 (9.6)	15.4 (12.0)	0.613
Median (min; max)	10.9 (0.1 ; 36.7)	12.6 (0.3 ; 47.7)	
ΔFEV₁ (ml)			
Mean (SD)	150.4 (106.7)	334.0 (206.5)	0.005
Median (min; max)	150.0 (-20.0 ; 430)	260.0 (-50.0 ; 730.0)	

¹⁾n=24

FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 second FEV₁/FVC: forced vital capacity to forced expiratory volume in 1 second ratio; FEF₂₅₋₇₅: forced expiratory flow at 25% to 75% vital capacity; RV: residual volume; TLC total lung capacity; sRtot: specic airway resistance; ΔFEV₁ difference between the pre and post bronchodilator FEV₁

Table 4 – Final cluster analysis presenting the 5 variables that proved the best adequability for group of diagnosis

		FVC %P	ΔFEV₁%t post-BD (ml)	SPT	<i>D. pteronyssinus</i> IgE (class)	Mosaic pattern
Cluster 1 (closer to OB)	n	8	8	8	8	8
	Median (min; max)	60.6 (32.8; 82.6)	45.0 (-20.0; 110.0)	0.0 (0; 22)	0.0 (0; 6)	5.5 (3; 6)
Cluster 0 (closer to Asthma)	n	4	4	4	4	4
	Median (min; max)	95.6 (46.9; 105.0)	530.0 (460.0; 730.0)	26.0 (7; 48)	5.0 (3; 6)	3.0 (0; 6)
Cluster 3 (closer to 3 rd group)	n	23	23	23	23	23
	Median (min; max)	82.0 (35.3; 140.0)	220.0 (140.0; 330.0)	10.0 (0; 30)	3.0 (0; 6)	5.0 (0; 6)

SPT – skin Prick tests

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Online supplement:
Methods:

HRCT

HRCT images were acquired on inspiratory apnea from the lung apex to the diaphragm using 1 mm slice thickness at 10 mm intervals using a bone (high spatial detail) reconstruction algorithm, 50-80 mAs e 90-120 kVp (according to body volume) and 0,5 sec of rotation time. Images were photographed at lung window settings (1600/600) and mediastinal window settings (300/40) before March 2009. After March 2009 images were stored in PACS system. Most of the studies included inspiratory and expiratory images, typically one or two images at selected levels through the thorax with the patient in full expiration. In some cases volumetric acquisition (“combi”) was performed: 3,2/1,6 mm, 80-100 mAs e 90-120 kVp, 0,5 ms rotation time, 1,75 pitch, followed by a pre-selected multilevel acquisition (3 a 4) of expiratory high resolution images.

Each HRCT was reviewed by a -trained pediatric radiologist. A score sheet modified from Jensen et al. was used to record the presence and extent of 24 HRCT findings. Each lung was divided into upper, middle and lower zones for a total of six lung zones for each patient. Each of these zones was scored separately for the presence and/or extent of the 24 HRCT findings. Inspiratory decreased attenuation, expiratory air trapping and ground glass opacities were scored according to the cross-sectional area of lung involved in each zone 0 - no involvement; 1 – 25% of the cross-sectional area of the lung affected; 2 - 26–50% affected; 3 - 51–75%; 4 - 76–100% affected, bronchiectasis were classified according to [42] into mild with broncho-arterial (BA) ratio lower than 2, moderate, from 2 to 3 and severe if broncho-arterial ratio was higher than 3. If a bronchiectasic collapse was found, a grade of

2 or higher was considered. The remaining HRCT features shown in table 3 of the online supplement were scored as either present (score of 1) or absent (score of 0). Score sheets were then tabulated and composite scores for each HRCT feature were then derived by adding the scores from the six lung zones for each patient.

Statistical analysis

The demographic data and outcomes between groups were compared using two-sided χ^2 test for categorical variables and two-tailed Student's t-tests and oneway ANOVA for continuous variables. In small samples or in the absence of normality for continuous variables, non-parametric tests (Mann-Whitney and Kruskal-Wallis) were applied.

The ROC curve analysis only identified numerical parameters associated with diagnosis and cut-offs. The factors considered in the ROC analysis were: results from LFT (FVC%P; FEV₁%P; FEV₁/FVC; RV/TLC; change in FEV₁ after bronchodilator (ml and %); results from HRCT (inspiratory decreased attenuation, mosaic pattern, expiratory air trapping, bronchial wall thickening and bronchiectasies); for atopy [(skin prick test results, eosinophils (% of total cell)); total IgE and specific IgE to *D. Pteronyssinus*]; inflammation (leukocytes (total number of cells), sedimentation rate (SR), fibrinogen, C-reactive protein (CRP) and alpha-1-antitrypsin (AAT) (Table 0 of the online supplement). Subsequently, in order to identify a "3rd diagnostic group" a cluster analysis was performed (k-means clustering method, SPSS®). In an initial phase two clusters were identified in order to validate this method and followed by another cluster analysis forcing the solution of three clusters. After achieving the solution of three clusters in each parameter, a cross between the final solution and diagnosis was performed according with the following scheme (see table 1 of the online supplement).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

E-Table 0: Inflammation variables for diagnosis group

		OB	PSA	p-value*
		(n=25)	(n=15)	
Leukocytes (cells per cubic millimeter)	n	25	15	0,108
	Missing	0	0	
	Mean	7,44	8,22	
	Median	6,58	8,02	
	Std. Deviation	2,83	1,78	
	Minimum	4,53	5,41	
	Maximum	14,82	11,74	
Sedimentation rate (millimeters per hour)	n	24	15	0,280
	Missing	1	0	
	Mean	12,25	13,33	
	Median	6,50	11,00	
	Std. Deviation	14,75	10,64	
	Minimum	2	2	
	Maximum	52	35	
Fibrinogen (mg/dL)	n	21	13	0,710
	Missing	4	2	
	Mean	321,52	314,85	
	Median	302,00	300,00	
	Std. Deviation	82,56	44,31	
	Minimum	227	261	
	Maximum	588	394	
C-reactive-protein (mg/dL)	n	25	15	0,398
	Missing	0	0	
	Mean	0,40	0,29	

	Median	0,10	0,05	
	Std. Deviation	0,73	0,58	
	Minimum	0,00	0,00	
	Maximum	3,00	2,20	
Alpha 1 antitrypsin (mg/dL)	n	24	15	0,806
	Missing	1	0	
	Mean	145,83	142,80	
	Median	142,00	145,00	
	Std. Deviation	22,83	27,88	
	Minimum	109	106	
	Maximum	225	203	

E-Table 1: Three cluster analysis to identify the third diagnostic group (overlap syndrome)

	OB	PSA	Total
Cluster 0 (nearest asthma)	B	A	n0
Cluster 1 (nearest OB)	D	C	n1
Cluster 3 (indifferent to OB and PSA / identifies the third group)	F	E	n3

It should be noted that: A/n0 is the positive predictive value for zero cluster for PSA. D/n1 is the positive predictive value of a cluster for OB. After performing this analysis of 3 clusters for each variable, only variables that proved simultaneously to have a good adequability for identifying OB and PSA and a good appropriateness (>80%) were selected for a final cluster analysis (final solution) for recognizing the third group of diagnosis (overlap) .

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For individuals correctly classified as OB or PSA in this final cluster analysis, as well as those classified in the "3rd diagnostic group," a comparative analysis of means and medians of the variables selected for the final cluster analysis of these 3 groups were performed. With this comparative analysis the values of central tendency that most distinguish these 3 groups can be observed. Values of $p < 0,050$ were considered to be statistically significant.

For Peer Review

E-Table 2 – Anthropometric characteristics by group of diagnosis (OB, PSA)

		Obliterative bronchiolitis (n=25)	Problematic Asthma (n=15)	p-value
Weight, z-score	n	22	14	
	mean (SD)	-0.54 (1.69)	0.66 (1.24)	0.028
	median (min ; max)	-0.48 (-3.41 ; 2.00)	0.89 (-1.43 ; 3.13)	
Height, z-score	n	22	14	
	mean (SD)	-0.54 (0.92)	-0.39 (0.91)	0.633
	median (min ; max)	-0.66 (-2.19 ; 1.14)	-0.74 (-1.39 ; 1.50)	
BMI (Kg/m²)	n	25	15	
	mean (SD)	20.95 (6.10)	22.41 (5.35)	0.448
	median (min ; max)	20.55 (13.57 ; 40.14)	21.87 (15.84 ; 32.75)	
BMI, z-score	n	22	14	
	mean (SD)	-0.34 (1.87)	0.93 (1.39)	0.036
	median (min ; max)	-0.01 (-4.26 ; 2.87)	1.70 (-1.47 ; 2.96)	

BMI – body mass index

E-Table 3– Comparison of OB and PSA scores for HRCT

		Obliterative bronchiolitis n=25	Problematic Asthma n=15	p-value
Inspiratory decreased attenuation	n	25	15	
	median (min ; max)	12.0 (3.0; 23.0)	5.0 (0.0 ; 15.0)	<0.001
Expiratory air trapping	n	24	13	
	mean (SD)	12.7 (6.0)	5.2 (3.5)	<0.001
Mosaic pattern	n	25	14	
	median (min ; max)	6.0 (1.0 ; 6.0)	4.0 (0.0 ; 6.0)	0.020
Bronchial wall thickening	n	25	14	
	median (min ; max)	4.0 (0.0; 6.0)	1.5 (0.0 ; 6.0)	0.155
Bronchiectasis	n	25	15	
	median (min ; max)	3.0 (0.0 ; 17.0)	0.0 (0.0 ; 3.0)	<0.001

E-Table 4 – Atopy results by group of diagnosis

	Obliterative bronchiolitis n=25	Problematic Asthma n=15	p-value
Eosinophils (x10^9/L) median (min ; max)	130 (10 ; 1570)	410 (140 ; 710)	0.004
Total IgE (kU/L) median (min ; max)	33.4 (6.9 ; 3034.0)	388.0 (8.9 ; 1338.0)	0.007
<i>D. pteronyssinus</i> IgE (class) median (min ;max)	0 (0 ; 6)	4 (0 ; 6)	<0.001
Skin prick tests (total of mm, all tests) median (min ; max)	0.00 (0 ; 22)	15.00 (0 ; 48)	0.001

E-Table 5— Area under ROC curve (AUC) and concordance evaluation between the 2 clusters (cluster 1 as OB group patients and cluster 0 as PSA group patients) using Kappa Cohen coefficient for Lung Function results

	AUC	Cut-off	Kappa Cohen coefficient	p-value
FVC% predicted	0.899	77.79	0.605	<0.001
FEV₁% predicted	0.899	55.00	0.641	<0.001
FEV₁/FVC% predicted	0.747	79.82	0.392	0.011
RV%TLC	0.872	36.88	0.395	0.004
ΔFEV₁%t post-BD (ml)	0.800	235.00	0.333	0.012
ΔFEV₁%t post-BD (%)	0.545	-----	0.000	>0.999

AUC – area under ROC curve

E-Table 6 – Area under ROC curve (AUC) and concordance evaluation between the 2 clusters (cluster 1 as OB group patients and cluster 0 as PSA group patients) using Kappa Cohen coefficient for HR-CT findings

	AUC	Cut-off	Kappa Cohen coefficient	p-value
Inspiratory decrease attenuation	0,863	6,5	0,518	<0,001
Expiratory air trapping	0,856	6,5	0,480	0,001
Mosaic pattern	0,713	4,5	0,195	0,221
Bronchial wall thickening	0,636	-	0,084	0,584
Bronchiectasis	0,861	1,5	0,125	0,102

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

E-Table 7 – Three clusters analysis. Adequability tax for LF results

	Adequability for the diagnosis of OB and PSA	Adequability for the diagnosis of the 3 rd group
FVC% predicted	94%	87%
FEV ₁ % predicted	96%	66.6%
FEV ₁ /FVC% predicted	74.1	61.6
RV%TLC	79.2%	37.6%
ΔFEV ₁ %t post-BD (ml)	89.5%	85.8%
ΔFEV ₁ %t post-BD (%)	60.7%	66.6%

E-Table 8– Three clusters analysis. Adequability tax for HR-CT results

	Adequability for the diagnosis of OB and PSA	Adequability for the diagnosis of the 3 rd group
Inspiratory decreased attenuation	75.9%	36.4%
Expiratory air trapping	81.2%	76.2%
Mosaic pattern	80.8%	92.4%
Bronchial wall thickening	66.7%	40.0%
Bronchiectasis	58.1%	0.0%

E-Table 9– Three clusters analysis. Adequability tax for atopy results

	Adequability for the diagnosis OB and PSA	of Adequability for the diagnosis of the 3 rd group
Skin prick tests (total of mm, all tests)	84%	80%
Eosinophils (x10 ⁹ /L)	77.3%	77.8%
Total IgE (kU/L)	68.6%	0.0%
<i>D. pteronyssinus</i> specific IgE (class)	88.5%	83.4%