La Medicina del Lavoro Med Lav 2012; *103*, 1: 17-25

Occupational nonasthmatic eosinophilic bronchitis: current concepts

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Key words
Eosinophilic bronchitis; occupational allergy; occupational asthma

Parole chiave
Bronchite eosinofila; allergia professionale; asma professionale

Summary
Background: *Nonasthmatic eosinophilic bronchitis (NAEB) is an important cause of chronic cough, since it is present in 10-15% of patients referred for specialist investigation. The syndrome is considered a variant of occupational asthma when it develops as a consequence of occupational exposure, hence it should be considered in the spectrum of work-related airway diseases.* **Objectives and Methods:** *The aim of this paper was to update and expand the previous reviews on the clinical and pathophysiological features of NAEB and analyze available data on the occupational causes of the disease. Literature on the topic between the years 1990 and 2010 was reviewed with a Med Line search.* **Results:** *The disease is probably underdiagnosed and an occupational origin was demonstrated only in isolated cases, probably due to the rarity of the disease and the lack of systematic evaluation of bronchial inflammation.* **Conclusions:** *In view of the current knowledge on this condition and the development of techniques to evaluate bronchial inflammation, occupational NAEB cannot be neglected any more and has been rightly included in the spectrum of occupational respiratory disorders.*

Riassunto
«La bronchite eosinofila non asmatica professionale: lo stato dell'arte». **Introduzione:** *La bronchite eosinofila è una importante causa di tosse cronica, e viene considerata una variante dell'asma professionale quando si sviluppa a seguito di esposizione lavorativa, e deve pertanto essere considerata nello spettro delle patologie respiratorie correlate al lavoro. Sono sempre maggiori le evidenze del ruolo dei fattori occupazionali nello sviluppo della tosse cronica. Tuttavia, il loro reale contributo nella genesi di questa condizione non è mai stato indagato in maniera sistematica, e sono stati riportati solo una serie di casi isolati.* **Scopo del lavoro:** *Scopo di questo lavoro è un aggiornamento sulle caratteristiche cliniche e fisiopatologiche della bronchite eosinofila, ed una analisi dei dati attualmente presenti in letteratura sugli aspetti professionali della patologia.* **Risultati:** *La bronchite eosinofila è una condizione probabilmente sottodiagnosticata e la sua relazione con l'attività lavorativa è stata dimostrata solo in casi isolati, probabilmente per la rarità della patologia e la mancata sistematica valutazione dell'infiammazione bronchiale.* **Conclusioni:** *Le attuali conoscenze sulla bronchite eosinofila e lo sviluppo e la diffusione di tecniche per la valutazione della infiammazione bronchiale, impongono che questa condizione non venga più trascurata nella valutazione clinica quotidiana, anche in considerazione del fatto che è stata di diritto inclusa tra le patologie respiratorie professionali.*

Pervenuto il 23.3.2011 - Accettato il 9.9.2011
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Introduction

In 1989 Gibson et al. (17) described a group of 7 non-smoker subjects with corticosteroid-responsive chronic cough producing sputum, all of whom had normal lung function tests and methacholine airway responsiveness. These subjects showed eosinophilic inflammation in the induced sputum, hence the term *eosinophilic bronchitis without asthma* (17) or *nonasthmatic eosinophilic bronchitis* (NAEB) (11).

This condition was subsequently recognised as an important cause of chronic cough, since it is present in 10-15% of patients referred for specialist investigation (4, 10). Over the last 20 years there has been a growing interest in assessing airway inflammation in patients with chronic cough, encouraged by the development of easy-to-perform, non invasive methods to assess airway inflammation (25, 31, 34). One of the most interesting observations was that airway inflammation with eosinophils occurs not only in asthma but also in patients with isolated chronic cough without the abnormalities of airway function that characterize asthma. NAEB is defined as chronic cough in patients with no symptoms or objective evidence of variable airflow obstruction, normal airway responsiveness and sputum eosinophilia. NAEB is considered a variant syndrome of occupational asthma (OA) when it develops as a consequence of occupational exposure (3, 43), hence it should be considered in the spectrum of work-related airway diseases (42).

The aim of this paper was to update and expand the previous reviews on the clinical and pathophysiological features of NAEB and analyse available data on the occupational causes of the disease. Literature on the topic between the years 1990 and 2010 was reviewed via a Med Line search. Data on occupational NAEB come mostly from a number of case reports and only one cross-sectional study has been reported to date, hence most of the data on epidemiology, pathogenesis, management and therapy were derived from papers on non-occupational NAEB. A brief analysis of all the case reports on occupational NAEB is provided.

Epidemiology

There is increasing evidence of the involvement of occupational substances in the development of chronic cough (20). Studies in chronic cough patients (1, 10, 13) reporting the assessment of airway inflammation have shown that NAEB accounts for 10 to 30% of cases referred for specialist investigation. However, the burden of occupational factors in this specific condition has not been specifically investigated, and only a number of case reports have been published.

Pathogenesis

In patients with NAEB, there is a clear dissociation between sputum eosinophilia and airway hyperresponsiveness. The physiopathology of NAEB and the reason for the absence of airway hyperresponsiveness in this disease remains unclear.

NAEB and asthma share many immunopathological features, including a similar content of sputum (9,12) and biopsy eosinophilia, and a similar degree of basement membrane thickening (8, 12).

The two conditions are both associated with increased sputum concentrations of important effector mediators such as cysteinyl-leukotrienes and eosinophilic cationic protein (12).

Conversely, an increased mast cell number in airway smooth muscle in asthma but not in NAEB was shown by Brightling et al. (8). The number of airway smooth muscle mast cells was inversely correlated with airway hyperresponsiveness (8, 39). Gibson et al. found a significantly higher number of mast cells in bronchial brushings in subjects with NAEB than in those with asthma (19). In support of this, Brightling et al. (12) found that the sputum concentrations of mast cell-derived autacoid mediators histamine and prostaglandin D_2 (PGD_2) were increased only in NAEB, suggesting that mast cells activation in superficial airway structures is a peculiar feature of this condition and suggests the possibility that localisation of activated mast cells might differ in asthma and NAEB.

Sastre and co-workers (36) observed an inverse relationship between prostaglandin E_2 (PGE_2) and

leukotriene C_4 (LTC_4) concentrations in patients with asthma and NAEB. Whereas LTC_4 levels were more elevated in the asthmatic group, NAEB patients had increased PGE_2 levels, suggesting that the difference in airway function observed in subjects with NAEB and asthma could be due to the different ratio in the production of bronchoconstrictor (LTC_4) and bronchoprotective (PGE_2) lipid mediators.

Interleukin-13 (IL-13) expression is increased in bronchial submucosa, sputum, and peripheral blood T-cells (5, 30, 35, 37) of subjects with asthma compared to those with NAEB.

In summary, with the exception of the above reported remarks, the immunopathology of NAEB and asthma is very similar. This observation suggests that these features of airway inflammation, together with structural changes in the airway wall, are regulated independently of airway hyperresponsiveness (9). Thus, the key factors determining the different functional association of airway inflammation in NAEB and asthma might be the microlocalisation of mast cells into the airway smooth muscle bundle, increased IL-13 expression, airway narrowing resulting in airway hyperresponsiveness and variable airflow obstruction, and an epithelial infiltration producing bronchitis and cough.

NAEB AND OCCUPATIONAL EXPOSURE

Cases of NAEB have been reported in relation to exposure to both HMW- (High Molecular Weight) and LMW- (Low Molecular Weight) occupational allergens or sensitizers (table 1).

CASE REPORTS

HMW-agents

Natural rubber latex

A 31-year-old nurse, exposed to latex gloves for 15 years (33), 5 years after starting to use the gloves presented with contact urticaria, rhinoconjunctivitis and subsequently non-productive chronic cough without wheezing or dyspnoea. Specific inhalation challenge (SIC) with powdered NRL gloves showed no changes in FEV_1, but a pronounced eosinophilia (90%) in the sputum was observed 24 h after the latex challenge.

Lysozyme

Quirce diagnosed NAEB caused by lysozyme (32) in a 54-year-old man who had been working

Table 1 - Agents causing non-asthmatic eosinophilic bronchitis

Causative agent	Occupation	Author and Reference
High-molecular-weight agents		
Latex	Nurse	Quirce et al. (32)
Hypsizigus marmoreus	Mushroom workers	Tanaka et al. (41)
Lysozyme	Baker	Quirce et al. (34)
Flour	Baker	Di Stefano et al. (16)
Alfa-amylase and wheat flour	Baker	Barranco et al. (2)
Storage mites	Baker	Pala et al. (29)
Low-molecular-weight agents		
Acrylates	Weather strips worker	Lemiere et al. (26)
Chloramine	Nurse	Krakowiak et al. (24)
Formaldehyde	Laboratory worker	Yacoub et al. (44)
Stainless steel	Welder	Yacoub et al. (44)
Methylene diphenyl isocyanate	Foundry worker	Di Stefano et al. (16)
Epoxy resin hardener	ND	Kobayashi (23)
Ammonium persulphate	Hairdresser	Pala et al. (28)

as a baker for 36 years. He suffered from non-productive chronic cough with occasional wheezing, but not dyspnoea, that worsened at work and subsided during holidays. A differential cell count in IS during a period of sick leave showed no eosinophils, whereas 8% eosinophils were found after SIC with lysozyme.

Flour

Di Stefano and co-workers (16) described a 41-year-old male baker, non-smoker, who had been exposed to flour for 10 years. In the previous 2 years he had developed a non-productive chronic cough without wheezing or dyspnoea. The cough worsened at work and waned during holidays. Sputum eosinophils percentage was 0% while asymptomatic and increased up to 54% after flour SIC.

Alfa-amylase and wheat flour

Barranco et al. (2) described a 51-year-old non-smoking woman who had been in charge of a bakery-patisserie for 14 years, with an 8-year history of persistent chronic cough and tenacious sputum, but no wheezing or dyspnoea. The patient developed dry cough during SICs with fungal α-amylase and wheat flour, but neither asthmatic reactions nor changes in methacholine responsiveness were observed 24 hours after SICs. The differential sputum cell count increased from less than 2% eosinophils to 33.3% 24 hours after SIC with α-amylase, and to 12.4% 24 hours after SIC with wheat flour. The patient was diagnosed with occupational NAEB due to sensitization to fungal α-amylase and wheat flour.

Storage mites

Our group described the first case of occupational NAEB due to storage mites in a 61-year-old ex-smoker atopical man employed as a baker since the age of 17, reporting 9 years later dry cough and throat hoarseness when baking or going into the flour storehouse. SIC with wheat flour with the occupational method (pouring the flour from one dish to another) elicited dry cough without any significant FEV_1 variation. Sputum eosinophils increased from 1.8 pre- to 15.2% post-SIC. The offending agent was identified by means of the basophil activation test (29).

LMW-agents

Acrylates

Lemiere et al. (26) reported a 50-year-old woman employed for 2 years in an enterprise that produced weather strips for vehicles. The job required her to use glue containing cyanoacrylate and methacrylate. Three months after starting the job she noticed shortness of breath, chest tightness, wheezing, and persistent dry cough, as well as nasal symptoms such as a runny, stuffy nose and sneezing when at work. SIC with glue showed IS increase in the eosinophil, metachromatic cell and neutrophil counts.

Chloramine

Krakowiak and co-workers (24) described a 61-year-old hospital nurse who developed a non-productive chronic cough without wheezing or dyspnoea ten years after starting work. She cleaned instruments with a chloramine-containing disinfectant throughout this period. No nasal, eye or skin symptoms at the workplace were reported. The eosinophil percentage in IS increased both 6h and 24h after SIC with chloramine (8% and 11% respectively) compared with baseline (1%).

Formaldehyde

Yacoub et al. (44) described a case of NAEB in a 38-year-old woman who worked in a laboratory for 10 years, examining biological samples and attending autopsies. Nine years after beginning this job she reported chronic cough with off-white expectoration and chest tightness which exacerbated during the night. On a control day sputum eosinophilia was assessed at 2.8%. On the following tow days, after exposure to evaporated formaldehyde for 30 and 120 minutes, IS eosinophilia increased to 4.2 and 22.3%, respectively, and a severe cough developed.

Stainless steel

Yacoub and co-workers (44) described the case of a 48-year-old man, employed for 12 years in an enterprise that produced metal parts. His job was to weld aluminium and mild steel and stainless steel. Nine years after starting the job, cough with reddish-brown expectoration, pharyngodynia, wheezing and mild dyspnoea appeared. SICs were performed in the laboratory and at the workplace. On two control days, sputum eosinophilia assessed 8 h after exposure was 13.5 and 13.2% respectively. Four days later, he welded stainless steel for 30 minutes and sputum eosinophilia increased to 50.8% by the end of the day.

Methylene diphenyl isocyanate

Di Stefano et al. (16) described the case of a 44-year-old man who had worked in a foundry for 8 years exposed to methylene diphenyl isocyanate (MDI). He had never had respiratory symptoms, but then developed a non-productive chronic cough without wheezing or dyspnoea. IS eosinophils were 0% when not exposed and 60% after SIC with MDI.

Ammonium persulphate

Our group described the first case of occupational NAEB due to ammonium persulphate in a 25-year-old woman working as a hairdresser since the age of 20 years and handling ammonium persulphate, who came under our observation for work-related rhinitis and cough. SIC with ammonium persulphate (27) elicited dry cough, without any significant change in FEV_1. Sputum induction was unsuccessful both before and after specific inhalation challenge. FeNO values significantly increased after specific inhalation challenge, suggesting a diagnosis of occupational NAEB due to ammonium persulphate (28).

Epoxy resin hardener

A report on NAEB due to epoxy resin hardener was found in the literature (23) but details are not available because the original article is in Japanese.

Cross-sectional survey

Mushroom spores

In a cross-sectional health survey conducted on 69 mushroom farm workers who cultivated *Hypsizigus marmoreus,* Tanaka et al. (41) found that 3 out of 42 subjects complaining of chronic cough at the workplace had NAEB.

Diagnosis

The most obvious reason for recognizing a patient with cough caused by NAEB is that identification of the disease and the offending agent may lead to environmental and personal preventive measures in order to prevent aggravation of the disease.

As with other causes of cough, details of the nature and timing of the cough are of limited help in establishing a diagnosis of NAEB. Therefore, the latter requires the assessment of lower airway inflammation after other causes of cough have been excluded by clinical, radiological, and physiological assessment (*i.e.*, spirometry and methacholine challenge test) (6). In addition, the diagnosis of occupational NAEB requires the demonstration of the link between the disease and workplace exposure (figure 1).

According to the most recent findings, the diagnostic criteria proposed by Quirce (32) can be detailed as follows:

- Clinical history of isolated persistent cough (lasting more than 3 weeks) present solely at work or that worsens at work and improving or disappearing after a consistent period off work.
- Sputum eosinophilia ≥3% either in spontaneous or induced sputum (IS) strictly correlated to workplace exposure. Increases in sputum eosinophils related to exposure to the offending agent should be firstly proved by IS performed during a period at work and off work, and finally confirmed by SIC. The best timing for the collection of IS with respect to exposure to occupational agents is probably 7-24 hours after

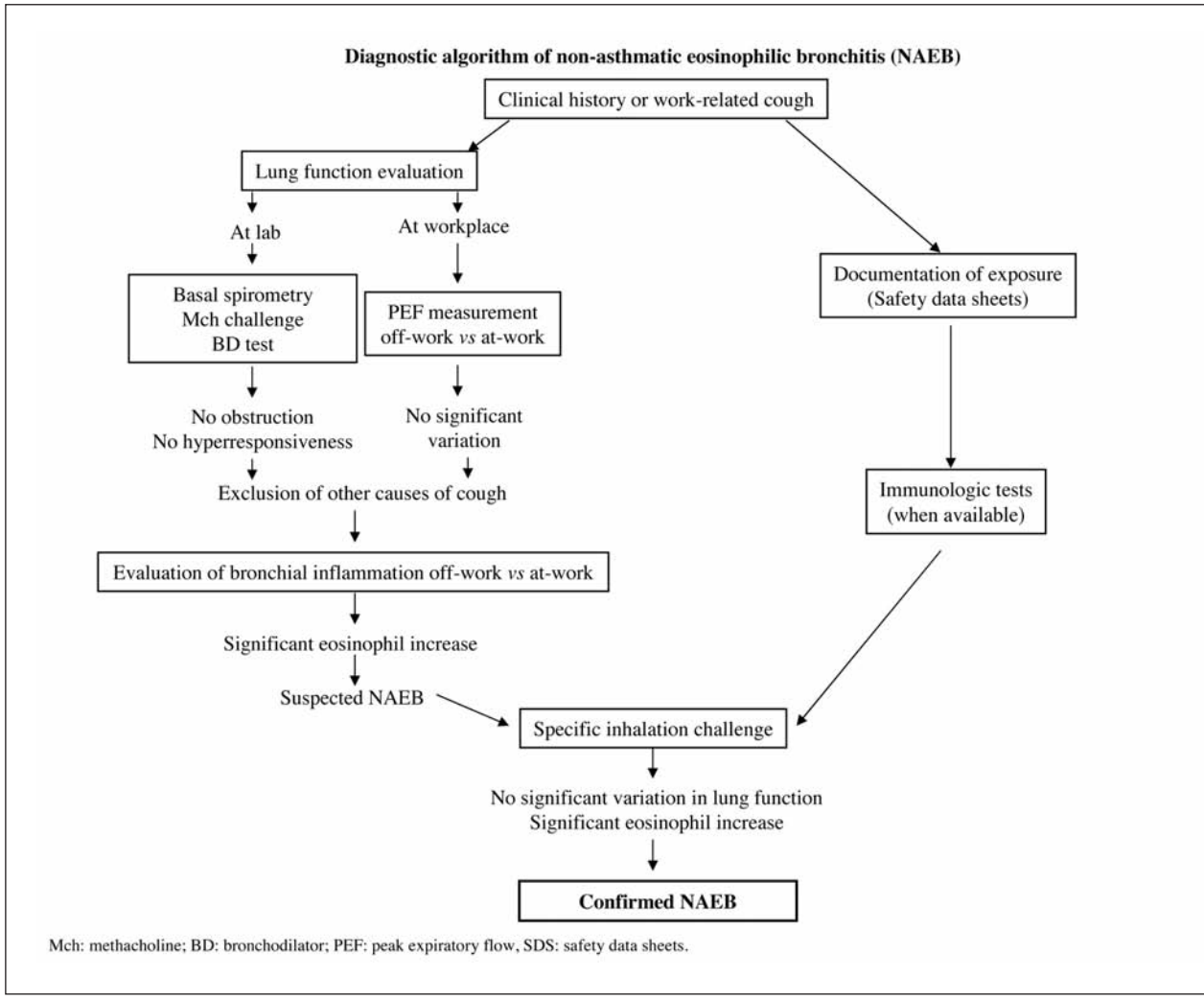

Figura 1 - Diagnostic algorithm of non-asthmatic eosinophilic bronchitis (NAEB)

exposure (34). Airway inflammation should ideally be measured by IS analysis (22,34). Measurement of fractional exhaled nitric oxide (FeNO) was proposed as an alternative to IS tests (15,28), but its role in the diagnosis of NAEB was not formally evaluated (34).

- Spirometric parameters within normal limits and not significantly affected by exposure to the offending agent (either at work or after SIC). Spirometry, bronchodilator test and serial peak expiratory flow measurement should be performed as indicated for diagnosis of OA.
- Absence of airway hyper-responsiveness to MCH challenge both at work and away from work. Recently, Singapuri et al. (40) demonstrated that patients with NAEB are not responsive to either direct or indirect bronchial challenges. Besides MCH challenge test, mannitol and AMP may be used to further confirm the diagnosis.
- Other causes of chronic cough ruled out.

A diagnosis of occupational NAEB requires that all the criteria be fulfilled and the offending agent identified by means of SPTs or sIgE, when available, and confirmed by SIC. The basophil activation test has recently been proposed as a new tool in the diagnosis of occupational NAEB (29), but its usefulness needs to be further confirmed.

Natural history

Few studies have examined the natural history of NAEB because of the lack of large case series, hence the prognosis of NAEB in terms of subsequent asthma, airway remodelling, and the development of fixed airflow obstruction is unknown. A 10-year follow-up evaluation of 12 patients with NAEB suggests that this condition is generally benign and self-limiting (21). Conversely, the results of another study on a larger series of patients seems to demonstrate that the condition is rarely self-limiting (4). Although airway remodelling is a feature of both asthma and NAEB, the consequent effect upon airway geometry is distinct, with airway narrowing observed only in asthma (38). In spite of this area of uncertainty, continued exposure might induce chronic inflammation and, consequently, aggravation of the disease in terms of chronic airway obstruction (7). Therefore, a benign prognosis may be linked to the elimination of the causes that elicited the disorder.

Management and treatment

When the onset appears to be related to an inhaled allergen, occupational exposure or an identifiable trigger, avoidance strategy is initially recommended for the management of NAEB (7, 15). When the offending agent has been identified, complete avoidance seems to be effective both for bronchial inflammation and symptoms (29).

Inhaled corticosteroids (ICS) is the main anti-inflammatory treatment proposed for NAEB. Patients improve symptomatically and have a significant fall in their sputum eosinophil count following treatment with ICS (11, 18).

There are no data currently available to guide the choice of which ICS should be used for the treatment of NAEB, at which dose, and for how long. The efficacy of inhaled corticosteroids remains to be determined in placebo-controlled randomized trials. Very occasionally, treatment with oral corticosteroids are required to control symptoms and eosinophilic inflammation (6). Although there may be thickened basement membrane and other changes to suggest airway remodelling (8), it remains unclear whether treatment for non-asthmatic eosinophilic bronchitis should be discontinued when symptoms resolve. The role of other potential therapeutic agents such as antihistamines and antileukotrienes needs to be fully explored (6).

Conclusions

The development of sputum induction has provided a safe non-invasive method for assessing airway inflammation. One of the most interesting early observations made using this method was the identification of a group of patients with sputum eosinophilia identical or comparable to that seen in asthma, but with normal airway function. The disease is probably underdiagnosed and an occupational origin has been demonstrated only in isolated cases, probably due to the rarity of the disease and the lack of systematic evaluation of bronchial inflammation. The latter could be due to IS analysis technical factors (*i.e.* time consuming technique requiring specific facilities available only in specialized centres). This restriction may be overcome by FeNO measurement, an easy to perform method to evaluate bronchial eosinophilic inflammation. Although at present usefulness of FeNO measurement in NAEB has been demonstrated in only one report (28), in the near future it could be included in the medical surveillance programme of workers exposed to airborne sensitizers. NAEB is an intriguing disease because its pathophysiological features challenge the conventional view of a direct relationship between eosinophilic airway inflammation and airway hyperresponsiveness, which is thought to be one of the hallmarks of asthma, and defies our knowledge of the true role of eosinophils in airway disorders. In view of the current knowledge on this condition and the development of techniques to evaluate bronchial inflammation, occupational NAEB cannot be neglected any more and has been rightly included in the spectrum of occupational respiratory disorders (3, 42, 43).

No potential conflict of interest relevant to this article was reported

References

1. Ayik SO, Basoglu OK, Erdinc M, et al: Eosinophilic bronchitis as a cause of chronic cough. Respir Med 2003; *97*: 695-701
2. Barranco P, Fernández-Nieto M, del Pozo V, et al: Nonasthmatic eosinophilic bronchitis in a baker caused by fungal alpha-amylase and wheat flour. J Investig Allergol Clin Immunol 2008; *18*: 494-495
3. Bernstein IL, Bernstein DI, Chan-Yeung M, Malo JL: Definition and classification of asthma in the workplace. In Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI (eds): *Asthma in the workplace.* 3rd ed. New York: Taylor & Francis, 2006: 1-7
4. Berry MA, Hargadon B, McKenna S, et al: Observational study of the natural history of eosinophilic bronchitis. Clin Exp Allergy 2005; *35*: 598-601
5. Berry MA, Parker D, Neale N, et al: Sputum and bronchial submucosal IL-13 expression in asthma and eosinophilic bronchitis. J Allergy Clin Immunol 2004; *114*: 1106-1109
6. Brightling CE: Chronic cough due to nonasthmatic eosinophilic bronchitis: ACCP evidence-based clinical practice guidelines. Chest 2006; *129* (suppl 1): 116-121
7. Brightling CE: Cough due to asthma and nonasthmatic eosinophilic bronchitis. Lung 2010; *188* (suppl 1): 13-7
8. Brightling CE, Bradding P, Symon FA, et al: Mast-cell infiltration of airway smooth muscle in asthma. N Engl J Med 2002; *346*: 1699-1705
9. Brightling CE, Symon FA, Birring SS, et al: Comparison of airway immunopathology of eosinophilic bronchitis and asthma. Thorax 2003; *58*: 528-532
10. Brightling CE, Ward R, Goh KL, et al: Eosinophilic bronchitis is an important cause of chronic cough. Am J Respir Crit Care Med 1999; *160*: 406-410
11. Brightling CE, Ward R, Wardlaw AJ, et al: Airway inflammation, airway responsiveness and cough before and after inhaled budesonide in patients with eosinophilic bronchitis. Eur Respir J 2000; *15*: 682-686
12. Brightling CE, Ward R, Woltmann G, et al: Induced sputum inflammatory mediator concentrations in eosinophilic bronchitis and asthma. Am J Respir Crit Care Med 2000; *162*: 878-882
13. Carney IK, Gibson PG, Murree-Allen K, et al: A systematic evaluation of mechanisms in chronic cough. Am J Respir Crit Care Med 1997; *156*: 211-216
14. Castano R, Gautrin D, Thériault G, et al: Occupational rhinitis in workers investigated for occupational asthma. Thorax 2009; *64*: 50-54
15. Desai D, Brightling C: Cough due to asthma, cough-variant asthma and non-asthmatic eosinophilic bronchitis. Otolaryngol Clin North Am 2010; *43*: 123-130
16. Di Stefano F, Di Giampaolo L, Verna N, et al: Occupational eosinophilic bronchitis in a foundry worker exposed to isocyanate and a baker exposed to flour. Thorax 2007; *62*: 368-370
17. Gibson PG, Dolovich J, Denburg J, et al: Chronic cough: eosinophilic bronchitis without asthma. Lancet 1989; *1*: 1346-1348
18. Gibson PG, Hargreave FE, Girgis-Gabardo A, et al: Chronic cough with eosinophilic bronchitis: examination for variable airflow obstruction and response to corticosteroid. Clin Exp Allergy 1995; *25*: 127-132
19. Gibson PG, Zlatic K, Scott J, et al: Chronic cough resembles asthma with IL-5 and granulocyte-macrophage colony-stimulating factor gene expression in bronchoalveolar cells. J Allergy Clin Immunol 1998; *101*: 320-326
20. Groneberg DA, Nowak D, Wussow A, et al: Chronic cough due to occupational factors. J Occup Med Toxicol 2006; *2*: 3
21. Hancox RJ, Leigh R, Kelly MM, et al: Eosinophilic bronchitis. Lancet 2001; *358*: 1104
22. Keatings VM, Evans DJ, O'Connor BJ, et al: Cellular profiles in asthmatic airways: a comparison of induced sputum, bronchial washings, and bronchoalveolar lavage fluid. Thorax 1997; *52*: 372-374
23. Kobayashi O: A case of eosinophilic bronchitis due to epoxy resin system hardener, methlenedomethylene tetrahydrophthalic anhydride. Arerugi 1994; *43* (5): 660-662
24. Krakowiak AM, Dudek W, Ruta U, et al: Occupational eosinophilic bronchitis without asthma due to chloramine exposure. Occup Med (Lond) 2005; *55*: 396-398
25. Lemiere C, Biagini RE, Zeiss CR: Immunological and inflammatory assessments. In Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI (eds): *Asthma in the workplace*. 3rd ed. New York: Taylor & Francis, 2006: 179-197
26. Lemière C, Efthimiadis A, Hargreave FE: Occupational eosinophilic bronchitis without asthma: an unknown occupational airway disease. J Allergy Clin Immunol 1997; *100*: 852-853
27. Moscato G, Pala G, Perfetti L, et al: Clinical and inflammatory features of occupational asthma caused by persulphate salts in comparison with asthma associated with occupational rhinitis. Allergy 2010; *65*: 784-790
28. Pala G, Pignatti P, Moscato G: The use of fractional exhaled nitric oxide in investigation of work-related cough in a hairdresser. Am J Ind Med 2011; *54*: 565-568
29. Pala G, Pignatti P, Perfetti L, et al: Usefulness of basophil activation test in diagnosis of occupational nonasthmatic eosinophilic bronchitis. Allergy 2010; *65*: 927-929

30. Park SW, Jangm HK, An MH, et al: Interleukin-13 and interleukin-5 in induced sputum of eosinophilic bronchitis: comparison with asthma. Chest 2005; *128*: 1921-1927
31. Pignatti P, Delmastro M, Perfetti L, et al: Is dithiothreitol (DTT) affecting cells and soluble mediators during sputum processing? A modified methodology to process sputum. J Allergy Clin Immunol 2002; *110*: 667-668
32. Quirce S: Eosinophilic bronchitis in the workplace. Curr Opin Allergy Clin Immunol 2004; *4*: 87-91
33. Quirce S, Fernández-Nieto M, de Miguel J, et al: Chronic cough due to latex-induced eosinophilic bronchitis. J Allergy Clin Immunol 2001; *108*: 143
34. Quirce S, Lemière C, de Blay F, et al: Noninvasive methods for assessment of airway inflammation in occupational settings. Allergy 2010; *65*: 445-458
35. Saha SK, Berry MA, Parker D, et al: Increased sputum and bronchial biopsy IL-13 expression in severe asthma. J Allergy Clin Immunol 2008; *121*: 685-691
36. Sastre B, Fernández-Nieto M, Mollá R, et al: Increased prostaglandin E2 levels in the airway of patients with eosinophilic bronchitis. Allergy 2008; *63*: 58-66
37. Siddiqui S, Cruse G, McKenna S, et al: IL-13 expression by blood T cells and not eosinophils is increased in asthma compared to non-asthmatic eosinophilic bronchitis. BMC Pulm Med 2009; *14*: 34
38. Siddiqui S, Gupta S, Cruse G, et al: Airway wall geometry in asthma and nonasthmatic eosinophilic bronchitis. Allergy 2009; *64*: 951-958
39. Siddiqui S, Mistry V, Doe C, et al: Airway hyperresponsiveness is dissociated from airway wall structural remodelling. J Allergy Clin Immunol 2008; *122*: 335-341
40. Singapuri A, McKenna S, Brightling CE, et al: Mannitol and AMP do not induce bronchoconstriction in eosinophilic bronchitis: further evidence for dissociation between airway inflammation and bronchial hyperresponsiveness. Respirology 2010; *15*: 510-515
41. Tanaka H, Saikai T, Sugawara H, et al: Workplace-related chronic cough on a mushroom farm. Chest 2002; *122*: 1080-1085
42. Tarlo SM, Malo JL: Third Jack Pepys Workshop on Asthma in the Workplace Participants. An official ATS proceedings: asthma in the workplace: the Third Jack Pepys Workshop on Asthma in the Workplace: answered and unanswered questions. Proc Am Thorac Soc 2009; *1*: 339-349
43. Vandenplas O, Malo JL: Definitions and types of work-related asthma: a nosological approach. Eur Respir J 2003; *21*: 706-712
44. Yacoub MR, Malo JL, Labrecque M, et al: Occupational eosinophilic bronchitis. Allergy 2005; *60*: 1542-1544