

# PostScript

## LETTERS TO THE EDITOR

### Is there an association between impaired pulmonary function and mortality in never smokers?

I read with great interest the article by Mannino *et al*<sup>1</sup> on the association between impaired pulmonary function and mortality, and wish to comment on two statements in the paper.

Firstly, the authors report that "an interesting finding in (their) analysis was that, in never smokers, moderate or severe COPD did not have a significantly increased mortality risk". In never smokers with severe COPD the point estimate for the hazard ratio forming the basis of this statement is 1.3 with 95% confidence intervals ranging from 0.7 to 3.1. However, these confidence intervals overlap with the point estimate of the hazard ratios in current smokers with severe COPD. There were only 92 participants with severe COPD in the entire sample of the population, hence the wide confidence intervals. The estimates are similar in those with moderate COPD. Furthermore, this trend was also evident in patients with mild COPD who had never smoked. In fact, in the latter group the point estimates were identical in current smokers and never smokers. The authors should therefore be cautious in concluding that never smokers with COPD do not have an increased risk of mortality. An analysis of continuous pulmonary function data in relation to mortality in never smokers independent of the GOLD classification or in all patients with COPD may result in statistically significant results. How would one interpret such a finding? The analysis in never smokers should be seen in the context of other studies reporting increased mortality risks in never smokers,<sup>2</sup> as they may be due to small sample size in spite of the overall large sample size in NHANES I. The authors' statement could be misinterpreted to suggest that never smokers would not require screening, a question that is not yet resolved.

Secondly, our study did report both FEV<sub>1</sub>% in quintiles as well as continuous variables.<sup>3</sup>

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### Toll-like receptor (TLR) 4 polymorphisms and COPD

Neutrophil and monocyte activation contribute to the pathology of chronic obstructive pulmonary disease (COPD). We hypothesised that a known polymorphism in a key lipopolysaccharide (LPS) response gene might reduce the severity of COPD through a decreased cellular response to activators inhaled in cigarette smoke. TLR4 is the protein enabling signalling to bacterial LPS and perhaps to endogenous mediators of inflammation, and is an important regulator of leucocyte function.<sup>1</sup> Functional polymorphisms in TLR4 have been described and their roles investigated in a number of diseases. Most studies have focused on the Asp299Gly polymorphism, with the rare allele (Gly299) causing LPS hyporesponsiveness.<sup>2</sup> In a study of more than 800 subjects the presence of the TLR4 polymorphism was associated with a reduced risk of atherosclerosis.<sup>3</sup> Smaller studies have potentially associated TLR4 polymorphisms with increased risk of sepsis<sup>4</sup> but, in a large study of patients with meningococcal disease, Asp299Gly was not associated with either altered risks of, or outcomes following, meningitis;<sup>5</sup> although a recent study has suggested that rarer polymorphisms in TLR4 may be important in this disease.<sup>6</sup>

We screened a population of smokers recruited on the basis of age >40 and a smoking history of at least 10 pack years for the presence of the TLR4 polymorphism by established techniques in our group.<sup>5</sup> Data were available on 289 subjects, of which 260 were Asp299 homozygotes and 29 heterozygotes. No Gly299 homozygotes were detected (these data correlate closely with the known frequency of the polymorphism in our region<sup>2</sup>). The presence of the TLR4 polymorphism did not have any significant impact on lung function (measured as forced expiratory volume in 1 second (FEV<sub>1</sub>) before and after bronchodilator challenge).

These data do not exclude the possibility that the well characterised and relatively common Asp299Gly TLR4 polymorphism might have a small effect on the severity of COPD. To examine fully the role of this TLR4 polymorphism, large populations (>1000)

will be required to give adequate power to exclude small effects on FEV<sub>1</sub> or reversibility. However, the current study shows that this polymorphism is unlikely to have a major impact on the severity of COPD at the population level.

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### British guidelines on the management of asthma

As a nurse consultant in respiratory diseases, I am writing to express my concern in relation to the lack of guidance in the section on patient education and self-management in the recently published BTS/SIGN guideline on the management of asthma<sup>1</sup>. Although I fully support the importance of patient education as a key component to effective asthma management, I do have unease around the issue of inhaled steroids. I appreciate that doubling the dose of an inhaled steroid at the time of an exacerbation is of unproven value; however, anecdotally, I

think we can all bring patients to mind where this has happened and their asthma symptoms have settled. I now feel slightly bewildered, like many of my nurse colleagues, as to the advice patients should be given. It appears that the only options available during an exacerbation are to increase the use of bronchodilator therapy and, if this fails, to seek medical help or commence a course of prednisolone. The latter option concerns me as this may result in an increase in prednisolone usage, some of which may be unnecessary.

The lack of clarity on the pharmacological management during an exacerbation may result in groups of professionals coming together to write their own guidance, which could potentially create disparity of treatment interventions and standards of care. The National Asthma Campaign personal diary and action plan, which is promoted by the new guidelines, could be interpreted as suggesting a change in the inhaled steroid dosage during an exacerbation.

I appreciate the hard work and dedication of the committee involved in reviewing the literature before these new asthma guidelines were produced. However, do you envisage any further work being undertaken on the asthma action plan in relation to pharmacological management during an exacerbation?

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## Authors' reply

We are grateful to Karen Clancy for raising an issue which has emerged in discussion at numerous meetings on the new asthma guidelines.

The BTS/SIGN guideline on the management of asthma<sup>1</sup> strongly advocates the use of asthma action plans because they have been shown to improve several important outcome measures. Most such plans advise patients to double their usual dose of inhaled corticosteroid for a few days to cover non-severe exacerbations of their asthma. We therefore looked for evidence on the efficacy of this specific manoeuvre, but could not find any. This is potentially confusing. Asthma action plans work, but there is no evidence to support one of their key features.

It is important to emphasise exactly what is stated in the asthma guideline. We do not say that doubling the dose of inhaled corticosteroid does not work, but we do say that the value of this intervention is unproven. We do not recommend amendment of existing plans until there is a proven alternative. It may be useful to know precisely why asthma action plans do work, and further research here would be interesting. It is possible that, in patients who do not regularly take their full daily dose of inhaled steroid, "doubling" their prescribed dose improves compliance, at least temporarily.

In the meantime we would advise that health professionals continue to use asthma

action plans which have been shown to be effective and with which they are familiar.

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## Reference

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## Peak flow meters still useful but require consistency rather than accuracy

I read with interest the editorial by Dr Brusasco on the usefulness of peak expiratory flow measurements<sup>1</sup> in which he suggests that they may become obsolete. As a pioneer of the use of regular peak flow measurements in hospital patients in the 1970s,<sup>2,3</sup> it might seem natural that I would be reluctant to see them go, but I do think I can rationally defend their place for two purposes—one dating from the start and the other from the end of my career.

The characteristic of asthma is variable airway obstruction. Despite the potential difficulties, variation in peak flow is of value in patients in whom asthma has been diagnosed as an adjunct to establishing the pattern of disease in the contexts of causation and management. Much of Dr Brusasco's argument is dichotomous, which is inappropriate in developing an overall strategy when there are limitations to all approaches—for example, under-perception and over-perception of symptoms. Cheating does occur, but blinded readings may be used to obtain useful results. Symptoms may precede deterioration in peak flow but, in practice, a relevantly lower reading on the second attempt is one of the best early indications of onset of a deterioration in a consistent performer. Guidelines suggest that serial recordings may have a place in the diagnosis of occupational asthma<sup>4</sup>—for example, in aluminium workers.<sup>5</sup> We have shown that, despite the difficulties relating to the patient's best reading, there is an association between peak flow and symptoms,<sup>6</sup> and overall mortality independent of and in addition to spirometric measurements.<sup>7</sup>

The second use of peak flow is as a useful check of quality in the diagnosis of minimal COPD when measured at the same time as and by the same instrument as forced expiratory volume in 1 second (FEV<sub>1</sub>). A normal peak flow should be of the same order as FEV<sub>1</sub> and, in subjects with mild COPD, the geometry of the curve demands that peak flow is less affected than FEV<sub>1</sub>.

In the first case, accuracy of calibration is irrelevant as the absolute value of peak flow is not used in the assessment. Consistency is vital and that is achieved by the simple instruments. In the second case, again it is not the absolute value that matters but consistency against the definitive measurement, FEV<sub>1</sub>. Provided that it is accepted that the absolute value of peak flow rarely has any value, measurement of peak flow remains very useful in these two particular circumstances and it follows that, when restricted to these uses, elaborate calibration of the absolute value of peak flow is unnecessary.

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## Author's reply

The letter from Dr Connolly gives me the opportunity to clarify some points not specifically addressed in my editorial<sup>1</sup> leading the paper by Miller *et al*<sup>2</sup> on the assessment of portable peak flow meters.

The first argument raised by Dr Connolly in defence of peak expiratory flow (PEF) measurement in asthma is that it may give additional information on the pattern of disease in patients in whom the asthma is already diagnosed. I respect this opinion, which was the basis for proposing the use of PEF for asthma monitoring and management, but this is exactly what has not received experimental support by controlled studies in two decades.<sup>3</sup> Dr Connolly also argues that PEF measurements may be useful in the diagnosis of occupational asthma and that cheating can be detected by blinded recording. I am aware that electronic recording may help to identify fabricated or wrongly recorded data,<sup>4</sup> but this would require more expensive devices and it is not known whether or not it increases adherence by itself. Furthermore, a smart cheater asking for compensation may easily realise that blows started from submaximal lung inflation will result in low PEF values, and I do not see how this can be detected even electronically in unsupervised measurements without recordings of forced vital capacity. Apart from these considerations, the assumption that accurate validation of flow meters is unnecessary for monitoring purposes is patently wrong for simple physical reasons. Even if the ability to measure true values in serial measurements is not crucial, the assessment of the dynamic response of the flow meter needs to be accurate. What Dr Connolly calls consistency is, according to the International Standards Organization,<sup>5</sup> a combination of repeatability and reproducibility. Testing of repeatability is based on percentage and absolute differences between sequential measurements of known flows generated by suitable waveforms. Therefore, accuracy is necessary. In this context, it must be remembered that an inadequate dynamic response of a flow meter may affect



measurements depending on the frequency content of the input signal, thus making any comparison of serial measurements impossible. Reproducibility is the ability to measure the same flow with different devices. Accuracy of measurements is therefore necessary if a given patient does not use the same peak flow meter for his/her whole life, which is not unlikely to be the case.

The second argument put forward by Dr Connolly is that comparison of PEF and FEV<sub>1</sub> may be useful to confirm the diagnosis of minimal COPD, but no reference is given. I do not question the usefulness of looking at PEF on flow-volume curves to evaluate the quality of manoeuvres (my editorial was on the use of peak flow meters and not on spirometry) but, even in this case, accurate assessment of the dynamic response of the measuring device is imperative. If the system does not measure PEF and flows at lower lung volumes with the same accuracy, any inference from the shape of the flow-volume curve or derived parameters would be wrong and totally useless.

Finally, although Dr Connolly asserts that it is accepted that absolute values of PEF are rarely useful, the most recent guidelines on asthma management<sup>6</sup> maintain that the severity of the disease can be classified based on PEF as percentage predicted. I agree that this may be inadequate, but we should acknowledge that a patient with PEF constantly below 200 l/min should be approached differently from a patient with PEF constantly above 500 l/min, even if the percentage variability of serial measurements is the same. As pointed out by Miller *et al.*,<sup>2</sup> an underdamped flow meter would give readings much greater than the true ones.

In conclusion, an accurate test of the dynamic characteristics of peak flow meters is imperative if their use is to be recommended. Even so, the usefulness of PEF measurements in asthma may be limited for reasons not related to instrument accuracy, which is what I tried to explain in my editorial.

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## Pneumocystis pneumonia in humans is caused by *P jiroveci* not *P carinii*

I read with interest the illustrative case by Boyton *et al.*<sup>1</sup> on the subject of HIV associated pneumonia, which highlights the improved survival among HIV infected patients with *Pneumocystis* pneumonia (PCP) admitted to ICU since the introduction of both PCP prophylaxis and highly active antiretroviral therapy (HAART). This article will help inform physicians and intensivists about the optimal management of patients with PCP and respiratory failure and enable identification of individuals who will most benefit from ICU. The article raises two issues—firstly, the name used to describe human *Pneumocystis* infection and, secondly, the choice of second line treatment for PCP.

From its description by Chagas in 1909 until recently, *Pneumocystis* was thought to be a protozoan. In 1988, by DNA analysis, the organism was revealed to be a fungus.<sup>2</sup> Additional DNA data have subsequently shown that *Pneumocystis* organisms derived from different mammalian host species are quite different<sup>3</sup>; furthermore, attempts at cross infection between host species have not been successful, indicating host species specificity and that *Pneumocystis* infection in humans is not a zoonosis. The organism that causes human PCP is now named *Pneumocystis jiroveci* Frenkel 1999—in honour of the Czech parasitologist Otto Jírovec who was one of the first researchers to describe *Pneumocystis* infection in humans.<sup>4,5</sup> *Pneumocystis carinii* is now only used to describe the rat derived infection.<sup>4,5</sup> The acronym “PCP” used to describe the clinical syndrome of pneumonia in humans and other mammalian hosts still applies—*Pneumocystis pneumonia. Pneumocystis jiroveci* (pronounced “yee-row-vetsee”) is already widely used in publications describing human *Pneumocystis* infection.<sup>6–8</sup>

Some physicians caring for HIV infected patients would not use trimethoprim-dapsone as second line treatment for mild to moderately severe PCP, nor would they use intravenous pentamidine as second line treatment for severe PCP; instead clindamycin-primaquine would be second line treatment, regardless of disease severity. Evidence in support of this choice of second line treatment comes from two sources. In patients with mild and moderately severe PCP the efficacy of clindamycin-primaquine was shown in a multicentre randomised prospective trial to be similar to co-trimoxazole (76% and 79%, respectively), with clindamycin-primaquine being the better tolerated of the two regimens.<sup>9</sup> In patients unresponsive to first line treatment for PCP, evidence for the efficacy of clindamycin-primaquine as “salvage” therapy comes from a meta-analysis of 27 drug trials, case series, and case reports.<sup>10</sup> This analysis showed that clindamycin-primaquine (81–92% response rate) was better than atovaquone (80%), intravenous pentamidine (39%), or trimetrexate (30%).

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## Authors' reply

We thank Dr Miller for his interest in the illustrative case of HIV associated pneumonia recently published in this journal.<sup>1</sup> The case presented was that of a patient with HIV associated pneumonia successfully treated in the ICU. The improved mortality of HIV infected patients admitted to ICU since the introduction of PCP prophylaxis and highly active antiretroviral therapy (HAART) was also discussed.

Dr Miller quite correctly makes the point that at a *Pneumocystis* nomenclature meeting in 2001 at the Seventh International Workshops on Opportunistic Protists, it was recommended that the organism that causes *Pneumocystis* pneumonia in humans should be referred to as *Pneumocystis jiroveci*.<sup>2</sup> We hope it will be appreciated that, in the interest of maintaining accessibility to general physicians who may not all be familiar with recent developments in *Pneumocystis* nomenclature, we opted for the more widely used and understood usage and stayed with the familiar term, *Pneumocystis carinii*. We should also point out that the key publication from Dr Miller and colleagues on the proposed change in nomenclature appeared while our manuscript was in press.<sup>3</sup>

The additional comment about the use of clindamycin-primaquine as second line treatment is well taken. The meta-analysis that Dr Miller cites showing the effectiveness of clindamycin-primaquine “salvage therapy” for patients with PCP unresponsive to conventional agents shows that this is an effective alternative treatment.<sup>4</sup> As will be

appreciated from the comments accompanying table 2 in our paper, our aim was to give an overview of the available options without being unduly prescriptive. In the paper we strongly promote close collaboration between general, respiratory, HIV, and intensive care physicians in order to deliver optimal care.

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## Adenocarcinoma of lung presenting with dysgeusia

A 69 year old woman, a smoker for 40 years, presented with an altered taste sensation. Investigations revealed hyponatraemia with a serum sodium level of 122 mmol/l. Serum osmolality ranged between 248 and 255 mosm/kg; corresponding urine osmolality was between 430 and 835 mosm/kg. Biochemical tests of thyroid, adrenal, renal and pituitary functions were normal. Computed tomographic (CT) and magnetic resonance imaging (MRI) scans of the brain and pituitary gland were normal. Her serum sodium level returned to normal with fluid restriction. A chest radiograph showed a

3 cm spiculated opacity in the retrocardiac region. A CT scan confirmed a mass in the lower lobe of the left lung which proved to be a moderately differentiated adenocarcinoma. It revealed significant mediastinal lymphadenopathy. Mediastinoscopy failed to identify any nodal involvement. A left lower lobectomy was performed with lymph node sampling. Immediately before surgery the serum sodium level was 137 mmol/l.

Her initial recovery from surgery was uneventful. However, the serum sodium levels started to fall from the fourth post-operative day and reached 117 mmol/l. She again complained of dysgeusia. Fluid restriction was commenced and her serum sodium levels recovered to 133 mmol/l with concurrent symptomatic improvement. Histopathological examination revealed a moderately differentiated adenocarcinoma, stage T2 N2 MX. At 6 weeks follow up her progress was satisfactory without any evidence of recurrence or metastasis. Her sodium values were now normal and she was symptom free.

Dysgeusia is a known manifestation of hyponatraemia.<sup>1</sup> The association between hyponatraemia due to the syndrome of inappropriate antidiuretic hormone (SIADH) and small cell lung cancer is well known.<sup>2,3</sup> There are strict criteria for diagnosis of SIADH,<sup>3</sup> all of which were fulfilled in this patient. In small cell lung cancer serum sodium levels return to normal within 1–3 weeks of initiating chemotherapy in about 80% of patients.<sup>3</sup> In our patient the levels returned to normal 2 weeks after surgery. Endocrine paraneoplastic syndromes are well documented with small cell lung cancer but are less common with other forms of lung cancers.<sup>4</sup> This is an interesting and unusual presentation of adenocarcinoma of the lung with dysgeusia as the sole symptom.

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## NOTICE

### The Dr H M (Bill) Foreman Memorial Fund

The trustees of the above fund invite applications for grants relating to study in respiratory disease and allied fields (e.g. 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 for 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, UK.