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 (2438 metres), equivalent to breathing approximately 15% oxygen. This may expose individuals with cardiopulmonary 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 children and adults 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.2

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 children and adults 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 2 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 given (cases 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 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 supplementary 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 flight1 and in normal infants at sea level.3

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References

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. The disease is characterised by hypoxia induced pulmonary oedema associated with endothelial dysfunction and intravascular fluid retention.4 5 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 selection for 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 investigated the Gnu298Asp and 4b/4a polymorphisms of the endothelial nitric oxide synthase gene (eNOS) and −344T/C, inton-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 3600 m, and 136 highland natives (HLs) from Pakistan, 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 nitrite 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 (90.33 (29.71) μM) (p<0.0001 for each). The nadir NO levels in the order HLs > LLs > HAPE support earlier reports of impaired NO synthesis in HAPE7 and increased NO levels in mountain dwellers.8 Previous studies, however, measured the NO level which is not the exact measure of endogenous NO production. The highest NO levels in HLs signify its importance in the
<table>
<thead>
<tr>
<th>Case no</th>
<th>Sex</th>
<th>Age (months)</th>
<th>Spo2 in air</th>
<th>Spo2 in 15% O2</th>
<th>Spo2 in 15% O2 + nasal cannulae O2</th>
<th>Clinical</th>
<th>Destination</th>
<th>Advice given</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>2</td>
<td>98</td>
<td>88</td>
<td>100</td>
<td>Right hypoplastic lung</td>
<td>Malta</td>
<td>Have O2 available</td>
<td>Did not fly</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>14</td>
<td>98</td>
<td>90</td>
<td>100</td>
<td>Right hypoplastic lung</td>
<td>Malta</td>
<td>Well without O2</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>11</td>
<td>97</td>
<td>71</td>
<td>100</td>
<td>Severe tracheobronchomalacia; Right pulmonary artery narrowing; gastro-oesophageal reflux; Ehlers Danlos syndrome; receiving O2 at night</td>
<td>Qatar</td>
<td>Have O2 available 2 l/m</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>19</td>
<td>99</td>
<td>90</td>
<td>97</td>
<td>Ex-preterm 27 w; CLD; receiving 0.1 l/min O2 at night</td>
<td>Pakistan</td>
<td>Have O2 available 2 l/m because uncertain about sleep</td>
<td>Trip cancelled - non medical reasons</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>4</td>
<td>97</td>
<td>88</td>
<td>97</td>
<td>Persistent tachypnoea at 4 m unknown aetiology - possible mild pulmonary hypoplasia</td>
<td>New York, USA</td>
<td>Well without O2</td>
<td>NA</td>
</tr>
<tr>
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<td>M</td>
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<td>97</td>
<td>90</td>
<td>97</td>
<td>Persistent tachypnoea at 4 m unknown aetiology - possible mild pulmonary hypoplasia, bronchomalacia</td>
<td>New York, USA</td>
<td>Well without O2</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>45</td>
<td>92</td>
<td>86</td>
<td>92</td>
<td>Cyanotic episodes of unknown aetiology</td>
<td>Greece</td>
<td>Have O2 available</td>
<td>Received O2 via mask on outward and return journeys; no problems</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>54</td>
<td>98</td>
<td>92</td>
<td>98</td>
<td>Cyanotic episodes with colds; unknown aetiology</td>
<td>Greece</td>
<td>Wall without O2</td>
<td>&quot;Very tired&quot; at end of flight</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>20</td>
<td>97</td>
<td>87</td>
<td>97</td>
<td>Paraplegic with scoliosis on intermittent home O2</td>
<td>Malta</td>
<td>Have O2 available 2 l/min</td>
<td>Received O2 via nasal prongs outward, mask return; no problems; Uneventful flight</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>9</td>
<td>97</td>
<td>92</td>
<td>97</td>
<td>Left upper lobe congenital lobar emphysema</td>
<td>Switzerland</td>
<td>Well without O2</td>
<td>Uneventful flight</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>2</td>
<td>100</td>
<td>94</td>
<td>100</td>
<td>Ex-preterm 25 w; CLD; on O2 0.1 l/min at night</td>
<td>Jamaica</td>
<td>Well without O2</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>7</td>
<td>98</td>
<td>90</td>
<td>100</td>
<td>Ex-preterm 26 w; CLD; off O2</td>
<td>Mauritius</td>
<td>Well without O2</td>
<td>Uneventful flight</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>6</td>
<td>99</td>
<td>92</td>
<td>100</td>
<td>Ex-preterm 28 w; intrauterine growth retardation; CLD; off O2</td>
<td>Pakistan</td>
<td>Well without O2</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>11</td>
<td>100</td>
<td>94</td>
<td>100</td>
<td>Ex-preterm 24 w; intrauterine growth retardation; CLD; off O2</td>
<td>UAE</td>
<td>Wall without O2</td>
<td>Uneventful flight</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>6</td>
<td>100</td>
<td>94</td>
<td>100</td>
<td>Ex-preterm 34 w; CLD; VSD; off O2</td>
<td>Yugoslavia</td>
<td>Well without O2</td>
<td>NA</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>2</td>
<td>100</td>
<td>95</td>
<td>100</td>
<td>Repaired neonatal diaphragmatic hernia</td>
<td>Kuwait</td>
<td>Well without O2</td>
<td>NA</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>3</td>
<td>99</td>
<td>92</td>
<td>100</td>
<td>Ex-preterm 34 w</td>
<td>Thailand</td>
<td>Well without O2</td>
<td>Uneventful flight</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>3</td>
<td>98</td>
<td>91</td>
<td>100</td>
<td>Ex-preterm 34 w; CLD; off O2</td>
<td>Thailand</td>
<td>Well without O2</td>
<td>Uneventful flight</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>42</td>
<td>96</td>
<td>89</td>
<td>98</td>
<td>Cystic fibrosis</td>
<td>Majorca</td>
<td>Well without O2</td>
<td>NA</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>49</td>
<td>100</td>
<td>94</td>
<td>98</td>
<td>Right middle lobe bronchus vascular ring</td>
<td>Greece</td>
<td>Well without O2</td>
<td>NA</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>8</td>
<td>94</td>
<td>88</td>
<td>98</td>
<td>Pharyngomalacia</td>
<td>Canary Isles</td>
<td>Have O2 available 2 l/m</td>
<td>O2 was available but not administered; Uneventful flight</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>5</td>
<td>100</td>
<td>94</td>
<td>97</td>
<td>Ex-preterm 23 w; CLD; off O2</td>
<td>S Africa</td>
<td>Have O2 available 2 l/m</td>
<td>NA</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>19</td>
<td>98</td>
<td>88</td>
<td>97</td>
<td>Spinal muscular atrophy + left lower lobe collapse</td>
<td>Phoenix, AZ, USA</td>
<td>Have O2 available 2 l/m</td>
<td>NA</td>
</tr>
</tbody>
</table>

SpO2, oxygen saturation; CLD, chronic lung disease; VSD, ventricular septal defect; NA, data not available.
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 (109.9) pmol/l; p = 0.05), LLs (155.5 (109.9) pmol/l; p = 0.00001), or both (p < 0.0001). This finding is in agreement with the hypothesis that antidiuresis followed by fluid retention is one of the mechanisms in which aldosterone plays a pivotal role. NO inhalation therapy and the use of diuretics to treat HAPE 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. The presence of the Asp variant renders the enzyme susceptible to intracellular proteases. In severe altitude illness, increased NO levels may lead to impaired vasodilation and endothelial dysfunction in a hypoxic environment, increasing susceptibility to HAPE. In the present study, endothelial dysfunction in a hypoxic environment was increased in HAPE subjects compared with HLs (p = 0.03) whereas the homozygotes were over-represented in the HLs compared with LLs (p = 0.01). 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.

**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)

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>HLs (n = 136)</th>
<th>LLs (n = 64)</th>
<th>HAPE (n = 59)</th>
<th>x²</th>
<th>p value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glu298Asp</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glu298Glu</td>
<td>105 (78%)</td>
<td>39 (61%)</td>
<td>22 (37%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glu298Asp</td>
<td>29 (21%)</td>
<td>23 (36%)</td>
<td>35 (59%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glu298Glu</td>
<td>2 (1%)</td>
<td>2 (3%)</td>
<td>2 (4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glu298Asp</td>
<td>239 (88%)</td>
<td>101 (79%)</td>
<td>79 (68%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asp</td>
<td>33 (12%)</td>
<td>27 (21%)</td>
<td>39 (32%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alleles</td>
<td>23.92</td>
<td>0.0000001</td>
<td>3.58</td>
<td>2.11</td>
<td>6.07</td>
<td></td>
<td></td>
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<tr>
<td>Genotypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LLs v HAPE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alleles</td>
<td>7.03</td>
<td>0.03</td>
<td>1.85</td>
<td>1.04</td>
<td>3.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLs v LLs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alleles</td>
<td>4.47</td>
<td>0.03</td>
<td>1.78</td>
<td>0.94</td>
<td>3.41</td>
<td></td>
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<td></td>
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<td>4b/4a</td>
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<td>Genotypes</td>
<td>5.77</td>
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<td>1.94</td>
<td>1.11</td>
<td>3.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alleles</td>
<td>5.48</td>
<td>0.02</td>
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<td>3.61</td>
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<td>1.78</td>
<td>1.04</td>
<td>3.27</td>
<td></td>
<td></td>
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<tr>
<td>Alleles</td>
<td>3.78</td>
<td>0.05</td>
<td>1.89</td>
<td>0.99</td>
<td>3.61</td>
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</table>

**References**


**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...
importation of infection from recent immigrants. 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. 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, TB 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 were healthcare assistants, and three healthcare students. 22 (68%) were originally of overseas origin with a median age of 30 (range of 20–35) years, 11 were 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. 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. The NHS workforce in our sector was estimated at 26 273. In order to calculate a rate of tuberculous 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. 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 employees 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 tuberculosis. The Department of Health in the UK has recently produced draft guidelines regarding TB screening for NHS employees. 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.

### Table 1

<table>
<thead>
<tr>
<th>No of affected staff</th>
<th>Non-UK born</th>
<th>BCG vaccinated</th>
<th>Pulmonary disease</th>
<th>Extrapulmonary disease</th>
<th>HIV antibody positive</th>
<th>African origin</th>
<th>Indian origin</th>
</tr>
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<tbody>
<tr>
<td>Hospital 1</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>2</td>
<td>3</td>
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<td>5</td>
</tr>
<tr>
<td>Hospital 2</td>
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<td>10</td>
<td>9</td>
<td>6</td>
<td>5</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Hospital 3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Hospital 4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>22</td>
<td>18</td>
<td>17</td>
<td>8</td>
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<td>18</td>
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</table>

EPD levels in pulmonary fibrosis

We read with interest the paper by Simler et al investigating angiogenic cytokines in patients with idiopathic interstitial pneumo-

n.a.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.

A 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.5,6 Interestingly, one of the 49 patients (28.5%) were on immuno-

suppressant drugs which potentially reduce the platelet count. This may be an alternative explanation 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.7

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.8,9 Furthermore, previous investigators have reported reduced levels of alveolar VEGF in patients with idiopathic pulmonary fibrosis.10 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.11 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 cells12 and lung targeted VEGF inactivation leads to an emphysema phenotype in mice.13 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


Vitamin E supplements in asthma

Pearson et al.14 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 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.15 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,16 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 approxi-

mately one doubling dilution.17 It is important to point out in the present study14 that patients in both groups at baseline had neither demonstrable symptoms nor short acting bronchodilator use. This highlights the fact that these patients were clinically stable and there was no actual signal from which a discernable improve-

ment 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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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, and use of institutional resources in different settings. The Pneumonia Severity Index (PSI) is a prediction rule for the short-term risk of death in patients with CAP, improving the efficiency of patient care. 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. 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 (GeSPOEx, 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, dyspnea, 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, 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. 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 (15%) 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.
PostScript

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The authors do not have any competing interests regarding this study.

References


Plasma cell mucositis of the distal airways

Plasma cell mucositis is a rare idiopathic condition consisting of a marked infiltration of the 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 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 hypoxic 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 and was changed to “between 0 and 6%”. The authors' names should have been directly spelt. The authors' names should have been directly spelt. The authors' names should have been directly spelt. The authors' names should have been directly spelt. The authors' names should have been directly spelt. The authors' names should have been directly spelt. The authors' names should have been directly spelt.

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.4 No cases with progression of disease to lymphoma have been reported.

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The authors have no competing interests.

References


CORRECTIONS

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BTS Winter Meeting abstracts

In abstract P30 on page i52 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.

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