the tools of the former could be vital to aid the latter: within Peru the MDR epidemic could worsen should fitter drug resistant Beijing strains evolve or enter the country and within the UK where the lineage profile is highly dynamic.

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Contrasting relationship between the Beijing genotype of *Mycobacterium tuberculosis* and MDR-TB in England *versus* Peru. http://ow.ly/qjxTG

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Helicobacter pylori seroprevalence in patients with idiopathic pulmonary fibrosis

To the Editor:

In 2007, the *European Respiratory Journal* published a letter by Ibrahim [1] in which it was suggested that micro-aspiration of *Helicobacter pylori* from gastric juice secondary to gastro-oesophageal reflux disease (GORD) may cause or contribute to the development of idiopathic pulmonary fibrosis (IPF) through recurrent lung insult. This hypothesis was derived from the observation that GORD is common in IPF patients [2, 3], while in the general population the prevalence of GORD exceeds that of IPF. Ibrahim [1]

postulated that only a small proportion of subjects with GORD develop IPF, probably those with *H. pylori* in their gastric juice. This theory has not yet been investigated and no data is available in the literature on the relationship between *H. pylori* infection and IPF.

H. pylori is a Gram-negative, spiral bacterium. There are two major groups of *H. pylori* microorganisms: type I, which expresses the vacuolating cytotoxin VacA and the cytotoxin-associated gene CagA and is responsible for mucosal damage, inducing local inflammatory response; and type II, which expresses neither of these proteins and does not determine any injury [4]. Type I strains, which have the chromosomal insertion called Cag, are endowed with increased inflammatory function that may determine further augmentation of local and systemic cytokines [5].

H. pylori infection is very common all over the world and does not seem to have sex or racial prevalence. CagA *H. pylori* strains play a role in gastroduodenal ulcers and the development of gastric cancer. *H. pylori* infection was recently demonstrated to protect against gastro-oesophageal reflux disease and reflux esophagitis [6], to be associated with several extragastric disorders [7] and to play a role in respiratory disorders, such as chronic bronchitis and lung cancer [4, 8, 9]. A protective function in bronchial asthma, rhinitis and T-helper cell type 2 (Th-2) driven disorders in general has been proposed [10].

In order to contribute to the analysis of *H. pylori* infection in IPF, we designed a pilot study that included serological analysis. We evaluated serum-prevalence of total anti-*H. pylori* antibodies (anti-HP Ab) and anti-CagA antibodies (anti-CagA Ab) in a population of IPF patients. 45 patients with IPF (33 males, mean age 66.2±10.2 years, 12 out of 45 had a histologically confirmed diagnosis and 33 out of 45 had a definite high-resolution computed tomography (HRCT) diagnosis) monitored at the Regional Referral Center for Sarcoidosis and other Interstitial Lung Diseases at Siena University (Siena, Italy), were enrolled, consecutively, in the study. Inclusion criteria were: 1) a documented history of IPF of >1 year; 2) diagnosis of IPF performed according to American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Asociacion Latinoamericana del Tórax guidelines [11]; 3) regular follow-up with chest HRCT (almost one a year); 4) pulmonary function tests (PFTs) performed according to guidelines (almost every 6 months). Patients with malignancies and pulmonary hypertension were excluded.

The results were compared with a population-based sample of 797 age- and sex-matched controls with a comparable socioeconomic background (Siena Osteoporosis Cohort) [12], obtained from primary care registers of Siena residents.

All participants gave their written informed consent to the study that was approved by the local ethics committee.

Serum IgG antibodies to *H. pylori* were analysed in all patients and controls by ELISA having a sensitivity and specificity of 96% (Diesse Diagnostica Senese, Monteriggioni, Italy); serum anti-CagA IgG antibodies were determined by ELISA with a sensitivity of 95% and a specificity of 90% (CagA-IgG; Genesis Diagnostics Ltd., Cambridgeshire, UK). Cut-off values of 6.2 $IU \cdot mL^{-1}$ for anti-HP antibodies and 5.5 $IU \cdot mL^{-1}$ for anti-CagA antibodies were based on previous studies [5].

Statistical analysis was performed using GraphPad Prism version 4.0 for Macintosh, $p < 0.05$ was considered significant. Differences between the two groups were studied by Mann–Whitney test; analysis of variance was done by Kruskal–Wallis test, while Fisher's exact test or the Chi-square test was applied to evaluate prevalence by contingency tables. All data was expressed as mean±SD.

Table 1 reports the prevalence of anti-HP Ab and anti-CagA Ab in the IPF population together with demographic data, functional test parameters at baseline and at 1-year follow-up, bronchoalveolar lavage (BAL) cell pattern, CD8:CD4 ratio, and 6-month and 1-year mortality rates.

Serum IgG antibodies against *H. pylori* proved positive in 18 out of 45 patients with IPF (prevalence 40%), 10 of whom were also positive to anti-CagA serum antibodies (55%). The population-based control group showed a *H. pylori* infection prevalence of 51.4% (410 out of 797), 206 of whom were positive to anti-CagA serum antibodies (50.2%).

Prevalence of *H. pylori* infection was not significantly different in patients and the general population (OR 0.62, 95% CI 0.43–1.16; p=0.16,), and the same was found for infection by CagA-positive *H. pylori* strains (OR 1.23, 95% CI 0.47–3.20; p=0.81). No significant difference between antibody titres of anti-HP Ab (p=0.06) and anti-CagA Ab (p=0.06) was found.

IPF patients testing positive for *H. pylori* showed significantly lower values of forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and total lung capacity (TLC) than those testing negative for *H. pylori* (p=0.016, p=0.026, and p=0.037, respectively) (table 1). No statistically significant difference was found for D_{LCO}, although the number of patients unable to perform the test due to severe lung impairment

TABLE 1 Prevalence of anti-*Helicobacter pylori* antibodies and anti-CagA antibodies in an idiopathic pulmonary fibrosis population along with demographic data, functional-test parameters and mortality rates

	H. pylori positive	*H. pylori* negative	p-value
Patients n	18	27	
Age years	66.8±10.8	65.7±9.8	NS
Males n	16	19	NS
Pulmonary function tests			
FVC % pred	53.6±20.3	70.1±23.1	0.016
FEV_1 % pred	57.4±18.7	72.1±21.9	0.026
FEV_1/FVC	87.6±11.3	82.8±7.6	NS
RV % pred	75.1±25.9	87.6±25.6	NS
TLC % pred	61.7±16.0	74.5±19.2	0.037
*D*LCO % pred	42.0±17.1	42.2±20.1	NS
*K*CO % pred	71.1±23.4	66.6±20.4	NS
ΔFVC %	-11	-5.3	0.05
Δ*D*LCO %	-12.6	-6	NS
Mortality %			
At 6 months	61.1	28	0.05
At 1 year	66.6	37	NS

Data are expressed as mean±SD, unless otherwise stated. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; RV: residual volume; TLC: total lung capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide; *K*CO: transfer coefficient of the lung for carbon monoxide; ΔFVC: decline rate expressed as % of FVC; Δ*D*LCO: decline rate expressed as % of *D*LCO; NS: not significant.

and oxygen-therapy was higher in *H. pylori*-positive (44.4%) IPF patients than the *H. pylori*-negative IPF patients (25.9%), suggesting their worse respiratory condition, although the difference was at the limits of significance ($p=0.07$).

6-month follow-ups recorded the death of 18 out of 45 IPF patients giving a mortality rate of 40%. There was a statistically significant difference in the mortality rate of the two subgroups: 11 (61.1%) out of 18 *H. pylori*-positive patients died *versus* 7 (28%) out of the 25 *H. pylori*-negative patients who died (two patients were lost to follow-up) ($p=0.05$). 1-year mortality rate was higher in the *H. pylori*-positive group when compared with the *H. pylori*-negative group (66.6% *versus* 37%, respectively; $p>0.05$).

1-year follow-up PFTs were available in six *H. pylori*-positive patients (12 died) and 15 *H. pylori*-negative patients (10 died and two were lost to follow-up), showing a significant decrement in FVC in both groups ($p<0.05$). The decrement was significantly greater in *H. pylori*-positive patients when compared with the *H. pylori*-negative patients (-11% *versus* -5.3%, respectively; $p<0.05$). Follow-up of *D*LCO was available in only four *H. pylori*-positive patients and 12 *H. pylori*-negative patients and the decrease was not significant in either group (-12.6% *versus* -6%, respectively; $p>0.05$).

No statistical differences in therapy and in BAL features were found between *H. pylori*-positive and *H. pylori*-negative IPF patients (data not shown).

No differences were observed in the prevalence of *H. pylori*-CagA positivity between patients and controls and no correlations were found between total anti-HP Ab or anti-CagA Ab and the clinical variables analysed.

In this pilot study, the prevalence of *H. pylori* infection in IPF patients was comparable to that of the general population and *H. pylori* antibodies were associated with a more severe disease (*i.e. H. pylori*-positive IPF patients had significantly lower FEV_1, FVC and TLC than *H. pylori*-negative patients). Interestingly, in the literature, GORD is reported to be highly prevalent in IPF patients and has been hypothesised as a potential cause of the disease [2, 3]. The role of *H. pylori* in the development of IPF has been postulated but never demonstrated [1].

In our study, the *H. pylori*-positive subgroup of IPF patients showed a more severe disease phenotype with higher rates of mortality and PFT decline, suggesting a possible role of this bacterium in disease progression. The theory put forward by IBRAHIM [1] is interesting and our study suggests the potential role of *H. pylori* in IPF progression. At a recent International Conference (6th WASOG Conference, held in Paris, June 6–7, 2013), HOGABOAM [13] reported positive *H. pylori* staining in lung biopsy specimens from severe IPF patients, sustaining the involvement of *H. pylori* in this disease. No other literature is available in this field of research.

The next step for our study will be direct determination, such as faecal *H. pylori* antigens or *H. pylori* determination in BAL (*i.e.* DNA PCR or culture), in a wide population of IPF patients. The effects of IPF pharmacological treatments on *H. pylori* infection remain to be established.

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***Helicobacter pylori* infection in IPF patients is associated with higher rates of mortality and PFTs decline** http://ow.ly/qKb3K

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Combined pulmonary fibrosis and emphysema syndrome associated with *ABCA3* mutations

To the Editor:

Herein, we present the first report of combined pulmonary fibrosis and emphysema (CPFE) in an adult patient who was compound heterozygous for mutations of the ATP-binding cassette subfamily A member 3 gene (*ABCA3*, MIM 601615).

A 41-year-old nonsmoking male presented with dyspnoea on mild exertion. The patient's medical history indicated neonatal respiratory distress, gastro-oesophageal reflux and pneumonia 8 years previously that resolved with antibiotics. His physical examination revealed a mild pectus excavatum, finger clubbing and bilateral basal crackles. High-resolution computed tomography (HRCT) of the chest showed voluminous