

PostScript

LETTERS TO THE EDITOR

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Pre-flight hypoxic challenge in infants and young children with respiratory disease

Modern aircraft flying at high altitude are cabin pressurised to an atmospheric partial pressure of up to 8000 feet (2348 metres), equivalent to breathing approximately 15% oxygen. This may expose individuals with cardiorespiratory disease to the risk of developing hypoxia. In 2002 the British Thoracic Society (BTS) issued recommendations for passengers with respiratory diseases who are planning to fly.¹ These recommendations included the use of a hypoxic challenge test in children with a history of respiratory disease too young to undergo conventional lung function tests. While pre-flight hypoxic challenge tests have been evaluated in older children² and adults³ with respiratory disease, there are few data on hypoxic responses in infants and young children with respiratory disease although one study has observed profound desaturation in a small number of healthy infants while asleep.⁴

In the last 6 years we have tested 20 children under 5 years of age with a history of chronic pulmonary disease in early infancy (table 1). At our institution fitness to fly testing using 15% oxygen has been performed as a routine test in older children² and adults³ with respiratory disease for some years, so formal ethical approval was not sought for this study. Children were exposed to a hypoxic challenge with 15% oxygen while sitting on the lap of a carer in a whole body plethysmograph (body box). Oxygen saturation was monitored by pulse oximetry (SpO₂) using a probe attached to the child's finger. After measuring SpO₂ of the child in air, nitrogen was passed into the body box at approximately 50 l/min to dilute the oxygen content of the air to 15% over a period of 5 minutes. Oxygen and carbon dioxide concentrations were measured via continuous flow sampling using a Centronics 200 MGA mass spectrometer. The SpO₂ could take up to approximately 20 minutes to reach a stable value (constant over 2–3 minutes). In none of the tests did the carbon dioxide concentration in the body box exceed 0.5%. In nine

cases oxygen was subsequently administered via nasal cannulae to restore the fall in SpO₂ to the original (air) value so that this flow of oxygen could then be recommended during the flight. However, because of lack of data on the range of the normal desaturation response and the clinical significance, advice was not always consistent (table 1, p 1001). No child was oxygen dependent at the time of the test although four children were receiving nocturnal or intermittent supplementary oxygen. Four children were tested a second time for subsequent flights (cases 1, 3, 4 and 5). Eight of the 20 children desaturated below 90% in 15% oxygen, six of whom had normal (>95%) saturations at rest in air. Outcome information was obtained from all seven families who had been advised to take supplementary oxygen (table 1, p 1001). Case 2 was notable for the profound desaturation episode that occurred during the flight. Information regarding the outcome of flights for children for whom supplementary oxygen was not advised was incomplete. Three cases did not fly and seven were lost to follow up.

We conclude that some children with a history of chronic pulmonary disease in early infancy may have normal oxygen saturations in room air but desaturate significantly below 90% when exposed to a 15% oxygen hypoxic challenge. These children may be at risk of hypoxia when flying at altitude. This uncontrolled observational series suggests that such infants should be advised to take supplemental oxygen during the flight. The hypoxic challenge test is a simple and practical test and may be performed in any lung function laboratory with a whole body plethysmograph, a source of nitrogen, and a means of measuring oxygen. As carbon dioxide concentrations do not reach clinically significant levels, oxygen concentrations in the body box could be measured with a conventional oxygen monitor. Further studies are required to evaluate fully the hypoxic challenge test in young children. SpO₂ measurements during flight on subjects and healthy control children are needed. Measurements should be undertaken both in the awake and sleep states because there is evidence that SpO₂ falls in some older children with cystic fibrosis while asleep during flight² and in normal infants at sea level.⁴

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References

- 1 **British Thoracic Society Standards of Care Committee.** Managing passengers with lung disease planning air travel: British Thoracic Society recommendations. *Thorax* 2002;57:289–304.
- 2 **Buchdahl RM, Babiker A, Bush A, et al.** Predicting hypoxaemia during flights in children with cystic fibrosis. *Thorax* 2001;56:877–8.
- 3 **Cramer D, Ward S, Geddes D.** Assessment of oxygen supplementation during air travel. *Thorax* 1996;51:202–3.
- 4 **Parkins KJ, Poets CF, O'Brien LM, et al.** Effect of exposure to 15% oxygen saturation in infants: interventional study. *BMJ* 1998;316:887–94.

eNOS allelic variants at the same locus associate with HAPE and adaptation

High altitude pulmonary oedema (HAPE) is a severe form of altitude illness that may develop in individuals on rapid ascent to altitudes above 2500 m.¹ The disease is characterised by hypoxia induced pulmonary vasoconstriction caused by endothelial dysfunction and intravascular fluid retention.^{2,3} While some families and individuals are at risk, those with a long ancestry at high altitude have a lower risk. Moreover, individuals who have had HAPE are at a greater risk of repeat events. Such data support a strong genetic component to HAPE susceptibility, perhaps associated with a founder effect. It is likely that long term exposure to high altitude provides a natural positive adaptive pressure to alleles that prevent the illness. We hypothesise that allelic variants at the same locus in a gene are involved in adaptation and HAPE.

We therefore investigated the Glu298Asp and 4b/4a polymorphisms of the endothelial nitric oxide synthase gene (*eNOS*) and –344T/C, intron-2 conversion and Lys173Arg polymorphisms of the aldosterone synthase gene (*CYP11B2*) in 59 patients with HAPE who developed the disease at 3400 m, 64 lowland controls (LLs) who had been to the same altitude two or three times and even to 5600 m, and 136 highland natives (HLs) from Leh, Ladakh (3400 m). The study groups consisted of unrelated and age matched men aged 30–40 years who had been inhabitants of their respective lands since ancient times. The HAPE patients and LLs were of the same ethnic origin and ascended in a similar manner. The diagnosis of HAPE was based on chest radiographs and other clinical symptoms. Blood samples were collected in the morning in the supine position after overnight fasting. Subjects abstained from smoking for 12 hours before sample collection. The institutional ethical committee approved the investigation and all subjects gave informed consent.

Genotype determination of the five polymorphisms in the two genes was performed by modified cycling conditions. Genotypes were randomly validated on a 377 DNA sequencer (Applied Biosystems, USA). Plasma nitric oxide (NO) estimated as nitrite by the enzymatic Griess method (Calbiochem, USA) and aldosterone levels were determined by radioimmunoassay (Immunotech, France). SPSS software for windows (release 10.0) was used for the statistical analysis.

This study is the first to report plasma NO and aldosterone levels in patients with HAPE and HLs. NO levels were significantly lower in the HAPE group (46.17 (13.94) μM) than in HLs (95.35 (27.56) μM) or LLs (90.53 (29.97) μM) (p<0.0001 for each). The NO levels in the order HLs > LLs > HAPE support earlier reports of impaired NO synthesis in HAPE⁴ and increased NO levels in mountain dwellers.⁵ Previous studies, however, measured the exhaled NO level which is not the exact measure of endogenous NO production. The highest NO levels in HLs signify its importance in the

Table 1 Hypoxic challenge test: subject details

Case no	Sex	Age (months)	SpO ₂ in air	SpO ₂ in 15% O ₂	SpO ₂ in 15% + nasal cannulae O ₂ (flow to achieve normal saturation)	Clinical	Destination	Advice given	Outcome
1	M	2	98	88	100 (0.5 l/min)	Right hypoplastic lung	Malta	Have O ₂ available	Did not fly
1	M	14	98	90		Right hypoplastic lung	Malta	Well without O ₂	NA
2	F	11	97	71	100 (1.0 l/min)	Severe tracheobronchomalacia; Right pulmonary artery narrowing; gastro-oesophageal reflux; Ehlers Danlos syndrome; receiving O ₂ at night	Qatar	Have O ₂ available 2 l/m	Flew without O ₂ until "collapse"; SpO ₂ 40%; given via mask O ₂ and continued for rest of trip
3	M	19	99	90		Ex-preterm 27 w; CLD; receiving 0.1 l/min O ₂ at night	Pakistan	Have O ₂ available 2 l/m because uncertain about sleep	Trip cancelled - non medical reasons
3	M	50	99	90		Ex-preterm 27 w; CLD; receiving 0.1 l/min O ₂ at night	Pakistan	Have O ₂ available 2 l/m because uncertain about sleep	Trip cancelled because chest infection
4	M	4	97	88	97 (1.0 l/min)	Persistent tachypnoea at 4 m unknown aetiology - possible mild pulmonary hypoplasia	New York, USA	Well without O ₂	NA
4	M	6	97	90		Persistent tachypnoea at 4 m unknown aetiology - possible mild pulmonary hypoplasia, bronchomalacia	New York, USA	Well without O ₂	NA
5	F	45	92	86	92 (1.0 l/min)	Cyanotic episodes of unknown aetiology	Greece	Have O ₂ available	Received O ₂ via mask on outward and return journeys; no problems
5	F	54	98	92		Cyanotic episodes with colds; unknown aetiology	Greece	Well without O ₂	"Very tired" at end of flight
6	F	20	97	87		Paraplegic with scoliosis on intermittent home O ₂	Malta	Have O ₂ available 2 l/min	Received O ₂ via nasal prongs outward, mask return; no problems
7	M	9	97	92		Left upper lobe congenital lobar emphysema	Switzerland	Well without O ₂	Uneventful flight
8	F	2	100	94		Ex-preterm 25 w; CLD; on O ₂ 0.1 l/min at night	Jamaica	Well without O ₂	NA
9	M	7	98	90		Ex-preterm 26 w; CLD; off O ₂	Mauritius	Well without O ₂	Uneventful flight
10	F	6	99	92		Ex-preterm 28 w; intrauterine growth retardation; CLD; off O ₂	Pakistan	Well without O ₂	NA
11	M	11	100	94	100 (1.0 l/min)	Ex-preterm 24 w; intrauterine growth retardation; CLD; off O ₂	UAE	Well without O ₂	Uneventful flight
12	M	6	100	94		Ex-preterm 34 w; CLD; VSD; off O ₂	Yugoslavia	Well without O ₂	NA
13	F	2	100	95		Repaired neonatal diaphragmatic hernia	Kuwait	Well without O ₂	NA
14	F	3	99	92	100 (1.0 l/min)	Ex-preterm 34 w	Thailand	Well without O ₂	Uneventful flight
15	F	3	98	91	100 (1.0 l/min)	Ex-preterm 34 w; CLD; off O ₂	Thailand	Well without O ₂	Uneventful flight
16	M	42	96	89		Cystic fibrosis	Majorca	Well without O ₂	Uneventful flight
17	M	49	100	94		Right middle lobe bronchus vascular ring	Greece	Well without O ₂	NA
18	F	8	94	88	98 (1.0 l/min)	Pharyngomalacia	Canary Isles	Have O ₂ available 2 l/m	O ₂ was available but not administered. Uneventful flight
19	F	5	100	94		Ex-preterm 23 w; CLD; off O ₂	S Africa	Well without O ₂	NA
20	M	19	98	88	97 (1.0 l/min)	Spinal muscular atrophy + left lower lobe collapse	Phoenix, AZ, USA	Have O ₂ available 2 l/m	O ₂ available. Received on return flight after getting distressed but would not tolerate either mask or nasal cannulae; eventually went to sleep.

SpO₂, oxygen saturation; CLD, chronic lung disease; VSD, ventricular septal defect; NA, data not available.

Table 1 Genotype and allele frequencies of endothelial nitric oxide synthase (eNOS) polymorphisms in highland dwellers (HLs), lowland dwellers (LLs) and patients with high altitude pulmonary oedema (HAPE)

Polymorphism	Frequency distribution			χ^2	p value	OR	95% CI
	HLs (n = 136)	LLs (n = 64)	HAPE (n = 59)				
Glu298Asp							
Glu298Glu	105 (78%)	39 (61%)	22 (37%)				
Glu298Asp	29 (21%)	23 (36%)	35 (59%)				
Asp298Asp	2 (1%)	2 (3%)	2 (4%)				
Glu	239 (88%)	101 (79%)	79 (68%)				
Asp	33 (12%)	27 (21%)	39 (32%)				
HLs v HAPE							
Genotypes				28.91	0.000001	–	–
Alleles				23.92	0.000001	3.58	2.11 to 6.07
LLs v HAPE							
Genotypes				7.03	0.03	–	–
Alleles				4.47	0.03	1.85	1.04 to 3.27
HLs v LLs							
Genotypes				5.77	0.05	–	–
Alleles				5.48	0.02	1.94	1.11 to 3.39
4b/4a							
4b/b	113 (84%)	45 (71%)	31 (53%)				
4b/a	23 (16%)	19 (29%)	28 (47%)				
4b	249 (92%)	109 (86%)	90 (76%)				
4a	23 (8%)	19 (14%)	28 (24%)				
HLs v HAPE							
Genotypes				19.88	0.000008	–	–
Alleles				16.89	0.00004	3.51	1.84 to 6.15
LLs v HAPE							
Genotypes				4.11	0.04	–	–
Alleles				3.14	0.08	1.78	0.94 to 3.41
HLs v LLs							
Genotypes				4.28	0.04	–	–
Alleles				3.78	0.05	1.89	0.99 to 3.61

maintenance of regular physical activity at high altitude, NO improves the ventilation/perfusion ratio and lowers the alveolar to arterial oxygen tension difference by increasing oxygen saturation. The levels of aldosterone in the HAPE group (467.0 (339.0) pmol/l) were significantly higher in the HLs (376.3 (169.5) pmol/l; $p = 0.05$), LLs (155.5 (109.9) pmol/l; $p < 0.0001$), or both ($p < 0.0001$). This finding is in agreement with the hypothesis that antidiuresis followed by fluid retention is one of the mechanisms leading to HAPE,³ in which aldosterone plays a pivotal role. NO inhalation therapy and the use of diuretics to treat HAPE² support the decreased levels of endogenous NO and increased levels of aldosterone observed in the present study.

The three groups were in Hardy-Weinberg equilibrium for the polymorphisms. The genotype and allele frequency analysis of the Glu298Asp and 4b/4a polymorphisms of the *eNOS* gene revealed that the Asp and 4a alleles were over-represented in the HAPE group and that the Glu and 4b alleles were over-represented in the HLs (table 1, above). A recent study also reported an association of mutant alleles with the disorder.⁶ The presence of the Asp variant renders the enzyme susceptible to intracellular proteases.⁷ Proteolysis may reduce NO levels which may lead to impaired vasodilation and endothelial dysfunction in a hypoxic environment, increasing susceptibility to HAPE. The over-representation of wild-type alleles in HLs suggests that the mutant alleles associated with HAPE are eliminated in HLs as a process of natural selection. Indeed, the tolerance of Himalayan populations to hypoxia, which is reflected in their metabolic

and physiological traits, is believed to be the result of adaptation.⁸ In the case of *CYP11B2* polymorphisms, the intron-2 conversion homozygotes were over-represented in the HAPE subjects compared with HLs ($p = 0.03$) whereas the –344T/C and Lys173Arg polymorphisms were not associated with the disorder (data not shown).

Our results suggest a significant role for NO and aldosterone in the pathogenesis of HAPE. The over-representation of *eNOS* Asp and 4a alleles in patients with HAPE associates these alleles with the disorder, whereas over-representation of Glu and 4b alleles in HLs suggests that they have a role in adaptation to high altitudes. These findings suggest, for the first time, that allelic variants at the same locus are involved in HAPE and adaptation.

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References

1 Hultgren HN. High-altitude pulmonary edema: current concepts. *Annu Rev Med* 1996;**47**:267–84.

2 Hackett PH, Roach RC. High-altitude illness. *N Engl J Med* 2001;**345**:107–14.

3 Hultgren HN. High-altitude pulmonary edema. In: Heggner AH, eds. *Lung water and solute exchange*. New York: Dekker, 1978:437–69.

4 Busch T, Bartsch P, Pappert D, et al. Hypoxia decreases exhaled nitric oxide in mountaineers susceptible to high-altitude pulmonary edema. *Am J Respir Crit Care Med* 2001;**163**:368–73.

5 Beall CM, Laskowski D, Stohl KP, et al. Pulmonary nitric oxide in mountain dwellers. *Nature* 2001;**414**:411–2.

6 Droma Y, Hanaoka M, Ota M, et al. Positive association of the endothelial nitric oxide synthase gene polymorphisms with high-altitude pulmonary edema. *Circulation* 2002;**106**:826–30.

7 Tesaro M, Thompson WC, Rogliani P, et al. Intracellular processing of the endothelial nitric oxide synthase isoforms associated with differences in severity of cardiopulmonary diseases: cleavage of proteins with aspartate vs glutamate at position 298. *Proc Natl Acad Sci USA* 2000;**97**:2832–5.

8 Hochachka PW, Gunga HC, Kirsch K. Our ancestral physiological phenotype: an adaptation for hypoxia tolerance and for endurance performance. *Proc Natl Acad Sci USA* 1998;**95**:1915–20.

Prevalence of TB in healthcare workers in south west London

In the UK, and London specifically, the rise in the incidence of tuberculosis (TB) has been ascribed to reactivation of latent disease and

Table 1 Basic demographic data for healthcare workers with tuberculosis

	No of affected staff	Non-UK born	BCG vaccinated	Pulmonary disease	Extrapulmonary disease	HIV antibody positive	African origin	Indian origin
Hospital 1	9	8	7	7	2	3	5	
Hospital 2	11	10	9	6	5	6	10	
Hospital 3	3	2	2	2	1	0	1	3
Hospital 4	2	2	0	2	0	0	2	
Total	25	22	18	17	8	9	18	3

importation of infection from recent immigrants.¹ The recent increase in the recruitment of healthcare workers from countries with a high prevalence of TB raises the possibility of healthcare workers being a significant source of disease. Previous estimates of TB infection among National Health Service (NHS) employees were calculated before the current levels of HIV infection and the mass migration of healthcare workers.^{2,3} The current number of healthcare workers with TB is unknown but an estimate of this would provide data on the risk that they pose for spreading TB infection.

We conducted a retrospective interrogation of the local TB database (Integrated Tuberculosis Surveillance System, ITSS) for all healthcare workers notified in 2002. Their medical notes were then reviewed and a basic dataset was collated. A healthcare worker was defined as doctor, nurse, healthcare assistant, physiotherapist, occupational therapist, radiographer, or student equivalent. The data collected included profession, age, sex, type of disease, HIV status, country of origin, length of time in the UK when diagnosed (if applicable), history of Bacillus Calmette Guérin (BCG) vaccination, and presence of accompanying scar.

372 patients were notified as having TB in 2002 within the south west London catchment area (as of April 2003). Of these, 25 were healthcare workers (6.7%). Four were doctors, 13 nurses, five healthcare assistants, and three healthcare students. 22 (88%) were originally of overseas origin with a median (range) of 3 (0.75–22) years residence in the UK before diagnosis. Three were originally from the Indian subcontinent, 18 came from Africa, and one from the Caribbean. 18 patients had evidence of BCG vaccination (14 had a scar, 13 born overseas) and 17 (68%) had pulmonary TB. Nine patients (36%) were diagnosed as being HIV antibody positive, although not all patients agreed to be tested (table 1).

Healthcare workers contribute significantly to the number of patients with TB. A large proportion (36%) were co-infected with HIV and this is consistent with previous estimates.⁴ The majority of patients identified were nurses which, in part, reflects the high proportion of nurses among healthcare workers. Over two thirds had pulmonary TB and would therefore be deemed a greater infection risk.

Previous estimates of TB infection among NHS workers were calculated more than a decade ago. The total number of cases reported annually ranged from 3 to 5 among nearly 22 000 NHS staff monitored.⁵ The NHS workforce in our sector was estimated at 26 273. In order to calculate a rate of tuberculosis infection in the population we assumed that, unless otherwise indicated, all these healthcare workers worked for the NHS and that the number of cases treated within

our sector, but working outside were equivalent to the number of south west London workers treated outside the sector. The TB rate for the south west London population has been estimated at 25 per 100 000 population per year, notably lower than the rate estimated for our healthcare worker population.⁵

No patient was diagnosed as part of pre-employment screening but the median time of 3 years from arrival in the UK to presentation suggests that most were unlikely to have had clinically apparent disease at the time of entry. It is unclear, however, if these patients had evidence of latent disease at this time. Currently there is no uniform health screening procedure for NHS workers. The British Thoracic Society (BTS) has produced guidelines for screening immigrant employees⁶ which rely on questionnaire evaluation of suspicious symptoms and evidence of BCG vaccination to screen for high risk individuals. 18 out of 25 (72%) of our patients had evidence of BCG vaccination and may therefore have been considered low risk if they did not report suspicious symptoms. Accordingly, a chest radiograph would not have been deemed necessary, even though this could have picked up evidence of tuberculous infection. The Department of Health in the UK has recently produced draft guidelines regarding TB screening for NHS employees.⁶ Based on the BTS recommendations, they propose further screening manoeuvres for workers from areas of high TB prevalence (incidence levels greater than 40 per 100 000 population per year). These include universal tuberculin skin testing (TST), HIV testing for those with negative TST results, and a low threshold for chest radiography. We believe these new guidelines would increase the detection of both active and latent TB and accordingly reduce the risk represented by infected healthcare workers.

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References

- 1 Maguire H, Dale JW, McHugh TD, *et al*. Molecular epidemiology of tuberculosis in London 1995–7 showing low rate of active transmission. *Thorax* 2002;**57**:617–22.

- 2 Capewell S, Leaker AR, Leitch AG. Pulmonary tuberculosis in health service staff: is it still a problem? *Tubercle* 1988;**69**:113–8.
- 3 Lunn JA, Mayho V. Incidence of pulmonary tuberculosis by occupation of hospital employees in the National Health Service in England and Wales 1980–84. *J Soc Occup Med* 1989;**39**:30–2.
- 4 Bowen EF, Rice PS, Cooke NT, *et al*. HIV seroprevalence by anonymous testing in patients with *Mycobacterium tuberculosis* and in tuberculosis contacts. *Lancet* 2000;**356**:1488–9.
- 5 Joint Tuberculosis Committee of the British Thoracic Society. Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. *Thorax* 2000;**55**:887–901.
- 6 Ad Hoc Risk Assessment Group. *Health clearance for serious communicable diseases*. London: Department of Health, 2002. <http://www.doh.gov.uk/healthclear> (accessed 7 January 2004).

BOOK REVIEW

Wheezing Disorders in the Preschool Child

Martinez FD, Godfrey S. London: Martin Dunitz, 2003, £40.00. ISBN 1 84184 155 2

In this monograph Martinez and Godfrey have set out to inform clinicians about preschool wheeze—a condition that has as many labels (for example, wheezy bronchitis, infant asthma, preschool viral wheeze) as theories about its pathogenesis. The chapters unfold in a logical order: the epidemiology of preschool wheeze, immunological mechanisms, and finally differential diagnosis and treatment. Indeed, there is a coherence in this book that is rare in weightier multi-author textbooks. The initial “science” orientated chapters may appear at first sight to be rather dense—with their combination of small print and infrequent illustrations. However, they do contain nuggets of clinically useful information—I immediately used the up to date data on long term prognosis to counsel parents. I also liked the authors’ pragmatic approach to treatment. For example, they correctly cited the one study assessing the effectiveness of long acting β_2 agonists in preschool children and followed this with a sensible recommendation that cannot be found in the BTS guideline.

Overall, this book is essential reading for clinical and academic respiratory paediatricians and respiratory trainees. Furthermore, it provides an excellent and unbiased overview for anyone setting out to read the primary epidemiological literature on preschool wheeze.

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PostScript

LETTERS TO THE EDITOR

VEGF levels in pulmonary fibrosis

We read with interest the paper by Simler *et al* investigating angiogenic cytokines in patients with idiopathic interstitial pneumonia.¹ We were surprised by their reported high levels of vascular endothelial growth factor (VEGF) in the plasma in the normal control group. Several other groups—including the manufacturers of the ELISA (R&D Systems)—have previously quoted normal plasma VEGF levels in the range 36–76 pg/ml.^{2–3} Indeed, one of the authors of the paper previously quoted normal VEGF levels as 76 pg/ml using a matched pair ELISA.⁴ It is clear therefore that the levels of 648 pg/ml quoted for normal controls are nearly 10 times higher than those reported previously.

One possible explanation is the low centrifugal force used for preparation of the plasma (300g for 12 minutes). The manufacturer of the ELISA recommends 1000g for 15 minutes to reduce platelet contamination of the plasma. Platelet secretion of VEGF is the reason for increased serum levels of VEGF compared with plasma and might explain the extraordinarily high levels of VEGF found in these normal subjects.⁴ Interestingly, 14 of the 49 patients (28.5%) were on immunosuppressant drugs which potentially reduce the platelet count. This may be an alternative explanation as to why there was no difference between normal patients and those with pulmonary fibrosis, in contrast to earlier reports in patients with connective tissue disease related pulmonary fibrosis.⁵

Although the plasma levels of VEGF correlated with fibrosis based on the CT score, it is difficult fully to appreciate the relevance of this finding without knowing the concentration of VEGF within the lung compartment because, in normal individuals, epithelial lining fluid levels of VEGF at 9–11 ng/ml are several orders of magnitude greater than that found in the circulation.^{6–7} Furthermore, previous investigators have reported reduced levels of alveolar VEGF in patients with idiopathic pulmonary fibrosis.⁸ Low levels of VEGF are also seen in the bronchoalveolar lavage (BAL) fluid of patients with acute lung injury, sarcoidosis, emphysema, and lung transplants. It would therefore appear that a reduced alveolar level of VEGF is a common feature of diseases associated with alveolar epithelial damage. Indeed, in ARDS, alveolar levels of VEGF are lowest in those with the worst lung injury.⁹ This is probably a result of reduced epithelial cell secretion of VEGF and increased expression of its soluble receptor, sVEGFR-1, which acts as a natural inhibitor to the bioactivity of VEGF.

The trophic role of VEGF within the lung is supported by the fact that VEGF acts as a proliferative factor for fetal pulmonary epithelial cells¹⁰ and lung targeted VEGF inactivation leads to an emphysema phenotype in mice.¹¹ These studies suggest that reduced alveolar levels of VEGF may inhibit

epithelial repair in a wide variety of lung diseases.

In summary, we have some concerns about the validity/reproducibility of the VEGF levels reported in the study by Simler *et al*. Furthermore, based on the available evidence, we believe it is inappropriate to suggest that antagonising VEGF would be a successful potential treatment for patients with pulmonary fibrosis. On the contrary, we believe this would hasten epithelial cell apoptosis and promote alveolar septal cell loss with resultant honeycombing and functional deterioration.

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References

- 1 Simler NR, Brenchley PE, Horrocks AW, *et al*. Angiogenic cytokines in patients with idiopathic interstitial pneumonia. *Thorax* 2004;**59**:581–5.
- 2 Thickett DR, Armstrong L, Christie SJ, *et al*. Vascular endothelial growth factor may contribute to increased vascular permeability in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2001;**164**:1601–5.
- 3 Himeno W. Angiogenic growth factors in patients with cyanotic congenital heart disease and in normal children. *Kurume Med J* 2001;**48**:111–6.
- 4 Webb NJ, Bottomley MJ, Watson CJ, *et al*. Vascular endothelial growth factor (VEGF) is released from platelets during blood clotting: implications for measurement of circulating VEGF levels in clinical disease. *Clin Sci (Lond)* 1998;**94**:395–404.
- 5 Kikuchi K, Kubo M, Kadono T, *et al*. Serum concentrations of vascular endothelial growth factor in collagen diseases. *Br J Dermatol* 1998;**139**:1049–51.
- 6 Kaner RJ, Crystal RG. Compartmentalization of vascular endothelial growth factor to the epithelial surface of the human lung. *Mol Med* 2001;**7**:240–6.
- 7 Thickett DR, Armstrong L, Millar AB. A role for vascular endothelial growth factor in acute and resolving lung injury. *Am J Respir Crit Care Med* 2002;**166**:1332–7.
- 8 Koyama S, Sato E, Haniuda M, *et al*. Decreased level of vascular endothelial growth factor in bronchoalveolar lavage fluid of normal smokers and patients with pulmonary fibrosis. *Am J Respir Crit Care Med* 2002;**166**:382–5.
- 9 Perkins GD, Roberts J, McAnley DF, *et al*. Regulation of vascular endothelial growth factor bioactivity in patients with acute lung injury. *Thorax* 2005;**60**:153–8.
- 10 Brown KR, England KM, Goss KL, *et al*. VEGF induces airway epithelial cell proliferation in human fetal lung in vitro. *Am J Physiol Lung Cell Mol Physiol* 2001;**281**:L1001–10.
- 11 Tang K, Rossiter HB, Wagner PD, *et al*. Lung-targeted VEGF inactivation leads to an emphysema phenotype in mice. *J Appl Physiol* 2004;**97**:1559–66.

Vitamin E supplements in asthma

Pearson *et al*¹ have failed to tease out any additional benefit of vitamin E supplementation in patients with mild to moderate asthma. Before concluding that this is the

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case, it is relevant to highlight several points in their study.

It is notable that the authors failed to measure any surrogate marker of inflammation such as exhaled nitric oxide, sputum eosinophils, or airway hyperresponsiveness (AHR) to an indirect bronchoconstrictor stimulus. Indeed, non-specific AHR to methacholine is only very tenuously linked to underlying endobronchial inflammation and tends to be related to changes in airway calibre.^{2–3} In this respect, the use of adenosine monophosphate or mannitol to assess AHR may have provided information regarding the underlying inflammatory status as these agents, which act similarly,⁴ cause the release of inflammatory mediators rather than directly causing contraction of airway smooth muscle. Use of these bronchoconstrictor stimuli are also more akin to real life situations as cold air and exercise also act in a similar physiological fashion. Moreover, the use of adenosine monophosphate has been shown to be more sensitive in detecting shifts in AHR than methacholine by approximately one doubling dilution.⁵

It is important to point out in the present study¹ that patients in both groups at baseline had neither demonstrable symptoms nor short acting bronchodilator use. This in turn highlights the fact that these patients were clinically stable and there was no actual signal from which a discernable improvement in symptoms could be observed.

Before dietary manipulation with vitamin E is neglected, further studies are required in symptomatic asthmatics evaluating other important outcome parameters such as exacerbations and surrogate inflammatory biomarkers.

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References

- 1 Pearson PJK, Lewis SA, Fogarty A. Vitamin E supplements in asthma: parallel group randomised placebo controlled trial. *Thorax* 2004;**59**:652-6.
- 2 Van Den Berge M, Meijer RJ, Kerstjens HA, et al. PC₂₀ adenosine 5'-monophosphate is more closely associated with airway inflammation in asthma than PC₂₀ methacholine. *Am J Respir Crit Care Med* 2001;**163**:1546-50.
- 3 De Meer G, Heederik D, Postma DS. Bronchial responsiveness to adenosine 5'-monophosphate (AMP) and methacholine differ in their relationship with airway allergy and baseline FEV₁. *Am J Respir Crit Care Med* 2002;**165**:327-31.
- 4 Currie GP, Haggart K, Brannan JD, et al. Indirect bronchial provocation: inhaled adenosine monophosphate versus mannitol. *Allergy* 2003;**58**:762-6.
- 5 Wilson AM, Lipworth BJ. Dose-response evaluation of the therapeutic index for inhaled budesonide in patients with mild-to-moderate asthma. *Am J Med* 2000;**108**:269-75.

Authors' reply

The aim of our study was to investigate "the effect of 6 weeks regular supplementation with vitamin E on the clinical control of asthma".¹ We thus used a combination of objective and subjective measures of asthma as our outcomes. The entry criteria were designed to be as inclusive as possible and to cover a population with mild to moderate asthma.

However, as Currie *et al* highlight, our study population had few symptoms, with a median daytime and night time symptoms score of 0. A similar intervention study of vitamin C and magnesium from our group covering a comparable population also recruited a population with few asthma symptoms,² which was why we used bronchial responsiveness to methacholine as one of our entry criteria in the current study. We considered this the best measure of bronchial responsiveness when we designed the study, but agree that an alternative technique may have produced a different result.

We also agree with Currie *et al* that further studies of vitamin E are required in patients with asthma, including symptomatic asthmatics, particularly with regard to clinically relevant outcomes such as exacerbations.

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References

- 1 Pearson P, Fogarty A, Lewis S, et al. Vitamin E supplementation in the treatment of asthma: a randomised controlled trial. *Thorax* 2004;**59**:652-6.
- 2 Fogarty A, Lewis S, Scrivener S, et al. Oral magnesium and vitamin C supplements in asthma: a parallel group randomised placebo-controlled trial. *Clin Exp Allergy* 2003;**33**:1355-9.

Management of CAP using a validated risk score

The management of patients with community acquired pneumonia (CAP) is characterised by considerable variation in admission rates, length of hospital stay,¹ and use of institutional resources² in different settings. The Pneumonia Severity Index (PSI) is a prediction rule for the short term risk of death in patients with CAP,³ improving the efficiency of patient care.⁴ In the year 2000, 86% of patients with CAP presenting at the emergency department of our hospital were admitted. A retrospective analysis of the PSI scores of these patients showed that 37% of them were in low risk classes (1 and 2) based on their PSI results, so their admissions were potentially avoidable.^{4,5} We therefore designed a prospective study to assess the safety, feasibility, and efficacy of the PSI score for management decisions in patients with CAP. The study was approved by the local ethics committee and written informed consent was obtained from all patients.

The study was carried out in the 12 month period from 1 November 2001 to 31 October 2002. One hundred and seventeen adult patients diagnosed in the emergency department with CAP participated in the study and were managed using a computer based score with dedicated software (GesPorex, Saxos software, Modena, Italy) for PSI calculation and data collection. CAP was defined as the presence of a pulmonary infiltrate on the chest radiograph and symptoms consistent with pneumonia including cough, dyspnoea, and pleuritic chest pain. Patients with severe immunosuppression, those admitted to hospital in the previous 15 days, and patients infected with HIV were excluded. According to published data,³ patients with PSI scores of 90 points or lower are recommended for outpatient treatment while those with higher scores are recommended for hospital admission. The score was used only as a guide to the admission decision and did not supersede clinical judgement. Follow up consisted of two visits, the first within 10 days and the second about 1 month after discharge from hospital. The choice of antibiotic treatment, route of administration, duration of antibiotic treatment, and criteria for discharge were

according to local guidelines, mainly based on the recommendations of recently published guidelines.⁶ None of these interventions changed between the two study periods. To compare data before implementation of the protocol we retrospectively identified 116 consecutive patients admitted with CAP in the preceding year.

There were no statistically significant differences in demographic and co-morbidity data between the two groups (table 1). In both groups there was a significant proportion of patients in the lowest risk class; this probably reflects the attitude of patients in our healthcare structure to have frequent access to hospital services, particularly when the "family" doctor is unavailable such as at night or during the weekend. In the group managed after implementation of the protocol, 12 patients (10.3%) were admitted against PSI recommendations: six patients (or their relatives) strongly requested hospital admission, four were admitted for lack of adequate home care support, and two did not provide convincing assurance about compliance with treatment. Three (5.9%) of those admitted died; all were in class V of the PSI and two of the deaths were related to CAP. The implementation of PSI based management reduced the median duration of hospital stay from 9.1 (2.1) days to 7.9 (4.9) days, with a total reduction in bed days from 1070 to 463. Of the 1070 total bed days in the retrospective phase of the study, 348 (32.5%) were attributable to patients admitted with PSI scores in class I or II. All patients treated as outpatients were alive at the 1 month follow up visit and all returned to their usual activities. No adverse clinical outcomes, including admission to hospital or the intensive care unit, mortality or complications were detected. Compared with the historical data in the previous year, the rate of admission for CAP during the 12 month study period showed a 37% reduction (95% CI 26 to 49) which was statistically highly significant ($p < 0.001$). The Italian health system estimates the cost in the use of hospital resources as about 1900 Euros per CAP patient treated as an inpatient. Use of this critical pathway significantly decreased the prevalence of admission, theoretically saving about 110 000 Euros in 1 year.

Table 1 Characteristics of retrospective and intervention cohorts

	Before protocol (n = 116)	After protocol (n = 117)
Mean (SD) age (years)	54.5 (20.5)	60.4 (10.6)
Age >75 years	24.1%	23.9%
Sex (M/F)	56/60	68/49
Comorbidities		
COPD	15 (13%)	23 (20%)
Asthma	8 (7%)	5 (4%)
Cardiac failure	17 (15%)	28 (24%)
Cerebrovascular disease	12 (10%)	19 (16%)
Cancer	3 (2%)	6 (5%)
Chronic liver disease	1 (1%)	3 (2%)
Pneumonia Severity Index score		
Class I	36 (31%)	29 (25%)
Class II	24 (21%)	14 (12%)
Class III	22 (19%)	20 (17%)
Class IV	26 (22%)	43 (37%)
Class V	8 (7%)	11 (9%)
Mean (SD) hospital stay (days)	9.1 (2.1)	7.9 (4.9)
Admission rate	86%	49%*

* $p < 0.001$ (χ^2 test).

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References

- 1 McCormick D, Fine MJ, Coley CM, *et al.* Variation in length of hospital stay in patients with community-acquired pneumonia: are shorter stays associated with worse medical outcomes? *Am J Med* 1999;107:5–12.
- 2 Fine MJ, Pratt HM, Obrosky DS, Lave JR, McIntosh LJ, Singer DE, *et al.* Relation between length of hospital stay and costs of care for patients with community-acquired pneumonia. *Am J Med* 2000;109:378–85.
- 3 Fine MJ, Auble TE, Yealy DM, *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997;336:243–50.
- 4 Marrie TJ, Lau CY, Wheeler SL, *et al.* A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL Study Investigators. Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin. *JAMA* 2000;283:749–55.
- 5 Falguera M, Sacristan O, Nogues A, *et al.* Nonsevere community-acquired pneumonia: correlation between cause and severity or comorbidity. *Arch Intern Med* 2001;161:1866–72.
- 6 British Thoracic Society. BTS guidelines for the management of community acquired pneumonia in adults. *Thorax* 2001;56(Suppl IV):iv1–64.

Plasma cell mucositis of the distal airways

Plasma cell mucositis is a rare idiopathic condition consisting of a marked infiltration of mucosa by plasma cells that may involve the mucous membranes of the upper aerodigestive tract—namely, the oral mucosa, gingiva, supraglottic and glottic larynx, and the trachea. While plasma cell mucositis is usually considered benign, cases of critical stenosis of the upper airway have been reported.^{1,2} We present a case of plasma cell mucositis involving the trachea and bronchi. This pattern of lower respiratory tract involvement has not previously been described.

A 55 year old woman, a lifelong non-smoker, presented with chronic cough, dyspnoea, and stridor. Pulmonary function tests showed a moderately severe obstructive ventilatory defect with forced expiratory volume in 1 second (FEV₁) of 1.44 l (56% of

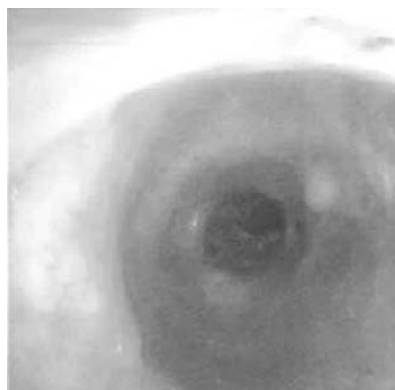


Figure 1 Left mainstem bronchus before treatment.

predicted), forced vital capacity (FVC) of 3.00 l (96% of predicted), and a FEV₁/FVC of 48%. Bronchoscopy revealed narrowing of the left mainstem bronchus (fig 1) and diffuse mucosal abnormalities of the bronchial tree. A biopsy specimen showed a dense plasma cell infiltrate of the mucosa consistent with plasma cell mucositis. Molecular analysis for heavy chain immunoglobulin rearrangement failed to demonstrate a clonal B cell population of lymphocytes. Before starting treatment the patient had an episode of hypoxaemic respiratory failure requiring intubation and mechanical ventilation secondary to a mucus plug occluding her left mainstem bronchus which was removed. She was placed on prednisone 1 mg/kg with improvement in her symptoms. Because of the severity of her symptoms, cytotoxic therapy was initiated with chlorambucil 30 mg with monthly pulses of prednisone 100 mg daily for 4 days. There was marked improvement in her symptoms during the pulse of corticosteroids but this was not sustained. After 4 months of treatment pulmonary function studies remained unchanged. Bronchoscopic examination revealed persistent bronchial mucosal abnormalities with plasma cell infiltrate on endobronchial biopsy. The patient remained symptomatic and underwent bronchoscopy with argon plasma coagulation with debridement of the affected mucosa and subsequent recanalisation of the left mainstem bronchus with dramatic symptomatic improvement.

Plasma cell mucositis was first described in 1952 by Zoon³ in the context of glans penis involvement and has now been reported to involve the vulva, buccal mucosa, lips, tongue, supraglottic larynx, glottic larynx, and the trachea. Although this condition is considered benign, previous reports have illustrated an aggressive clinical course. Two reported cases have described patients who ultimately required tracheostomy for airway compromise.² Surgical intervention and CO₂ laser excision have also been used in the setting of airway compromise.¹

Treatment for plasma cell mucositis is not established. Reports have described the use of both topical and systemic corticosteroids,^{4,5} cytotoxic and radiation therapy,² and surgical intervention.¹ In our patient debridement of the affected mucosal tissue of the left mainstem bronchus with argon plasma coagulation resulted in symptomatic improvement.

In many instances treatment regimes have resulted in stabilisation of disease but have not consistently been associated with disease regression.

Long term prognosis appears good. One case series of nine patients showed that patients were alive with disease up to 16 years after the initial diagnosis.¹ No cases with progression of disease to lymphoma have been reported.

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References

- 1 Ferreiro JA, Egorshin EV, Olsen KD, *et al.* Mucous membrane plasmacytosis of the upper aerodigestive tract. A clinicopathologic study. *Am J Surg Pathol* 1994;18:1048–53.
- 2 Fogarty G, Turner H, Corry J. Plasma cell infiltration of the upper aerodigestive tract treated with radiation therapy. *J Laryngol Otol* 2001;115:928–30.
- 3 Zoon JJ. [Chronic benign circumscribed plasmocytic balanoposthitis]. *Dermatologica* 1952;105:1–7.
- 4 Kaur C, Thami GP, Sarkar R, *et al.* Plasma cell mucositis. *J Eur Acad Dermatol Venerol* 2001;15:566–7.
- 5 Khan NA, McKerrrow WS, Palmer TJ. Mucous membrane plasmacytosis of the upper aerodigestive tract. A case report with effective treatment. *J Laryngol Otol* 1997;111:293–5.

CORRECTIONS

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BTS Winter Meeting abstracts

In abstract P30 on page ii52 of the 2004 BTS Winter Meeting abstracts (Suppl II) the text at the end of the Background section was incorrectly changed during the editing process. The original text read “between 6–10%” and was changed to “between 0 and 6%”. The publishers apologise for this error.

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Prevalence of TB in healthcare workers in south west London

In the Letter to the Editor entitled “Prevalence of TB in healthcare workers in south west London” which appeared in the November issue of *Thorax* (2004;59:1002–3) the name of one of the authors was incorrectly spelt. The authors' names should have appeared as follows: T B L Ho, C F J Rayner, T Lindfield, Y Young, and R J Whitfield. The publishers apologise for this error.