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Clinical Differentiation between Resistant Asthma and Chronic Bronchiolitis: Testing a Practical Approach

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ABSTRACT

Intractable asthma is a challenging clinical problem. This study was conducted to determine whether a subset of patients with Intractable asthma may be misdiagnosed and have a form of bronchiolitis instead and also to determine the effectiveness of macrolide therapy in these patients.

Seventy six patients with Intractable asthma were re-treated with recommended maximal doses of oral prednisolone for 5 days, beclomethasone, cromolyn sodium, salbutamol and ipratropium bromide for 30 days. Thirty five patients were considered as unresponsive and constituted the study group. They underwent high-resolution CT (HRCT) scan following which they were offered with video-assisted thoracoscopic surgical biopsy. Group 1 (n= 27) refused biopsy and each was treated with macrolide therapy, while Group 2 (n=8) underwent biopsy, and then received macrolide therapy. The patients were treated and followed for three months.

The study group consisted of 27 patients, with a mean age of 46.9 ± 11.1 years. The mean duration of time between the onset of symptoms and the start of this study was 8.1 years. In group 2, no patient had pathologic findings of asthma, and 7/8 had a form of bronchiolitis. There was significant improvement in dyspnea, cough and pulmonary function indices at the end of the 3-month in both groups ($p < 0.001$).

Our results suggest that patients with Intractable asthma could be misdiagnosed and some of them have some forms of chronic bronchiolitis. We believe that any patient who does not respond to standard treatments for Intractable asthma should be evaluated with expiratory HRCT; those with significant air trapping should be considered for a course of macrolide therapy or biopsy for better identification of the underlying disease.

Key words: Air trapping; Asthma; Bronchiolitis; Expiratory; High-resolution computed tomography; Macrolide

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INTRODUCTION

Asthma resistant to the usual armamentarium of medications is a challenging clinical problem. It has been defined as "failure to achieve control when maximally recommended doses of inhaled therapy are prescribed",[1] but little is known about its pathophysiology. Our recent experience with several patients has raised the question in our mind about whether all patients with "Intractable" asthma really have asthma at all. Since accurate diagnosis is essential for the best effective therapy, we undertook the current clinicopathologic study. The purpose of this study was to determine whether patients with Intractable asthma may be misdiagnosed. In addition, as of suspicion to a form of bronchiolitis in some patients with difficult asthma, and also reported studies on use of macrolide therapy in some forms of bronchiolitis, the effectiveness of macrolide therapy in this group of patients was also investigated.

MATERIALS AND METHODS

For the purposes of this study, we defined "difficult asthma" as occurring in patients, who had compatible symptoms (e.g. dyspnea, cough and wheezing) and carried a diagnosis of asthma as defined by American Thoracic Society Criteria,[2] but were resistant to 1) oral steroids 2) bronchodilators and 3) inhaled corticosteroids as treated by their referring physician.

The current study group was identified among 76 patients referred to our tertiary care centre (Baqiyatallah Hospital-2006) which specializes in difficult asthma as defined. Patients were excluded if they had a history of significant occupational or other environmental exposures or a connective tissue disease or smoking history. Also clinical history of mycoplasma infection and use of any macrolides in the recent 3 months were considered as exclusion criteria.

The corresponding author explained the treatment protocol for the patients and written informed consent (approved by the appropriate Institutional Board Review) was obtained from each patient prior to enrollment. None of the patients was forced to drop out of the study due to the type of treatment protocol or side effects. According to patients' history and medical documents, none of the patients had used any type of macrolides.

After initial evaluations, all patients were re-treated according to the following protocol: oral prednisolone (50 mg in the morning) for 5 days; with beclomethasone (7 puff q8h, totally 1000 micrograms/day), cromolyn sodium (20mg q6h), salbutamol (4 puffs q6h, 100 micrograms/puff) and ipratropium bromide (4 puffs q8h) for 30 days. Forty one patients had improved symptoms according to pulmonary function tests (PFT's). It was considered as airway obstruction reversibility and was diagnosed as having asthma. The remaining patients were considered as non-responders and are the subject of this report.

Patients with potential allergic bronchopulmonary aspergillosis i.e. with peripheral blood eosinophilia, sputum eosinophilia, or any sputum production and bronchectasis; a history of smoking; significant occupational or environmental exposures; or evidence on emphysema on chest high resolution computed tomography (HRCT) scan were excluded.

Due to their resistant disease, all patients underwent HRCT scan following which they were offered with surgical lung biopsy. Group 1 (n=27) declined biopsy and was treated with macrolide therapy, while Group 2 (n=8) underwent video-assisted thoracoscopic surgical (VATS) biopsy, and then macrolide therapy (In patients with gastroesophageal reflux: clarythromycine 500 mg or azithromycin 250 mg daily and in other patients erythromycine 400 mg) was added to their medications. First choice of macrolide was erythromycine. Whenever intolerance to erythromycine was reported by patients, they were switched over to clarythromycine or azithromycin. Patients were treated and followed for three months by utilization of a previously described Dyspnea Score (see below) and PFT.[3] In occasional cases, repeated chest HRCT was performed. Spirometry was repeated only in patients with obstructive PFT.

Dyspnea Scoring System

Dyspnea was defined as the perception of difficult breathing provoked by an activity not expected to produce it. The dyspnea indices are defined in Table 1.

Chest HRCT Technique and Interpretation

An axial GE Hi-speed advantage CT scanner (GE medical system, FXI-plus) at 120 kVp and 200-250 mAs with 1mm collimation and 10mm intervals from proximal trachea to the diaphragm was utilized.

The scans were obtained in supine position in deep

Table 1. Dyspnea Index (SEPAR).

0	No dyspnea except for very intense efforts
1	Dyspnea with accelerated upon walking or when climbing a hill
2	The patient walks more slowly than people at his/her age
3	The patient has to stop after walking for 5 minutes
4	Dyspnea at dressing or undressing; cannot leave home

inspiration and also in deep expiration. The HRCT films were reviewed by three expert radiologists using an eFilm workstation (Merge eFilm).

Air trapping was defined as the presence of a radiolucent region of the lungs on expiratory images.[3-5] The degree of air trapping was assessed by comparing end-inspiratory and expiratory images at similar anatomic levels and at each of the three levels. Air trapping was evaluated in three of the four anatomic levels in each case: upper lung zone, defined as the level of superior aspect of the aortic arch; middle lung zone, defined as the level of the carina; and lower lung zone, defined as the level 5-10 cm below the carina, according to the method used by Zhang et al.[6] Scores of > 25% cross sectional affected area were considered significant.

Pulmonary Function Testing Technique and Interpretation

Spirometry was performed according to American Thoracic Society criteria.[7] The forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) were measured, under the direction of physicians, using a standard spirometer (MasterScreen IOS; Jaeger/Toennies; Hochberg, Germany). Subjects were seated with a nose clip in place and were asked to perform at least three forced expiratory maneuvers. Both the patients and the technician received visual feedback from a monitor during the test, which was repeated until three technically satisfactory curves with a reproducible contour were obtained.

Pathology Interpretation

Biopsies were obtained in group 2 from two different lobes of the lung and at the interface between apparent normal and pathologic tissue, when such a demarcation was visualized. All patients had more than 25% air trapping in their HRCT. Specimens were sent fresh and sterile to pathology for frozen and permanent sections analysis. All lung biopsies were stained with hematoxylin and eosin, Masson trichrome and elastic tissue stains according to standard procedures.

All cases were reviewed in a blinded fashion without knowledge of clinical features by three pathologists, from the USA (Department of Laboratory Medicine and Pathology, Mayo Clinic Arizona) and Iran (Research Center of Chemical Injuries, Baqiyatallah Medical Sciences University and Shahid Beheshti University, Tehran). Standardized scoring sheets were developed based on previously published systems utilized in the assessment of lung pathology in idiopathic pulmonary fibrosis and nylon-flock workers[8] with special attention to bronchiolar pathology. After scoring all features individually, each pathologist provided a preliminary diagnosis for each case. A final diagnosis was rendered after the pathologists met with the attending pulmonologists and radiologists and reviewed the full clinical history, radiologic and pathologic findings.

The study was performed with the approval of the ethics committee board and in accordance with good clinical practice and the Declaration of Helsinki.

RESULTS

The study group consisted of 27 patients, 8 men and 19 women, with a mean age and standard deviation of 46.9 ± 11.1 years (range 24-63 years). The mean duration of time between the onset of symptoms and the start of this study was 8.1 years (range 1.5-23 years). The mean and standard deviation of symptomatic years prior to join to our study were 5.7 and 5.0 yrs in the group 2 (range 1.5-17 years). Persistent cough was invariably the first symptom, and most patients reported dyspnea and wheezing. No patients had history of childhood asthma or atopia. Pathologic diagnosis and response to treatment in Group 2 patients are shown in table 2. All patients had a diagnosis of "asthma" as the original diagnosis. No patient had histologic findings of asthma. Figure 2 shows one of the patients' pathology slide.

The dyspnea and cough indices at the end of the 3rd month of therapy in both groups are shown in Table 3. There was significant improvement in all parameters (Table 3). There was also significant improvement in PFT's 3 months after treatment in both groups (Table 4). All patients characteristics before and after the study are presented in table 5.

Table 2. Pathologic diagnosis and response to treatment in group 2.

	Age (year)	Sex	years before diagnosis	Diagnosis	DI (a)	DI (b)	CI (a)	CI (b)	FEV1 (a)	FEV1 (b)	FVC (a)	FVC (b)	MMEF (a)	MMEF (b)	PEF (a)	PEF (b)
1	43	F	5	Cryptogenic organizing pneumonia (bronchiolitis obliterans organizing pneumonia)	4	0	4	2	86	93	85	92	69	83	64.5	70.5
2	29	F	8	mild chronic peribronchiolitis	3	1	4	2	77	87.7	72.4	81	75.4	81	63.5	70
3	40	F	6	Cryptogenic organizing pneumonia (bronchiolitis obliterans organizing pneumonia	3	0	4	3	58.5	85.4	64.5	88.3	28.6	72.5	71	113
4	47	F	1.5	chronic cellular bronchiolitis	3	0	3	3	69.5	91	70.2	83	57.1	88	103	119
5	40	M	4	constrictive (obliterative) bronchiolitis	3	0	4	3	101	116	96	105	93	104	97	108
6	36	F	17	mild to moderate constrictive (obliterative) bronchiolitis	3	3	4	2	74	77.7	72.4	78	63.5	72.4	90.2	92.4
7	40	F	2	follicular bronchiolitis	3	0	4	4	72	81	69	82	80	84	85.5	90
8	66	F	2	acute and organizing fibrinous pneumonia	3	3	4	3	88	93	88.8	91	76	84	65.5	71

(a) Before treatment, (b) after treatment

Table 3. Dyspnea and cough indices changes after 3 months treatment in both groups.

Symptoms	Total	Without symptoms	Treatment Symptomatic	Value after treatment			
				Worse	No change	Improved	P value
Dyspnea indices	27	2	25	2(8%)	7(28%)	16(64%)	< 0.001
Cough indices	27	6	21	0	3 (14.3%)	18 (85.7%)	< 0.001

Table 4. Pre-treatment and post treatment PFT results in cases with abnormal PFTs*

Variables	Before treatment *Liters* (Percent)	After 3 month *Liters* (Percent)	P Value
FEV1 Measured	1.9 (52.7)	3.06 (71.7)	P<0.0001
FVC Measured	2.9 (68.8)	3.5 (82.8)	P<0.0001
FEV1/FVC Measured	62.8 (71.1)	69.2 (75.8)	P<0.0001
MMEF Measured	1.06 (29.7)	1.8 (49.7)	P<0.0001

* Twenty five had abnormal PFT (6 males and 19 females) with mean age of 56.9±19 and 10 had normal PFT (3 males and 7 females) with mean age of 50±17.6

Table 5. Patients' characteristics in two groups.

Groups	Male/ Female	Age (year)	Cough Index (1)*	Dyspnea Index (1)*	Cough Index (2)*	Dyspnea Index (2)*	FEV1 (1)	FEV1 (2)	FVC (1)	FVC (2)	MMEF (1)	MMEF (2)
Group(1)	8/19	48 (14.2)	2	4	1	3	37.6 (29.8)	47.3 (36.4)	47.2 (35.5)	55.7 (42)	19.3 (19.1)	31.6 (27.8)
Group(2)	1/7	44.8 (10.8)	3	4	0	2.5	78 (13)	90.6 (11.6)	78 (11)	86.8 (9.6)	68.5 (19.6)	83 (10.3)

Data are presented as mean(SD), *data are presented as Median

DISCUSSION

Our results confirmed the hypothesis that patients with difficult asthma would be frequently misdiagnosed. Despite the fact that all of our patients had been diagnosed with asthma for a mean of 8 years prior to the study, among those who underwent surgical lung biopsy, a wide variety of pathologies were identified, but no patient had classic pathologic findings of asthma. Seven had pathologic findings centered on the airways and a component of bronchiolitis or peribronchiolitis. The remainder could be either resistant asthma with air trapping or bronchiolitis but biopsy sampling and pathological evaluations were not possible for reaching definite diagnosis in all patients. However all showed desirable response to our macrolide treatment strategy. The results of our study therefore suggest that a majority of patients with presumed difficult asthma may have some form of bronchiolitis and that it is frequently responsive to macrolide therapy. Numerous reports have suggested that macrolide antibiotics may have anti-inflammatory properties.[9,10] Several human studies have demonstrated a reduction in inflammatory mediators including IL-8, tumor necrosis factor-α, and IL-1ß,[11,12] in patients receiving macrolide therapy. The current study lends further anecdotal support to the theory that macrolides may decrease inflammation, as most patients responded to macrolide therapy.

Whereas both air trapping and a response to macrolide therapy can be seen in patients with asthma, there are some reasons why diagnosis of severe asthma can be excluded in our group of patients: 1) Almost all patients had normal or near normal PFT and there were few patients with moderate to severe obstruction; 2) The role of HRCT in the diagnosis of bronchiolitis and severe case of asthma has been approved and air trapping more than 25% is only present in severe cases of asthma.[13,14] Our cases showed only mild to moderate airway obstruction; 3) The percent of abnormal lung in asthmatics as determined by quantitative computed tomography should have a significant correlation with the PFT (reflecting air trapping) , but this finding was not present in our patients. [4,14,15]

From a practical standpoint, patients whose asthma is not controlled on high dose inhaled corticosteroid therapy can be considered to have difficult/therapy-resistant asthma.[16] While previous studies demonstrated that additional inhalation of nebulized sodium cromoglycate with inhaled corticosteroids is effective even in patients with severe atopic asthma.[17] The patients all failed to respond to high dose anti-asthma therapy given by their local physicians and a repeated trial of aggressive anti asthma therapy administered by our group 5) Finally, pathology other than that described in association with asthma was identified in all group 2 patients. The results of this study suggest that patients with normal PFT and air trapping more than 25% on HRCT are likely to have a type of bonchiolitis, rather than asthma.

It has been suggested that patients with chronic cough in whom more common causes have been excluded, have nonbronchiectatic suppurative airway disease (bronchiolitis).[18] We found evidence of bronchiolitis even in our patients without suppurative complaints. Airway wall thickening, mosaic perfusion attenuation and air trapping have been reported previously in patients with severe asthma[19-21] in whom the alternative diagnoses e.g. bronchiolitis had not been considered. While characteristic image findings (like ground glass shadowing and centrilobular nodules) suggest the appearance of bronchiolitis.[22] In spite of optimal treatment, structural changes in both large and small airways may be responsible of a failure for a patient with asthma to respond as expected. While such patients may have asthma, the results of our study suggest that at least a subset of such patients may actually have bronchiolitis instead. Many patients with asthma are treated by local non-pulmonologists. Cases of unexplained persistent asthma resistant to usuall therapy should be brought to the attention of pulmonologists to consider alternative diagnoses.

A careful clinical history in this context is extremely important. In addition to relatively well recognized causes of bronchiolitis such as hypersensitivity pneumonitis, bronchiolitis obliterans has been reported in workers at a microwave popcorn plant,[23] after consumption of certain foods e.g. Asian shub leaf,[24] and after inhalation of toxic gases in the work place. Clinicians should cast a broad net and ask about any potential exposures to recognized hazards, some of which may not seem immediately relevant, or may have occurred many years prior to presentation. The implicated causal exposures usually arise from chemical spills or other unanticipated circumstances, rather than in the course of routine work.[25-28] In our previous studies, we reported that sulfur mustard even at a low dose can cause bronchiolitis after many years

of symptom free period.[29] Thus, the cases reported here may represent just "the tip of the iceberg" of all patients with "difficult asthma".

Since thin-section CT, including expiratory scans, may be of limited value in diagnosing early bronchiolitis obliterans after lung transplantation,[30] Thus a normal CT scan in the setting of a patient with "difficult asthma" should not exclude the possibility that a surgical biopsy will yield important information. However, sometimes, even in expert hands, the tissue samples obtained may be small, fragmented and distorted, thus rendering assessment of lung pathology difficult. Pathologists need to be made aware of the clinical differential diagnosis in such cases, as examining multiple levels of tissue samples and using special stains, particularly elastic stains may help in recognizing the presence of subtle bronchiolar pathology. Recognition of the typical HRCT features of bronchiolitis obliterans, as seen in this study, may obviate the need for biopsy in those with occupational exposure to a known agent. If patients refuse lung biopsy, and a diagnosis of some form of bronchiolitis is suspected based on the work-up suggested here, the results of our study suggest that a therapeutic trial of macrolides may be beneficial.

Our study has some limitations. First, we did not have a control group, although controlled trials evaluating the effectiveness of macrolides for airflow obstruction in established bronchiolitis obliterans syndrome have shown to be very effective.[9,10] Due to our sample size and related statistical limitation we did not compare the differences of effectiveness between the macrolides in this setting. Also it is possible that, improvement in symptoms and investigated factors were due to long term medication or macrolide as an adjuvant therapy in asthma since previous studies demonstrated low-dose and long-term macrolide therapy may be effective in asthma.[31] With more than 25% air trapping and bronchiolitis obliterans pathological findings which both were compatible with non asthma diagnosis and the response to macrolide therapy, evidence altogether suggest that the basic pathology in this group of patients which did not respond to asthma medication may be bronchiolitis obliterans and asthma diagnosis have to be reevaluated. Furthermore this hypothesis needs to be confirmed with clinically valid studies.

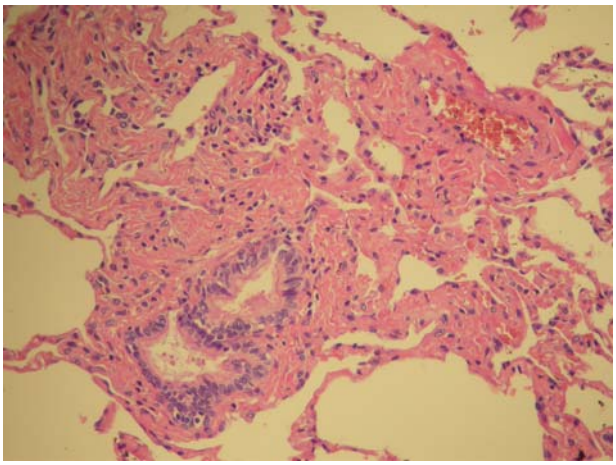

Figure 1. A section representing pathologic evidence of constrictive bronchiolitis, marked by peri-bronchial inflammation, infiltration and fibrosis which surround bronchioles.

The clinical distinction between severe asthma and bronchiolitis is often challenging and the clinician, even armed with the patient history, physical examination, and pulmonary function tests, may be uncertain about the specific diagnosis due to overlap in the clinical presentation and results of ancillary studies. Any patient who does not respond to standard treatment should be evaluated with expiratory chest HRCT for determining the level of air trapping and those with more than 25% air trapping should be considered for macrolide therapy or biopsy for definitive diagnosis. The approach we suggest and used in this study is to utilize a combination of PFT, HRCT imaging and pathology, as shown in Figure 1.

Previous studies had established that air trapping on expiratory CT can be seen in patients with tracheobronchomalacia[6] and in association with various airway diseases, including bronchiolitis obliterans.[32,33] Patients with tracheomalacia in the presence of significant air trapping or wheezing and normal PFT, patients with severe airway obstruction and normal lung sounds who do not show no complete improvement in PFT after aggressive anti asthma therapy, patients with normal PFT after carrying a long term diagnosis of asthma, and patients with normal PFT disproportionate to symptoms are highly likely to have a form of bronchiolitis and we suggest that they get a more focused work-up to prove it.

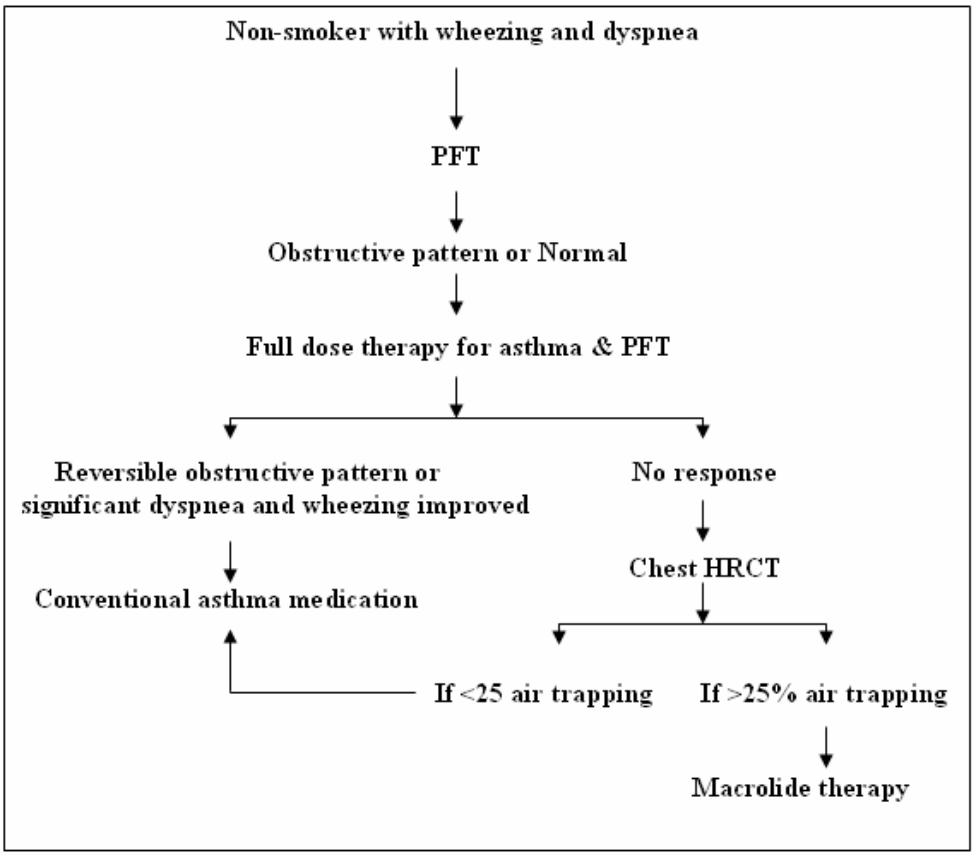

Figure 2. Suggested diagnostic and therapeutic approach containing combination of PFT's, HRCT imaging and pathology.

REFERENCES

1. Strek ME. Difficult asthma. Proc Am Thorac Soc 2006; 3(1):116-23.
2. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, November 1986. Am Rev Respir Dis 1987; 136(1):225-44.
3. Ghanei M, Panahi Y, Mojtahedzadeh M, Khalili AR, Aslani J. Effect of gamma interferon on lung function of mustard gas exposed patients, after 15 years. Pulm Pharmacol Ther 2006; 19(2):148-53.
4. Lee KW, Chung SY, Yang I, Lee Y, Ko EY, Park MJ. Correlation of aging and smoking with air trapping at thin-section CT of the lung in asymptomatic subjects. Radiology 2000; 214(3):831–836.
5. Austin JH, Müller NL, Friedman PJ, Hansell DM, Naidich DP, Remy-Jardin M, et al: Glossary of terms for CT of the lungs: recommendations of the Nomenclature Committee of the Fleischner Society. Radiology 1996; 200(2):327-31.
6. Zhang J, Hasegawa I, Hatabu H, Feller-Kopman D, Boiselle PM. Frequency and severity of air trapping at dynamic expiratory CT in patients with tracheobronchomalacia. AJR Am J Roentgenol 2004; 182(1):81-5.
7. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med 1995; 152(3):1107-36.
8. Boag AH, Colby TV, Fraire AE, Kuhn C 3rd, Roggli VL, Travis WD, et al. The pathology of interstitial lung disease in nylon flock workers. Am J Surg Pathol 1999; 23(12):1539-45.
9. Kudoh S, Azuma A, Yamamoto M, Izumi T, Ando M. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. Am J Respir Crit Care Med 1998; 157(6 pt 1):1829–32.
10. Gerhardt SG, McDyer JF, Girgis RE, Conte JV, Yang SC, Orens JB. Maintenance Azithromycin Therapy for

bronchiolitis obliterans syndrome. results of a pilot study. Am J Respir Crit Care Med 2003; 168(1):121-5.
11. Culić O, Eraković V, Cepelak I, Barisić K, Brajsa K, Ferencić Z, et al: Azithromycin modulates neutrophil function and circulating inflammatory mediators in healthy human subjects. Eur J Pharmacol 2002; 450(3):277–89.
12. Suzuki H, Asada Y, Ikeda K, Oshima T, Takasaka T. Inhibitory effect of erythromycin on interleukin-8 secretion from exudative cells in the nasal discharge of patients with chronic sinusitis. Laryngoscope 1999; 109(3):407–10.
13. Webb WR, Stein MG, Finkbeiner WE, Im JG, Lynch D, Gamsu G. Normal and diseased isolated lungs: high-resolution CT. Radiology 1988; 166(1pt 1):81–7.
14. Pipavath SJ, Lynch DA, Cool C, Brown KK, Newell JD. Radiologic and pathologic features of bronchiolitis. AJR Am J Roentgenol 2005; 185(2):354-63.
15. Newman KB, Lynch DA, Newman LS, Ellegood D, Newell JD Jr. Quantitative computed tomography detects air trapping due to asthma. Chest 1994; 106(1):105-9.
16. Brown KK. Chronic cough due to nonbronchiectatic suppurative airway disease (bronchiolitis): ACCP evidence-based clinical practice guidelines. Chest 2006; 129(1 Suppl):132S-7S.
17. Little SA, Sproule MW, Cowan MD, Macleod KJ, Robertson M, Love JG, et al. High resolution computed tomographic assessment of airway wall thickness in chronic asthma: reproducibility and relationship with lung function and severity. Thorax 2002; 57(3):247-53.
18. Gono H, Fujimoto K, Kawakami S, Kubo K. Evaluation of airway wall thickness and air trapping by HRCT in asymptomatic asthma. Eur Respir J 2003; 22(6):965-71.
19. Park JW, Hong YK, Kim CW, Kim DK, Choe KO, Hong CS. High-resolution computed tomography in patients with bronchial asthma: correlation with clinical features, pulmonary functions and bronchial hyperresponsiveness. J Investig Allergol Clin Immunol 1997; 7(3):186-92.
20. Kajiya T, Kuroda A, Hokonohara D, Tei C. Radiographic appearance of bronchiolitis obliterans organizing pneumonia (BOOP) developing during Bucillamine treatment for rheumatoid arthritis. Am J Med Sci 2006; 332(1):39-42.
21. Akpinar-Elci M, Travis WD, Lynch DA, Kreiss K. Bronchiolitis obliterans syndrome in popcorn production plant workers. Eur Respir J 2004; 24(2):298–302.
22. Higenbottam TW. Bronchiolitis obliterans following the ingestion of an Asian shrub leaf. Thorax 1997; 52 Suppl 3:S68-72.
23. Boswell RT, McCunney RJ. Bronchiolitis obliterans from exposure to incinerator fly ash. J Occup Environ Med 1995; 37(7):850–5.
24. King TE Jr. Bronchiolitis obliterans. Lung 1989; 167:69–93.
25. Simpson FG, Belfield PW, Cooke NJ. Chronic airflow limitation after inhalation of overheated cooking oil fumes. Postgrad Med J 1985; 61(27):1001–2.
26. Spain BA, Cummings O, Garcia JG. Bronchiolitis obliterans in an animal feed worker. Am J Ind Med 1995; 28(3): 437–43.
27. Ghanei M, Fathi H, Mohammad MM, Aslani J, Nematizadeh F. Long-term respiratory disorders of claimers with subclinical exposure to chemical warfare agents. Inhal Toxicol 2004; 16(8):491-5.
28. Lee ES, Gotway MB, Reddy GP, Golden JA, Keith FM, Webb WR. Early bronchiolitis obliterans following lung transplantation: accuracy of expiratory thin-section CT for diagnosis. Radiology 2000; 216(2):472-7.
29. Chung KF, Godard P, Adelroth E, Ayres J, Barnes N, Barnes P, et al. Difficult/therapy-resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task Force on Difficult/Therapy-Resistant Asthma. European Respiratory Society. Eur Respir J 1999; 13(5):1198-208.
30. Sano Y, Adachi M, Kiuchi T, Miyamoto T. Effects of nebulized sodium cromoglycate on adult patients with severe refractory asthma. Respir Med 2006; 100(3):420-33.
31. Hatipoglu U, Rubinstein I. Low-dose, long-term macrolide therapy in asthma: An overview. Clin Mol Allergy 2004; 2(1):4.
32. Stern EJ, Frank MS. Small-airway diseases of the lungs: findings at expiratory CT. AJR Am J Roentgenol 1994; 163(1):37-41.
33. Palombini BC, Villanova CA, Araújo E, Gastal OL, Alt DC, Stolz DP, et al: A pathogenic triad in chronic cough: asthma, postnasal drip syndrome, and gastroesophageal reflux disease. Chest 1999; 116(2):279-84.