

PostScript

LETTERS TO THE EDITOR

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COPD, restrictive syndrome and inflammation

In a recent issue of *Thorax* Gan *et al*¹ published a systematic review and meta-analysis of 14 reports which confirmed the strong association between COPD and biological markers of systemic inflammation. In six reports COPD was diagnosed by the presence of a ratio of forced expiratory volume in 1 second to forced vital capacity (FEV₁/FVC ratio) lower than 0.7. However, in the remaining eight studies this measure was not available, and the authors assumed that all participants in the lowest quartile of FEV₁% (and, in one study,² of FVC%) had a diagnosis of COPD. In these cases the corresponding highest quartile group served as control. Since a COPD diagnosis based on a decreased FEV₁/FVC ratio was lacking in eight reports, the possibility cannot be excluded that a certain number of patients included in the meta-analysis did not have COPD but, rather, a restrictive ventilatory defect. This could be particularly true for participants in the study by Engstrom *et al*² who were characterised only by a low FVC.

According to the current GOLD guidelines,³ only an FEV₁/FVC ratio lower than 0.7 indicates airflow obstruction, thus allowing a COPD diagnosis. Indeed, in the absence of particular pulmonary diseases, many subjects show a homogenous decrease in all dynamic lung volumes (FEV₁, FVC, PEF) without any change in the FEV₁/FVC ratio, and are thus considered to have "impaired lung function". The occurrence of respiratory symptoms,⁴ systemic inflammation,² and the increased risk of cardiovascular disease⁵ are the only features that subjects with restrictive disease share with COPD. In fact, whereas COPD is characterised by a decrease in body mass index and blood lipids, subjects with restrictive disease often have abdominal obesity, insulin resistance, and other metabolic risk factors.⁶

Although we believe that most of the included patients were affected by COPD, the possible inclusion of patients with restrictive lung disease may have altered the statistical conclusions of the meta-analysis.

In addition, the decision to select patients in the lowest quartile of FEV₁ and FVC prevented the authors from confirming the absence of inflammation in mild COPD

(GOLD stage I and II), a finding previously reported by the same group in a study not included in this meta-analysis.⁷

Because patients with restrictive lung disease and those with COPD have different features, the generic term "impaired lung function" should not be used. Future studies of the role of inflammation and other cardiovascular risk conditions in patients with respiratory disease, and those investigating the outcome in these subjects, should clearly distinguish between these two groups of patients.

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Authors' reply

We wish to thank Dr Fimognari and colleagues for highlighting the difficult issue of defining chronic obstructive pulmonary disease (COPD). In most circumstances a spirometric cut off is used to define COPD, but there is no uniform consensus on what that should be and different expert panels have promulgated different spirometric cut off values.¹⁻⁴ COPD is a disease characterised by lung inflammation and patient symptoms (most notably dyspnoea). Studies have shown that the relationship between airway inflammation and patient symptoms with forced expiratory volume in 1 second (FEV₁) is a continuum and is not threshold dependent.^{5,6} Thus, any attempts to impose FEV₁ (or the ratio of FEV₁ to forced vital capacity (FVC)) limits in defining COPD are bound to be arbitrary and contentious. Rather than

relying on arbitrary cut off values for large population based studies, it is reasonable (and useful) to compare the outcome of interest—in this case, systemic inflammation—between extremes of FEV₁ (that is, worst FEV₁ quartile to best quartile group). This method avoids imposing any arbitrary constraints in the definition of COPD and allows maximal utilisation of the data points. However, a potential limitation of this approach is the possibility of diagnostic misclassification between restrictive and obstructive lung diseases. To specifically address this concern, we excluded population based studies in which a FEV₁/FVC ratio was not used to define COPD⁷⁻⁹ and reanalysed the C-reactive protein (CRP) and fibrinogen data. Even after the exclusion of these studies, the standardised mean difference in the CRP level between COPD and control subjects was 0.68 units (95% confidence interval (CI) 0.38 to 0.98) or 4.85 mg/l (95% CI 1.92 to 7.78). For the fibrinogen data, the standardised mean difference between COPD and control subjects was 0.48 units (95% CI 0.43 to 0.54) or 0.42 g/l (95% CI 0.00 to 0.84). These results indicate that the possible contamination of individuals with restrictive defect in the groups with low FEV₁ or FVC did not influence the overall findings. Finally, we did not include data from one of our previous reports¹⁰ because the study sample was taken from the same source population as the study by Mannino and colleagues¹¹ which was included in the meta-analysis.

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TB screening and anti-TNF α treatment

Reactivation of tuberculosis (TB) is a major concern during treatment with TNF inhibitors.¹ Different guidelines to detect active and latent TB have been recommended in various countries before starting treatment with these drugs. There is evidence that their application has led to a significant reduction in the number of cases of TB,² but we do not know which is the most cost effective strategy.

In our department 69 consecutive patients with rheumatoid arthritis (n = 53), ankylosing spondylitis (n = 10), and psoriatic arthritis (n = 6) considered for treatment with TNF inhibitors have recently been screened for TB infection according to the Italian guidelines. All underwent a careful history, tuberculin skin testing by intradermal injection of 0.2 ml 10 TU PPD (Mantoux method), and chest radiography. In order to enhance the sensitivity of tuberculin testing we had stopped steroid treatment in all patients at least 1 week before performing the test. Patients were considered to be affected by latent TB if they had any of the following conditions: (1) unequivocal history of previous TB; (2) positive tuberculin reaction (at least 5 mm skin induration at 72 hours); (3) radiographic lesions consistent with old TB (calcified nodular lesions, apical fibrosis, pleural scarring). According to our guidelines, patients with latent TB undergoing treatment with TNF inhibitors receive preventive chemotherapy. Our patients were predominantly women (63.8%) with a mean age of 55.8 years (range 21–81). We found a history of previous TB in 2.9% of patients, tuberculin positivity in 8.7%, and radiographic lesions consistent with latent TB in 20.3%. Globally, a diagnosis of latent TB was made in 24.6% of our patients, six of whom underwent treatment with TNF inhibitors (notably, five of the six had a negative tuberculin test). We started preventive chemotherapy with isoniazid in all patients but this drug was discontinued in four because of liver toxicity.

Our data suggest that tuberculin skin testing is not sufficiently sensitive to detect latent TB in patients with rheumatoid arthritis and other spondyloarthropathies or in those with inflammatory bowel diseases.³ In these patients chest radiography is essential if we do not want to miss a significant proportion of cases. The Italian guidelines for TB screening before starting treatment with TNF inhibitors allow recognition of these cases,

increasing the indications for preventive chemotherapy. However, liver toxicity caused by isoniazid may be enhanced in these patients, probably due to concomitant treatment with other drugs such as methotrexate and NSAIDs. This suggests that the risk of chemoprophylaxis should be compared with the chance of contracting TB in the individual patient, and that a cost effectiveness evaluation of the different strategies used to minimise the risk of TB reactivation during treatment with TNF inhibitors is indicated.

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Risedronate induced BOOP complicated with sarcoidosis

Bisphosphonates are synthetic compounds that are taken up preferentially by skeletal tissue and suppress osteoclast mediated bone resorption. They are being used increasingly in the treatment of osteoporosis.¹ Bronchoconstriction caused by bisphosphonates has been described² but drug induced pneumonitis has not previously been reported.³ This is the first report of interstitial pneumonia induced by the bisphosphonate risedronate.

A woman developed an intramuscular mass in her right arm at the age of 51 years. Sarcoidosis was diagnosed by non-necrotising epithelioid granulomas in the resected specimen of the mass, bilateral hilar lymphadenopathy on the chest radiograph, a negative reaction to tuberculin test, and an increase in the serum angiotensin converting enzyme (ACE) level to 27.9 U/ml. She had pain in her right arm due to the mass and was treated with prednisolone for 10 years. The mass disappeared and the ACE level fell to 9.6 U/ml.

At the age of 66 years treatment was started with risedronate for osteoporosis. Two months later she developed a dry cough, high fever, and bilateral infiltrative shadows were seen on the chest radiograph (fig 1A). A high resolution CT scan showed multiple consolidation and ground glass opacity with interlobular and intralobular interstitial thickening (fig 1B). Mediastinal lymph nodes measuring about 1 cm and small amounts of bilateral pleural effusion were visible on the CT scan. Chest auscultation showed no crackles and neither the superficial lymph nodes nor the intramuscular mass lesions were palpable. Laboratory examination showed white blood cell (WBC) count of 9100/ μ l, C-reactive protein (CRP) 7.31 mg/dl, lactate dehydrogenase (LDH) 201 U/ml, ACE

5.3 U/ml, and lysozyme 8.9 U/ml. Total cell count of the bronchoalveolar lavage (BAL) fluid performed on left B⁴ was 4.18 \times 10⁵/ml with 43.4% macrophages, 15.8% neutrophils, 24.2% lymphocytes, and 16.0% eosinophils. The CD4+/CD8+ ratio of lymphocytes in the BAL fluid was 1.37. No pathogenic organisms were detected in the BAL fluid, and trans-bronchial lung biopsy specimens revealed no granulomas but cellular alveolitis with intraluminal polypoid organisation consistent with bronchiolitis obliterans organising pneumonia (BOOP). These findings ruled out reactivation of sarcoidosis.

Treatment with several antibiotics did not improve her symptoms and laboratory findings, so all her drugs (risedronate, pravastatin, neurotrophin, menatetrenone, and sairei-to) were stopped because drug induced pneumonitis was suspected. Her high fever began to resolve about 5 days after stopping the drugs and her symptoms and the abnormal shadows on the chest radiograph disappeared 2 weeks later. The WBC and CRP level were also normalised. A drug lymphocyte stimulation test (DLST) on her peripheral lymphocytes gave a positive reaction only to risedronate with a stimulation index of 265%. There was a negative reaction to the other four drugs, all of which had been administered to her for at least 4 years. She was therefore diagnosed with risedronate induced pneumonitis.

Amino-bisphosphonates including alendronate, pamidronate, and risedronate are reported to induce pro-inflammatory cytokines from macrophages in vitro and in vivo

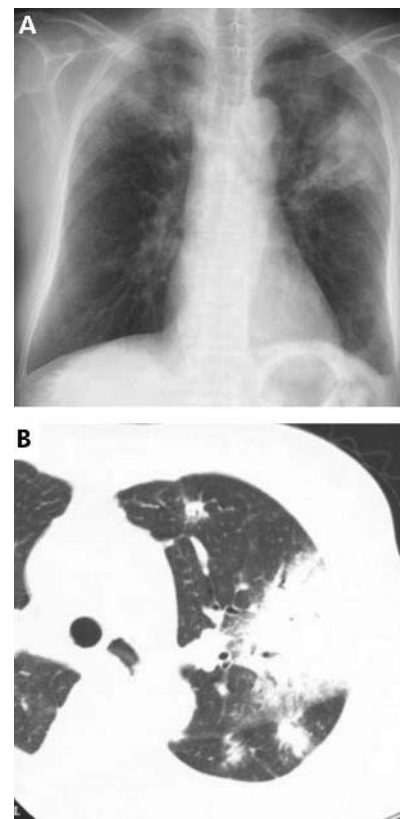


Figure 1 (A) Chest radiograph showing infiltrative shadows. (B) High resolution CT scan of the chest showing multiple consolidation and ground glass opacity with interlobular and intralobular interstitial thickening.

and to cause transient pyrexia, a flu-like syndrome, and serological changes resembling a typical acute phase reaction in some cases.⁴ They are also reported to induce anterior uveitis through these reactions or specific immunological responses.⁵ However, pneumonitis associated with amino-bisphosphonates has not been previously reported. In this case the specific immunological reaction to risedronate by DLST suggested that her lung disease was caused by the drug rather than by non-specific release of pro-inflammatory cytokines.

Osteoporosis is a common disease and bisphosphonates will be prescribed frequently. The possibility of pneumonitis caused by risedronate and other bisphosphonates needs to be kept in mind.

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Bacterial denitrification, nitric oxide and airway pH in CF

The recent findings of Ojoo *et al*¹ are of considerable interest. However, one confounding factor that appears to have been overlooked in recent studies of airway pH and exhaled breath nitric oxide (eNO) levels in cystic fibrosis (CF) is that of bacterial respiration. *Pseudomonas aeruginosa* adopts an anaerobic and biofilm mode of existence within the CF lung and, under such environmental conditions, it uses NO rather than oxygen as an electron donor to generate energy via oxidative phosphorylation. This bacterial denitrification results in the stepwise reduction of NO to nitrite (NO₂), nitrate (NO₃), and ultimately ammonium.^{2–3} It is surprising that such an important metabolic process has been ignored as the high energy requirements of large bacterial loads in the CF lung imply substantial consumption of NO. This could explain both the low levels of measured eNO and high (NO₂)/(NO₃) content described in the sputum and exhaled breath condensates of patients with CF. The products of denitrification are likely to alter the chemical milieu substantially, including the pH of the airway. Further research is needed to examine how the metabolic activity of bacteria and the host inflammatory response interact

to change the chemical composition of the lung microenvironment in CF.

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Authors' reply

We thank Dr Reid for his interest in our paper.¹ Bacterial denitrification involves the stepwise reduction of oxides of nitrogen to support oxidative phosphorylation.² Gaston *et al*³ have previously proposed that consumption of nitric oxide (NO) during this process might be one factor contributing to the low fractional exhaled NO concentration (F_{ENO}) seen in cystic fibrosis (CF). It is clearly not the only mechanism, however, as decreased F_{ENO} levels have been reported in infants with newly diagnosed CF,⁴ and reduced NO generation is also described in cystic fibrosis transmembrane conductance regulator (CFTR) deficient mice.⁵ Bacterial denitrification would be expected also to deplete nitrate (NO₃⁻) and nitrite (NO₂⁻) levels in the local milieu and to increase its pH.

In our study 14 of the 18 subjects with stable CF were chronically colonised with *Pseudomonas aeruginosa*. Interestingly, F_{ENO} levels were indeed significantly lower in CF subjects with *P aeruginosa* than in those without (2 (1) v 7 (5) ppb; p = 0.015). The median NO₂⁻ and NO₂⁻/NO₃⁻ levels in exhaled breath condensate (EBC) were also lower in subjects with *P aeruginosa*, although this difference did not reach statistical significance. Irrespective of the presence of the organism, values for both NO₂⁻ and NO₂⁻/NO₃⁻ were substantially higher in CF subjects than in healthy controls. There was little difference in the median pH of the EBC between CF subjects with and without *P aeruginosa*.

These further analyses provide support for the suggestion that denitrification by *P aeruginosa* may modulate the nitrogen redox balance in CF airways. They are consistent with the findings of Gaston *et al*³ who described NO consumption and ammonium (NH₄⁺) generation by *P aeruginosa* in vitro and also a reduction in NH₄⁺ levels in the sputum of CF subjects after antipseudomonal treatment. Further comparisons involving larger numbers of CF subjects with and without *P aeruginosa*, and investigation of the relative impact of antimicrobial therapies in the two groups, may help to define the extent to which this mechanism operates in CF airways in vivo. Its relevance to airway pathophysiology, however, will be more difficult to determine.

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Exhaled NO in diffuse alveolar haemorrhage

The syndrome of diffuse alveolar haemorrhage (DAH) is associated with a wide variety of diseases. Haemoptysis, falling haemoglobin, and air space opacities on the chest radiograph constitute a triad of features suggestive of DAH which should be confirmed by bronchoalveolar lavage (BAL).¹ However, haemoptysis can be absent in up to one third of patients. A sensitive marker of DAH is a sequential increase in the carbon monoxide lung transfer factor (Tlco). This results from the increased availability of haemoglobin within the alveolar compartment which avidly binds carbon monoxide.² Although informative, the Tlco often cannot be measured in patients with DAH as they might be too ill. Nitric oxide (NO) combines with haemoglobin much faster than carbon monoxide and is continuously produced in the respiratory tract. Exhaled NO can be measured either online or offline even in acutely ill patients by collection of exhalate in a bag for subsequent analysis.³ We reasoned that DAH could be associated with low levels of exhaled NO because of the increased availability of haemoglobin within the alveolar compartment binding NO.

A 52 year old non-smoking man with a history of allergic rhinitis and asthma was admitted with increasing dyspnoea. His asthma had been controlled by maintenance inhalation of salmeterol and fluticasone. In the previous 3 weeks the patient had experienced painful paraesthesias. On admission he was in mild respiratory distress with a peak expiratory flow rate of 415 l/min (92% of his personal best value), arterial oxygen tension (Pao₂) 8.6 kPa (65 mm Hg), haemoglobin 11 g/dl, and WBC 23 000 (eosinophils 23%). Exhaled air was collected in a sample bag according to American Thoracic Society recommendations (inspiratory air NO concentration <5 ppb, expiratory flow rate 350 ml/s)³ and NO was measured within 2 hours of collection using a chemiluminescent analyser (NIOX, Aerocrine, Solna, Sweden). The initial level of exhaled NO was 4 ppb (normal reference value in our laboratory is 12 (2) ppb). Twelve hours later the haemoglobin fell to 9.1 g/dl, Pao₂ was 7.2 kPa (54 mm Hg), and confluent air space opacities were apparent on the chest



Figure 1 Chest radiograph showing bilateral air space opacities at a time when a very low level of NO was measured in the exhaled air.

radiograph (fig 1). The exhaled NO level had fallen to 2 ppb and BAL confirmed the diagnosis of DAH and excluded infection. Antineutrophil cytoplasm antibodies were reported to be present with a high titre of antibodies against myeloperoxidase. Sensory motor mononeuritis multiplex was diagnosed by electromyographic and nerve conduction studies. The patient fulfilled the criteria for the diagnosis of Churg-Strauss syndrome (CSS) and was treated with intravenous pulse methylprednisolone 1 g for 3 days followed by oral prednisone 1 mg/kg and cyclophosphamide 2 mg/kg/day. His clinical condition and oxygenation rapidly improved, together with progressive clearing of the chest radiograph. Exhaled NO levels measured 2, 5 and 8 days after the diagnostic BAL rose to 5, 9 and 15 ppb, respectively.

CSS is an uncommon systemic vasculitis which involves the small blood vessels of the lungs, peripheral nerves, skin and, less frequently, the heart and gastrointestinal tract. The most frequently encountered chest radiographic pattern in CSS is ill defined infiltrates, often peripheral, which may simulate eosinophilic pneumonia.⁴ Alveolar haemorrhage occurs infrequently in CSS, while it has been reported in as many as one third of patients with microscopic polyangiitis. When a diagnosis of DAH is being considered, this case shows the potential diagnostic aid of measuring exhaled NO. The sequential measurements of exhaled NO showed a progressive increase, starting from a very low value, which correlated well with the clinical and radiographic improvement of the patient. It is interesting

that, in acute pneumonia (which should be considered in the differential diagnosis), exhaled NO levels have been reported to be high, at least in the one published case series.⁵

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NOTICES

Pharmacology of Asthma and COPD: 21-24 November 2005

This course will be held at Imperial College London at the National Heart and Lung Institute, in collaboration with Royal Brompton Hospital, Dovehouse Street, London SW3 6LY, UK.

This course is suitable for physicians or scientists with an interest in pharmacology and therapeutics of asthma and COPD (*Course Organiser*: Professor Peter Barnes).

Enquiries should be sent to: Postgraduate Education Centre, National Heart & Lung Institute, Imperial College London, Guy Scadding Building, Royal Brompton Campus, Dovehouse Street, London SW3 6LY. Tel: 020 7351 8172. Fax: 020 7351 8246. Email: shortcourses.nhli@imperial.ac.uk.

Epidemiology and Health Care Practice

The IEA-EEF European Congress of Epidemiology "Epidemiology and Health Care Practice" will be held in Utrecht, The Netherlands, from 28 June to 1 July 2006. The Congress is organised by epidemiologists from Utrecht University in collaboration with the Netherlands Epidemiology Society and will encompass a broad range of themes from the fields of epidemiology, public health and research in health care. For further information visit the website (www.euroepi2006.org) or email euroepi2006@fbu.uu.nl.

The Dr HM (Bill) Foreman Memorial Fund

The TRUSTEES of the above fund invite applications for grants relating to study in Respiratory Disease, and allied fields (for example, microbiology, histopathology, radiology, biochemistry, and molecular biology).

Limited funds are available for registered medical practitioners to assist in travelling to countries other than their own to study Respiratory Disease, and also support for clinical research abroad.

Intending applicants should write for further details to: Dr Brian H Davies, Llandough Hospital, Penarth, Vale of Glamorgan, CF64 2XX.

CORRECTION

EXHALED BREATH CONDENSATE IN CHRONIC COUGH

In the March issue of *Thorax* the letter entitled "Exhaled breath condensate in chronic cough" by A Morice, C F Everett, and S A Mulrennan which appeared on page 259 was inadvertently printed also on page 257 under the heading "EBC pH and chronic cough". The publishers apologise for this error.