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Comorbidity in elderly NSCLC patients

We read with interest the report by Janssen-Heijnen and associates on the effect of comorbidity on the treatment and prognosis of elderly patients with non-small cell lung cancer (NSCLC).[1] The authors concluded that the number of comorbid conditions had no significant influence on the treatment chosen for patients with non-localised disease. We share the authors' opinion that ''comorbidity had no independent prognostic effect''.

In their report, the authors used the Charlson comorbidity index and analysed the number of comorbid conditions.[1] However, they did not examine the scoring system of the index. We would like to know why the authors did not use the scoring of the index, and whether the conclusion would be changed if the scoring system was used.

In the original article by Charlson *et al* and other related studies,[2–5] ''angina pectoris'' was not evaluated as one of the cardiovascular comorbid diseases. However, Janssen-Heijnen *et al*[1] included ''angina pectoris'' as a comorbid disease although they did not describe it precisely. We consider this inclusion is reasonable, and we would appreciate hearing from the authors whether ''angina pectoris'' would be evaluated as one of the cardiovascular comorbid diseases in future studies to evaluate the effect on mortality, and what score it should be assigned.

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Authors' reply

Miyazaki and colleagues wonder why we did not use the scoring system of Charlson's comorbidity index and whether the conclusion would be different if the scoring system was used. We did not use the scoring system of Charlson's index because this was not available in the large population based database from which the data were derived. We were, however, able to analyse the prognostic impact of each condition and each combination of conditions. None of these had a significant prognostic impact.[1] The conclusion might have been different if we had used the scoring system. However, in two other recent studies[2 3] the hazard ratio for death for comorbidity was much lower for patients with a lethal tumour than for those with a tumour with a good prognosis.

We also included angina pectoris as a comorbid condition. We think it is important to include this condition in future studies. In other studies hospitalisation for angina or treated angina was classified as high severity for mortality, and angina not requiring hospitalisation or untreated angina was classified as moderate severity.[2 4–6] The severity index should be validated in future studies.

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Neutrophilic inflammation in childhood bronchial asthma

Although there is increasing evidence that neutrophilic inflammation is involved in enhanced bronchial reactivity and exacerbation of bronchial asthma,[1 2] the definitive role of neutrophil mediated inflammation in the pathophysiology has not been fully established. To investigate this further, we performed a historical cohort study of 64 children with primary autoimmune neutropenia (AIN) and compared the incidence of asthma with a control group. The study was approved by the Human Research Committee of Shinshu University.

Between January 1997 and December 2000, 64 patients (31 boys and 33 girls) of mean (SD) age 6.1 (1.9) years (range 4.8–10.3) were recruited from our hospitals (table 1). They were followed up for at least 3 years. All were diagnosed with AIN by the age of 12 months, and they had no signs of other autoimmune diseases or haematological disorders. Neutropenia is defined as an absolute neutrophil count of less than 1000/μl blood lasting for 6 months. The diagnosis of AIN was determined by the presence of antineutrophil antibodies and bone marrow findings. Neutropenia resolved in 46 patients (71.9%) within 16–60 months after diagnosis. 415 control subjects (218 boys and 197 girls) were recruited from lists of preschool children who resided in areas of Matsumoto, Toyoshina and Moriguchi. They were matched with each of the index children in terms of age, sex, and indoor family smoking. A diagnosis of bronchial asthma was established by interviewing the parents with the modified ATS-DLD structured questionnaire[3 4] and paediatric pulmonologists reviewed the clinical symptoms and responses to asthma medications under 5 years of age (before school age). The results were analysed using the χ^2 test (with Yate's correction) for categorical variables. The frequency of asthma and eczema in first degree relatives was identical for the two groups (8.2% *v* 7.1% and 16.1% *v* 18.2%, respectively).

In controls, the prevalence of asthma was 9.9%. By contrast, none of the patients with AIN developed asthma ($p = 0.0243$) during the neutropenic period and/or suffered from recurrent wheezing. Interestingly, some of them had episodes of respiratory infections but none showed typical bronchiolitis. More interesting was the fact that atopic dermatitis was observed in nine patients in the AIN group ($p>0.90$) and three developed wheezing episodes at >6 years of age (after the resolution of neutropenia). In addition, the incidence of asthma in AIN patients was significantly lower than reported in recent data from primary school children in the first grade in Fukuoka City, Japan (112/1456 (7.7%), $p = 0.0496$).[4]

Our findings strongly suggest that neutrophilic inflammation contributes to the onset of childhood asthma. It is well known that, in infants, common viral infections of the respiratory tract such as respiratory syncytial virus (RSV) can induce small airway bronchiolitis and persistent infantile wheezing without significant eosinophilia.[5] Injurious viral infections are common precipitants of exacerbations of asthma. It has been proposed that interleukin (IL)-8 and neutrophil elastase are key factors in this process. Antineutrophil antibodies in AIN usually recognise HNA-1 and HNA-2 antigens that are not detected on

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Table 1 No (%) of children diagnosed with infantile asthma and their history

	AIN	Controls
Boys	31	218
Girls	33	197
Asthma	0/64 (0.0%)	41/415 (9.9%)*
Mean (SD) age (years)	6.1 (1.9)	6.2 (0.3)
Smoking in family	12 (19.4%)	84 (20.2%)

*Significant difference between groups (p = 0.0243).

eosinophils and mast cells, and eosinophils are observed in the peripheral blood of patients with AIN. One possible explanation is that their propensity towards autoimmunity affects dysregulation of the Th1/Th2 balance. However, it has been reported that severe RSV bronchiolitis in infancy is highly associated with the development of asthma up to age 7.[5] We hypothesise that a large proportion of asthma cases may be the result of neutrophilic airway inflammation in early childhood.

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Protein C in pneumonia

Pneumonia is characterised by a disturbed alveolar fibrin turnover which is the net result of activation of coagulation and attenuation of fibrinolysis.[1 2] We have recently shown, in patients developing ventilator associated pneumonia (VAP), that suppression of fibrinolysis precedes the clinical diagnosis while procoagulant effects mainly occur afterwards.[2] We have extended these findings by investigating the relationship in time between changes in the anticoagulant protein C (PC) pathway and VAP.

Levels of PC, activated PC (APC), and soluble thrombomodulin (sTM) were measured in non-directed bronchial lavage fluid collected every other day from critically ill patients during mechanical ventilation. APC was measured with an enzyme capture assay using monoclonal antibody HAPC 1555 and chromogenic substrate Spectrozyme PCa (American Diagnostica, Greenwich, CT, USA);[3] PC activity was measured with an amidolytic assay using chromogenic substrate S2366 (Chromogenix, Milan, Italy); and sTM was measured with an ELISA (Diagnostica Stago, Asnières-sur-Seine, France). Serial data from patients were evaluated using analysis of repeated measures with a linear mixed model, as described previously.[2] Data are presented as medians (interquartile ranges).

The patient population was as previously described.[2] In short, specimen collection was initiated in 60 consecutive patients; 28 patients were selected for final analysis, which required at least three sample sets (minimum ventilation duration ⩾5 days). Nine patients developed VAP and 19 showed no signs of pulmonary infection during the clinical course. There were no significant differences between patients who did and did not develop VAP with regard to baseline characteristics, mechanical ventilation settings, and baseline levels of PC, APC, and sTM. Median (IQR) baseline concentrations for patients without and with VAP were as follows: PC: 0.78 (0.69–0.89) *v* 0.82 (0.72–0.90) U/ml; APC: 0.52 (0.44–0.59) *v* 0.47 (0.36–0.59) ng/ml; sTM: 102 (79–123) *v* 98 (75–131) ng/ml (differences not statistically significant). In patients who developed VAP the clinical diagnosis was preceded by a fall in pulmonary PC levels, as measured in lavage fluids, from 0.69 (0.45–0.86) U/ml before VAP to 0.47 (0.24–0.56) U/ml on the day of diagnosis of VAP ($p<0.0001$; fig 1). In patients who did not develop VAP, pulmonary PC levels remained unchanged ($p = 0.07$). The decline in PC levels in the infected lungs was accompanied by a decrease in levels of APC, which fell from 0.40 (0.25–0.46) ng/ml before VAP to 0.21 (0.21–0.37) ng/ml on the day of diagnosis ($p<0.01$; fig 1). The suppression of APC occurred before the clinical diagnosis of VAP was made. Furthermore, in patients who developed VAP a significant increase in sTM levels was observed. Local levels of sTM increased from 95 (120–151) ng/ml before VAP to 214 (186–312) ng/ml on the day of diagnosis ($p<0.0001$; fig 1), thereafter increasing to 274 (311–362) ng/ml 8 days after VAP was diagnosed. In patients who did not develop VAP during the study, sTM increased to a lesser extent from 102 (79–123) ng/ml at admission to 130 (102–156) ng/ml on day 10 of mechanical ventilation ($p<0.01$; fig 1).

In sepsis, low levels of APC contribute, at least in part, to the systemic procoagulant shift of the haemostatic balance, potentially evolving into disseminated intravascular coagulation.[4] Correction of the systemic haemostatic balance has been acknowledged as a pivotal goal in the treatment of patients with sepsis. Indeed, treatment with recombinant human APC has been found to reduce mortality in patients with severe sepsis.[5] Our results show that, during the pathogenesis of pneumonia, the PC pathway is locally suppressed. We suggest that this is the net result of increased PC consumption, cleavage of PC by neutrophil elastase, as well as inadequate PC activation due to oxidation of TM and shedding of TM from the cell surface (resulting in soluble fragments of TM).[4] Presumably, the insufficient anticoagulant PC system contributes to the local procoagulant environment at the site of infection during pneumonia. Correction of the local PC system may be a target in the treatment of pneumonia.

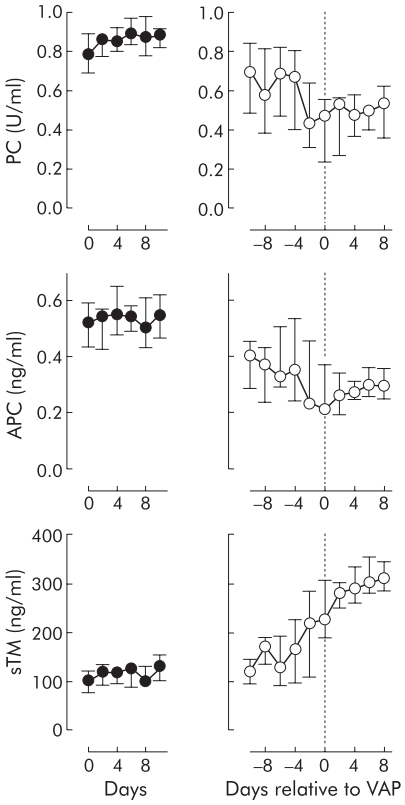

Figure 1 Levels of protein C (PC), activated protein C (APC), and soluble thrombomodulin (sTM) in non-directed bronchial lavage fluid prospectively collected in mechanically ventilated patients. Left panels: patients who did not develop pneumonia; day 0 denotes start of mechanical ventilation. Right panels: patients who developed ventilator associated pneumonia (VAP); day 0 corresponds to the day at which VAP was clinically diagnosed. Data represent medians with interquartile ranges.

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Surgery for difficult persistent asthma

A 35 year old non-smoking woman was referred to hospital for advice regarding poorly controlled atopic asthma. Despite good compliance with fluticasone 2 mg/day, a long acting β_2 agonist, anticholinergic agent, nebulised bronchodilators plus theophylline, she experienced persistent symptoms necessitating frequent courses of oral corticosteroids. It became apparent that her asthma control deteriorated before menstruation—a pattern which was not influenced by premenstrual or continuous oral corticosteroids. Trials with various combined oral contraceptive pills failed to improve asthma control. Some improvement was observed with 6 months of treatment with a gonadorelin analogue (goserelin); although premenstrual symptoms did persist, exacerbations were less marked resulting in a significant reduction in oral corticosteroid use. Gonadorelin analogues produce an initial phase of stimulation followed by downregulation of gonadotrophin releasing hormone receptors, thereby reducing the release of gonadotrophins and subsequent inhibition of oestrogen production. On discontinuation of goserelin (contraindicated for use longer than 6 months) symptomatic asthma recurred, requiring repeated monthly courses of oral corticosteroids. Following discussion with the patient and her gynaecologist, it was decided that, given the cyclical severity of symptoms, the need for frequent oral corticosteroids, and partial success with a gonadorelin analogue, definitive surgical treatment should be considered.

Four years after initial referral a bilateral oophorectomy and subtotal hysterectomy was performed without complication and an oestrogen alone hormone replacement was implanted. In the year following surgery the patient had a single exacerbation of asthma that coincided with the end of the effectiveness of her oestrogen implant (with consequent rise in gonadotrophin levels due to lack of suppression by oestrogen). She was subsequently commenced on regular oestrogen only hormone replacement therapy to good effect. One year after surgery the patient has discontinued alternate day oral prednisolone, is asymptomatic, and maintained on 250 µg/day fluticasone combined with salmeterol.

This unusual case highlights the importance of enquiring about the possible temporal relationship between worsening asthma control and the menstrual cycle. Premenstrual exacerbations of asthma are well recognised and do not always respond to more aggressive anti-inflammatory treatment. Some success has been observed with the institution of oral oestrogen and intramuscular progesterone administration.[1 2] We believe this to be one of the first documented cases of difficult asthma where marked improvement in asthma control has been achieved after a beneficial therapeutic trial of a gonadorelin analogue, followed by bilateral oophorectomy and subtotal hysterectomy plus oestrogen replacement. An initial improvement in asthma control was observed when gonadotrophin levels were low (as a result of the gonadorelin analogue) and a deterioration occurred when gonadotrophin levels were likely to have been rising (towards the end of the effectiveness of the oestrogen implant). This, in turn, suggests that high (or rapidly increasing) gonadotrophin levels, rather than oestrogen/progesterone, were implicated in adversely affecting asthma activity.

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Is there a relationship between *Mycobacterium tuberculosis* strain type and TB paradoxical reaction?

Paradoxical reaction (PR) in tuberculosis (TB) is defined as transient worsening of symptoms and signs or the appearance of new lesions after beginning appropriate antituberculosis chemotherapy. Recent studies suggest that PR occurs in 10–35% of patients. It is more common and more severe in HIV co-infected individuals with disseminated disease.[1] PR is thought to be an immune mediated phenomenon but the reasons for its occurrence are unknown.[1]

Infection by *Mycobacterium tuberculosis* (MTB) results in highly variable outcomes between individuals. The characterisation of MTB strains by molecular typing techniques suggests this may be a reflection of the infecting organism, as well as host response and environmental factors. MTB strains with distinct genotypes have been shown to evoke different immunopathological events in mouse models[2] and variable clinical manifestations in human population based studies.[3] Furthermore, individual strain types have been linked to particular clinical outcomes; for example, a significant association was seen between the Beijing MTB lineage and transient fever unrelated to disease severity, toxicity, or drug resistance in early treatment.[4]

We sought to investigate the hypothesis that the risk of PR may be strain dependent as defined by IS*6110* restriction fragment length polymorphism (RFLP) typing.

Between January 2002 and December 2003 all adult patients seen at our centre with culture positive MTB had IS*6110* RFLP typing performed on one isolate. A case note review was performed retrospectively for clinical evidence of PR.[1] IS*6110* RFLP typing was undertaken using a modification of the standard international protocol.[5] All patterns were entered onto a database using Bionumerics Edition 3.0 package (Applied Maths, Kourtrai, Belgium). Comparison of DNA fingerprints and cluster analysis of profiles was performed by calculation of the Dice coefficient; optimisation was set at 1% and position tolerance at 1.2%. A cluster was defined as a series of isolates with 100% identity. A putative lineage was identified as a series of isolates with 70% or greater similarity.[6]

145 patients had isolates that were typed. 100 (69%) sets of notes were reviewed. 45 were excluded (24 were unavailable or incomplete; 21 patients were lost to follow up or care was transferred). Of the 100 patients' notes reviewed, 52 were male, age range 16–81 years. 48% were black African, 16% Asian, and 19% from the UK. Table 1 shows the TB site and HIV status of the patients. PR occurred in 20 patients (20%) (HIV positive 10/26 (38%); HIV negative or unknown 10/74 (14%)). All patients with PR had distinct IS*6110* RFLP profiles suggesting 20 separate strains.

There was only one identified lineage with a similarity of 70% within the whole patient cohort. This was not associated with increased risk of PR. The group comprised 10 patients who were all black African, only one of whom had a PR. The similarity is likely to represent an original strain of African descent (data not shown).

IS*6110* typing is the recognised gold standard for MTB strain typing and has widespread application in epidemiological and outbreak investigations of TB.[5] Using this method we found one lineage, but no association between strain type and PR. The power of our study is limited by its small sample size and retrospective nature. However, the rate of PR (20% and three times higher in HIV positive subjects: 38% *v* 14%) is in line with previous work.[1] IS*6110* typing is not a definitive phylogenetic marker and other molecular techniques such as single nucleotide polymorphism may demonstrate an association.

The possibility exists that paradoxical TB reactions may be a consequence of specific host response genes. Particular MHC haplotypes have been linked to ''immune reconstitution disease'' in HIV positive patients starting antiretroviral therapy.[7] A larger study

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Table 1 Site of TB and HIV status of patients with and without clinically evident paradoxical reactions (PR)

	Pulmonary TB		Lymph node TB		Other primary site		
	HIV+	HIV−/NK	HIV+	HIV−/NK	HIV+	HIV−/NK	Total
PR	7	3	2	6	1	1	20
No PR	10	46	4	8	2	10	80

NK, not known.

is needed to focus on both strain type and consequent host immune response.

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Bosentan in inoperable chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is a devastating disease in which the pulmonary vasculature becomes obstructed by organised fibrotic material, presumed to be the consequence of incomplete resolution of pulmonary emboli. The ensuing increased pulmonary vascular resistance and right ventricular dysfunction results in severe exercise limitation, symptomatic right heart failure, and markedly impaired survival.

Recent studies suggest that the frequency of this condition is higher than previously appreciated, occurring in up 3.8% of patients following acute pulmonary embolism after 2 years.[1] The treatment of choice is pulmonary endarterectomy (PEA), a potentially curative surgical procedure in which the fibrotic material is removed from the proximal pulmonary arteries during periods of circulatory arrest.[2]

However, in response to increased flow and shear stress through vascular segments unobstructed by proximal thrombotic material, some individuals also develop a small vessel arteriopathy. This so called "distal CTEPH" has a pathophysiology not dissimilar to that of idiopathic pulmonary arterial hypertension.[3] In such patients, PEA may be unsuccessful in alleviating the pulmonary hypertension, and at the present time there is no licensed medical treatment for this condition.

As the national referral centre for PEA for the UK, we sought to assess the efficacy of the oral endothelin receptor antagonist bosentan in patients with distal CTEPH. This agent has established efficacy in pulmonary arterial hypertension, and in distal CTEPH endothelin-1 is thought to play an equally important role in the progressive nature of pulmonary vascular remodelling.[4]

Twenty patients with established distal CTEPH were recruited to the study, 15 deemed inoperable because of the distribution of their disease on imaging and five with persisting pulmonary hypertension following PEA. All subjects received open label bosentan 125 mg twice daily for at least 3 months. Assessments of change in 6 minute walk distance (6MWD), modified New York Heart Association Classification (NYHA), and haemodynamics were made. After at least 3 months of treatment there were significant improvements in 6MWD, NYHA classification, cardiac index, total pulmonary resistance, and pulmonary vascular resistance (table 1). All patients were alive at 3 months and no significant adverse events were reported as a result of the treatment. In particular, hepatic transaminases, which were monitored on a monthly basis, remained within the acceptable range in all participants.

Although uncontrolled, these preliminary data suggest that treatment with bosentan in this otherwise progressive condition results in improvement in exercise capacity, function, and haemodynamic prognostic markers. It is likely that, by inhibiting the action of endothelin-1, bosentan reduces the abnormal endothelial and smooth muscle cell proliferation stimulated by high shear stress within non-occluded pulmonary arterioles. This gradual reversal of vascular remodelling is the most likely reason for the reduction in pulmonary vascular resistance and right ventricular afterload and improved cardiac output observed in our subjects.

Pulmonary endartectomy remains the treatment of choice for proximal CTEPH. However, in patients with established distal arteriopathy deemed unsuitable for this surgical intervention, bosentan may offer an option by which to delay the progression of this otherwise devastating disease.

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Table 1 Mean (SD) 6MWD and cardiac haemodynamics at baseline and after at least 3 months of treatment with bosentan

	Baseline	3 months	Change from baseline	p value
NYHA class II/III/IV	5/14/1	8/11/1		
6MWD (m)	262 (106)	307 (100)	45 (53)	0.001
CI (l/min/m^2)	1.9 (0.62)	2.3 (0.59)	0.4 (0.3)	>0.001
TPR (dyne.s/cm^5)	1165 (392)	918 (275)	−247 (322)	0.003
PVR (n = 15) (dyne.s/cm^5)	964 (406)	690 (271)	−274 (300)	0.005
mPAP (mm Hg)	48 (13)	45 (11)	−3 (7.6)	0.09
mRAP (mm Hg)	9.4 (6.5)	7.7 (4.8)	−1.6 (6.6)	0.28
Mixed venous saturations (%)	59 (8.6)	63 (7.7)	3.8 (9.6)	0.15

6MWD, 6 minute walk distance; CI, cardiac index; TPR, total pulmonary resistance; PVR, pulmonary vascular resistance; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure. Two sided p values as indicated.

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