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Helicobacter pylori and upper gastrointestinal symptoms in bronchiectasis

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ABSTRACT: The recently reported increase in seroprevalence of *Helicobacter pylori*, the causative pathogen in peptic ulceration, in bronchiectasis is unexplained. Therefore, the association of antibodies directed against cytotoxin-associated gene A(CagA), whose expression indicates virulence of *H. pylori*, and upper gastrointestinal symptoms in patients with stable bronchiectasis and healthy volunteers evaluated.

One hundred patients (mean±SD age 55.1±16.7 yrs) and 94 healthy asymptomatic subjects (54.6±7.6 yrs) underwent clinical and physiological assessment and serum levels of anti-*H. pylori* CagA were determined using standard clinical and enzyme-linked immunosorbent assay techniques.

Samples were positive for anti-*H. pylori* CagA in 11.7% of controls and 24% of bronchiectatic subjects (p=0.03). There was, however, no association between serum *H. pylori* CagA immunoglobulin G level and forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), sputum volume, respiratory symptoms or upper respiratory gastrointestinal symptoms (p>0.05). Patients who suffered from acid regurgitation or upper abdominal distension had significantly lower FEV_1 and FVC (as a percentage of the predicted value) compared to their counterparts.

The results of anticytotoxin-associated gene A measurements in this study contrasted with the previous finding that anti-*Helicobacter pylori* immunoglobulin G correlated with sputum volume. These findings, therefore, suggest that *Helicobacter pylori*, should it have a pathogenic role in bronchiectasis, could act *via* noncytotoxin-associated gene A-mediated mechanisms, and, in this context, gastro-oesophageal reflux might be of importance in bronchiectasis.

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The discovery of *Helicobacter pylori*, a Gram-negative motile bacterium, in 1982 and its recognition as the cause of gastritis [1], peptic ulceration [1], gastric lymphoma [2] and gastric adenocarcinoma [3] has reconceptualized the treatment of these diseases. Intensive research on *H. pylori* has resulted in an ever-expanding list of extradigestive conditions associated with increased *H. pylori* seroprevalence. These include coronary artery disease [4], cerebrovascular disease [4], rosacea [5]; urticaria [6], idiopathic thrombocytopenia [7] and Henoch-Scholein purpura [8]. Although small-scaled and lacking in controlled data, some of these studies showed that eradication of *H. pylori* resulted in improvement of rosacea [5], urticaria [6] and Henoch-Schölein purpura [8]. Whilst these claims of efficacy need further evaluation, they nevertheless suggest a role for *H. pylori* in extradigestive diseases, particularly inflammatory conditions. Bronchiectasis is a common and largely idiopathic disease amongst the Chinese, in which chronic tracheobronchial inflammation and infection lead to recurrent exacerbations and chronic sputum production [9]. The high seroprevalence of *H. pylori*-specific immunoglobulin (Ig)G in patients with bronchiectasis (76%) compared with healthy subjects (54.3%) has recently been reported [10]. In addition, *H. pylori* IgG level correlated with disease activity in bronchiectasis, although the precise role of *H. pylori* in the pathogenesis of bronchiectasis remains to be determined.

The development of *H. pylori*-related gastrointestinal diseases is more likely with *H. pylori* strains which express an immunodominant outer membrane protein known as "cytotoxin-associated gene A" (CagA), seropostivity for which strongly correlates with cytotoxin production [11]. Detection of serum anti-*H. pylori* CagA is currently the most practical investigation for predicting bacterial virulence and disease development in *H. pylori* infection [12]. Therefore, this prospective study was performed in order to determine the presence of serum anti-*H. pylori* Cag A and the prevalence of upper gastrointestinal symptoms in the authors' original cohort of 100 bronchiectasis patients, and these were correlated with clinical parameters.

Methods

Subject recruitment

The same cohort of 100 consecutive bronchiectatic patients, who had proven bronchiectasis (confirmed by high-resolution computed tomography (HRCT)) and who had been previously assessed for blood levels of *H. pylori* IgG,

were contacted to reattend the authors centre within 3 months of the initial assessment [10]. The patients were followed up weekly until they were in steady-state bronchiectasis, which was defined as no significant changes in respiratory symptoms or signs over the previous 3 weeks. When in the steady state, the patients underwent physical examination, history taking including assessment of upper gastrointestinal symptoms and further venesection for determination of anti-*H. pylori* CagA level and status. Blood specimens, collected from the cohort of previously recruited healthy subjects who were asymptomatic for gastrointestinal cerebrovascular, coronary artery and respiratory diseases, were retrieved from storage at -70°C for determination of anti-*H. pylori* CagA antibody level. The procedures had approval from the institutional ethics committee on human research.

Evaluation of upper gastrointestinal symptoms

Upper gastrointestinal symptoms were investigated by a research physician (C.S. Ho) in each patient using the Chinese version of a previously validated bowel symptom questionnaire [13]. This included direct enquiry regarding the presence within the previous 12 months, or otherwise, of upper abdominal (hypochondrial or epigastric) pain or abdominal distension (bloating or a sensation of fullness in the upper abdomen not accompanied by visible distension), vomiting, heartburn, acid regurgitation and previous history of upper gastrointestinal haemorrhage. Heartburn was defined as retrosternal burning or hot sensation, and acid regurgitation as a feeling of acidity in the mouth or throat. A history of haematemesis (bright red blood or coffee ground vomiting) or melaena (passing tarry black stool) was considered to indicate upper gastrointestinal bleeding [13].

Clinical parameters

Clinical assessment included determination of exacerbation frequency and the number of bronchiectatic lung lobes for each patient and spirometry. Exacerbation frequency, defined as the number of exacerbations occurring in the previous 12 months, was determined by meticulous history taking and review of clinical notes. An exacerbation was defined as persistent (≥24 h) deterioration in at least three respiratory symptoms including cough, dyspnoea, haemoptysis, increased sputum purulence or volume, and chest pain, with or without fever (≥37.5°C), radiographic deterioration, systemic disturbances, or deterioration in physical signs in the chest including crackles and dullness on auscultation and percussion, respectively [9]. Spirometry (forced expiratory volume in one second (FEV_1), and forced vital capacity (FVC)), expressed as a percentage of the predicted value, was carried out between 10:00 and 12:00 h using a SensorMedics 2200 package (SensorMedics, Yorba Linda, CA, USA). Thoracic HRCT was performed, within 12 months of the initial assessment, using a General Electric Hispeed Advantage Scanner (General Electric Medical System, Milwaukee, WI, USA) to perform standard 1-mm-thick sections at 10-mm intervals in the supine position. The number of lung lobes (including lingula) affected by bronchiectasis was determined by a thoracic radiologist (G.C. Ooi) using standard protocols. Briefly, bronchiectasis was defined by the bronchial segment or subsegment being larger than the accompanying artery [14].

Assessment of 24-h sputum volume

Twenty-four-hour sputum volume was determined as the mean of three consecutive 24-h collections as described previously [9]. Briefly, sputum was collected at home (09:00–09:00 h) and stored at 4°C. The patients had been trained to completely empty the contents of their mouth before expectoration. The volume of a 24-h sputum specimen was determined to the nearest 0.5 mL by a research technician (R. Leung) [9].

Anti-Helicobacter pylori cytotoxin-associated gene A assay in bronchiectasis and control subjects

The methodology for determining anti-*H. pylori* CagA has been described recently [15]. Briefly, 100 μL·well^{-1} CagA 17/12 (recombinant fragment) fusion protein (1.25 μg·mL^{-1} in 0.1 M carbonate buffer (pH 9.6)) was used to coated microenzyme-linked immunosorbent assay (micro-ELISA) plates (Immuno Plate F69; TWC Biosearch International, Hong Kong, China) for 16 h at 4°C. The plates were washed three times with phosphate-buffered saline (PBS; pH 7.3–7.5) containing 0.05% Tween 20, and each of the wells were blocked with 200 μL 1% bovine serum albumin (BSA) in PBS/Tween 20 for 1 h at room temperature (22°C). After three washes with PBS/Tween 20, diluted serum (1:75 in PBS/1% BSA) from each subject was added to the wells and incubated for 2 h at room temperature in duplicate. The plates were then washed three times with PBS/Tween 20 and incubated with 100 μL·well^{-1} of an alkaline phosphatase-tagged goat antihuman IgG (Sigma, St Louis, MO, USA) diluted 1:2,000 in PBS/1% BSA) for 90 min at room temperature. After three washes, 100 μL of a substrate solution containing 1 mg·mL^{-1} *p*-nitrophenylphosphate in a diethanolamine (1.5 g·L^{-1})/$MgCl_2$ (0.06 g·L^{-1}) buffer were added to each well (Bio-Rad Laboratories). The plates were read at 405 nm using a micro-ELISA plate reader (Titertek Multi-Scan MCC/240 (MKII); Bio-Rad Laboratories, Hercules, CA, USA) after incubation for 20 min at room temperature.

A titration curve constructed from serial dilutions (1:10–1:2,000) of four strongly anti-*H. pylori* CagA-positive pooled sera was included in each enzyme-linked immunosorbent assay plate as an internal standard. The results were finally expressed in arbitrary units of anti-CagA with reference to this titration curve. Samples giving results above the top range of this titration curve were repeated after further dilution. Previous experience showed that dilution at 1:75 yielded concentrations closest to the middle of the standard curve and was adopted in this batch. Previous experience also showed that this assay had intraplate and interplate variations of 8.0% (range 4.6–11.8%) and 11.2% (range 6.9–13.6%) respectively. The cut-off limit was calculated, in a previous study, as the mean±2 SD of the levels of anti-CagA in 100 *H. pylori*-negative controls, which was adopted as ≥0.68 U·mL^{-1} for this study [15]. Samples with anti-CagA levels at or below 0.68 U·mL^{-1} were regarded as equivocal or negative regarding anti-CagA status respectively.

Statistical analysis

Data were compared between groups using the Chi-squared, unpaired Student's t- and nonparametric Wilcoxon rank-sum tests and presented as frequency, mean±SD and median (interquartile range) as appropriate. The relationship between various respiratory and gastrointestinal variables was analysed using the nonparametric Wilcoxon rank-sum test. This analysis was performed using SAS software (SAS Institute, Inc., Cary, NC, USA) [16]. A p-value <0.05 was taken as statistically significant.

Results

Subject demography and other clinical features

The clinical details, past medical history and medications of the control and bronchiectatic subjects are published elsewhere [10]. All 100 bronchiectatic subjects (mean±SD age 55.1±16.7 yrs; 38 males; FEV1 66.6±29.6% pred; FVC 74.5±26.1% pred; 24-h sputum volume 23.5±25.3 mL) and 94 healthy control subjects (age 54.6±7.6 yrs; 32 males) returned for reassessment between January 1997 and June 1997. The aetiology of the bronchiectasis was considered to be idiopathic (82), post-tuberculous (eight), post-pneumonic (one), Kartagener's syndrome (six) and diffuse panbronchiolitis (three) [10]. Total serum IgG, IgA and IgM concentrations were raised in eight, 13 and four patients respectively and no patient in the cohort had concentrations below the lower limits of normal. The other details are as shown in table 1.

Anti-Helicobacter pylori cytotoxin-associated gene A and clinical parameters

Samples were positive for anti-*H. pylori* CagA in 11 (11.7%) control subjects and 24 (24%) bronchiectasis patients (p=0.026). Two patients (1 male, 60 and 63 yrs of age; both *H. pylori* IgG seropositive) had anti-CagA levels of exactly 0.68 U·mL^{-1}, *i.e.* equivocal anti-CagA status. The mean±SD serum anti-*H. pylori* CagA levels were 0.15±0.13 U·mL^{-1} (range 0.02–0.76, median 0.10 U·mL^{-1}) in the bronchiectatic subjects, which were significantly higher than those in the controls (0.07±0.03; range 0.03–0.22, median 0.06 U·mL^{-1}; p<0.0001). Patients who were anti-*H. pylori* CagA-positive had a significantly higher level of anti-*H. pylori* IgG compared with those who were negative (p=0.0008). However, there was no significant difference in anti-*H. pylori* IgG seropositivity between anti-*H. pylori* CagA-positive and -negative patients (p=0.44). Similarly, there was no significant difference between these two groups on the basis of the aforementioned clinical parameters, namely FEV1 and FVC, 24-h sputum volume, number of lung lobes with bronchiectasis, exacerbation frequency, age and sex (p>0.05; table 1).

Upper gastrointestinal symptoms, clinical respiratory parameters and Helicobacter pylori *serology*

Amongst the bronchiectatic patients, 21, 34, 22, 8, 24 and 2% of the cases had upper abdominal pain, upper abdominal distension, vomiting, heartburn, acid regurgitation and a history of gastrointestinal haemorrhage, respectively. Patients who suffered from acid regurgitation and upper abdominal distension had significantly lower FEV1 (p=0.02 and 0.01 respectively) and FVC (p=0.006 and 0.04 respectively) compared with their counterparts (table 2 and figs. 1 and 2). None of the control subjects had any gastrointestinal symptoms on assessment. The presence of upper abdominal pain or distension was associated with a significantly greater number of lobes affected by bronchiectasis (table 2). Patients who suffered from any of the upper gastrointestinal symptoms were not significantly different from their counterparts in anti-*H. pylori* CagA or *H. pylori* IgG levels (table 2). No relationship was found between other upper gastrointestinal symptoms and the assessed clinical parameters, including 24-h sputum volume, number of lung lobes with bronchiectasis, exacerbation frequency, age or sex (table 2).

Patients who were *H. pylori* IgG-positive and suffered acid regurgitation had a lower FEV1 and FVC than their counterparts (64.6±29.2 and 72.9±25.7 *versus* 79.5±28.0 and 85.6±25.2%; p=0.04, 0.05 respectively). There was otherwise no significant relationship between *H. pylori* IgG or anti-*H. pylori* CagA-positivity and any of the aforementioned gastrointestinal symptoms.

Table 1. – Clinical parameters in control and bronchiectasis subjects

	Control	Bronchiectasis				
		All patients	CagA-positive	CagA-negative	p-value^{+}	p-value$^{\#}$
Subjects n	94	100	24	74		
Age yrs	54.6±7.6	55.1±16.7	60.8±12.7	53.0±17.6	0.88	0.02
H. pylori IgG U·mL^{-1}	29.1±23.8	41.0±26.0	57.4±26.2	36.9±24.9	0.0005	0.0008
H. pylori IgG seropositivity %	54.3	76.0	83.3	75.7	0.006	0.44
Female sex %	66.0	62.0	79.2	55.4	0.50	0.04
FEV1 % pred	–	67.4±29.7	64.3±27.6	68.4±30.5	–	0.54
FVC % pred	–	75.6±26.2	70.3±25.5	77.3±26.4	–	0.25
24-h sputum volume mL	–	12.5 (5–35)	11.3 (5–35)	16.3 (7.5–40)	–	0.49
Exacerbation frequency events·yr^{-1}	–	1.5 (0.5–3.5)	1.8 (0.2–3.5)	1.5 (0.5–3.5)	–	0.71
Lung lobes with bronchiectasis n	–	2 (2–4)	2 (1.5–3.5)	2 (2–4)	–	0.32

Data are presented as mean±SD or median (interquartile range). *: *H. pylori* cytotoxin-associated gene A (CagA); $^{+}$: control *versus* all bronchiectasis; $^{\#}$: *H. pylori* Cag A-positive *versus*-negative patients. Two bronchiectasis patients had equivocal anti-CagA status and their data are not tabulated in view of the sample size of this subgroup. FEV1: forced expiratory volume in one second; FVC: forced vital capacity.

Table 2. – Relationship between upper gastrointestinal symptoms, respiratory parameters and *Helicobacter pylori* serology in bronchiectasis patients

	Respiratory parameter					Anti-*H. pylori* CagA U·mL^{-1}	*H. pylori* IgG U·mL^{-1}
	FEV1 % pred	FVC % pred	Exacerbation frequency events·yr^{-1}	Bronchiectatic lung lobes n	24-h sputum volume mL		
Upper abdominal pain							
Absent	83 (46–100)	96 (62–96)	2.5 (0.5–3.5)	2 (1–2)	20 (10–40)	48 (28–62)	0.09 (0.07–0.19)
Present	61 (41–93)	70 (53–70)	1.5 (0.3–4)	3 (2–4)	10 (5–30)	38.6 (21–63.5)	0.11 (0.07–0.20)
p-value	0.28	0.38	0.94	0.0006	0.27	0.66	0.49
Upper abdominal distension							
Absent	81 (58–98)	91 (69–98)	1.5 (0.4–3.5)	2 (1–3)	10 (5–25)	45 (21–66.3)	0.10 (0.08–0.22)
Present	53.5 (37–83)	69.5 (49–92)	1.8 (0.5–4.3)	3 (2–4)	20 (7.5–40)	38.6 (22.8–58.5)	0.10 (0.06–0.18)
p-value	0.01	0.04	0.60	0.0002	0.20	0.49	0.73
Vomiting							
Absent	65.6 (36–93)	84 (53–100)	3.5 (1–5.5)	2 (2–3)	22.5 (10–40)	45.3 (20.5–64.9)	0.09 (0.06–0.18)
Present	66 (43–96)	73 (54–94)	1.5 (0.3–3.0)	2 (2–4)	10 (5–30)	38.3 (22.8–62.8)	0.10 (0.07–0.24)
p-value	0.85	0.51	0.08	0.56	0.13	0.83	0.40
Heartburn							
Absent	82.5 (75–100.5)	88 (78.5–100.5)	3.5 (0.8–4.5)	2 (1.5–3.5)	11.3 (7.5–17.5)	46 (14–65.4)	0.09 (0.05–0.22)
Present	60 (41–95)	70 (52–97)	1.5 (1.5–3.5)	2 (2–4)	15 (5–35.7)	40.7 (21.9–63.1)	0.10 (0.07–0.19)
p-value	0.07	0.08	0.28	0.55	0.52	0.88	0.58
Acid regurgitation							
Absent	90.5 (64.5–98.5)	92.5 (70–102.5)	2 (0.3–4)	3 (1–4)	11.3 (5–27.5)	40.5 (32.4–65.4)	0.10 (0.07–0.19)
Present	58 (41–81)	70 (51–91)	1.5 (0.5–3.5)	3 (2–4)	18.8 (7.5–40)	41.5 (20.3–63.1)	0.10 (0.07–0.20)
p-value	0.02	0.006	0.96	0.08	0.35	0.57	0.60
History of upper gastrointestinal haemorrhage							
Absent	67 (27–67)	84 (70–98)	0.8 (0–1.5)	2.5 (1–4)	13.8 (5–22.5)	37.2 (35.2–39.2)	0.05 (0.02–0.07)
Present	66 (42–95)	73 (53–96)	1.8 (0.5–3.5)	2 (2–4)	12.5 (5–35)	42.5 (21–63.5)	0.10 (0.07–0.20)
p-value	0.98	0.56	0.23	0.72	0.60	0.83	0.08

Data are presented as median (interquartile range). Analysis was performed using the nonparametric Wilcoxon rank-sum test. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; CagA: cytotoxin-associated gene A; IgG: immunoglobulin G.

Discussion

Similarly to the recent description of a high seroprevalence of *H. pylori*-specific IgG [10], anti-*H. pylori* CagA is also raised in patients with bronchiectasis compared with healthy controls. However, there was no significant difference in sputum, volume produced, lung function parameters or the number of lung lobes affected by bronchiectasis between patients according to their anti-*H. pylori* CagA status. Up to 32% of bronchiectatic patients suffered from upper gastrointestinal symptoms. Patients who suffered acid regurgitation or upper abdominal distension had a significantly lower FEV1 and FVC compared with their counterparts. The presence of upper abdominal pain and distension was also associated with the number of lobes affected by bronchiectasis. These findings suggest that there might be a relationship between upper abdominal pathology and the development of bronchiectasis.

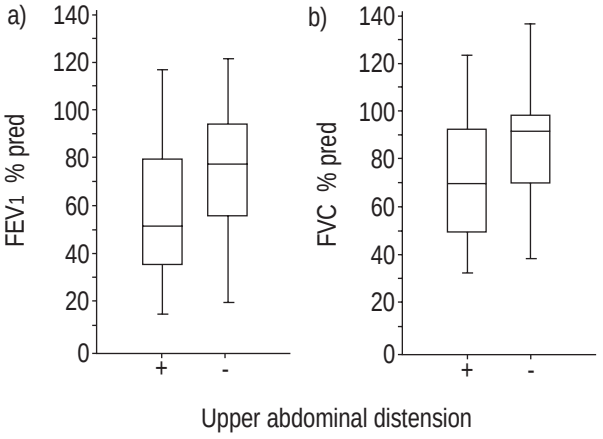

Fig. 1. – Box and whisker plots showing the median and first and third quartiles, with the vertical bar representing 1.5 times the interquartile range, of a) forced expiratory volume in one second (p=0.01); (FEV1) and b) forced vital capacity (p=0.01) (FVC) among bronchiectasis patients with (+; n=34) and without (-; n=66) upper abdominal distension.

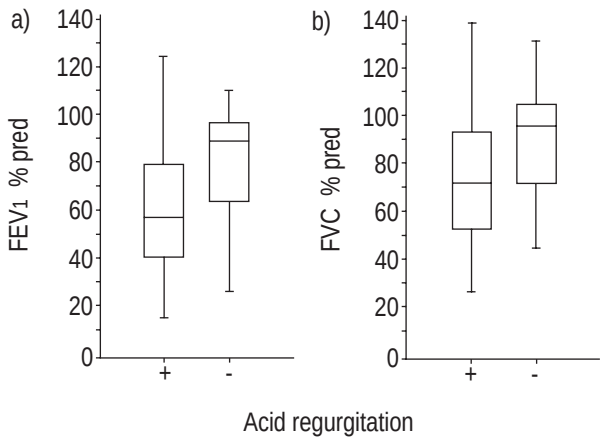

Fig. 2. – Box and whisker plots showing the median and first and third quartiles, with the vertical representing 1.5 times the interquartile range, of : a) forced expiratory volume in one second (p=0.02); (FEV1) and b) forced vital capacity (p=0.006) (FVC) among bronchiectasis patients with (+; n=24) and without (-; n=71) acid regurgitation.

The significance of the previous finding of a high seroprevalence of *H. pylori* IgG in bronchiectasis is unknown, and this is compounded by a failure to isolate *H. pylori* from sputum [10]. Although it is possible that many patients have had a recent *H. pylori* infection, this does not exclude a pathogenic role for *H. pylori* in bronchiectasis. As there is no known association between bronchiectasis and peptic ulcer disease, and the only known niche of *H. pylori* is the stomach, it is logical to investigate whether or not *H. pylori* could be identified in the stomach of the present bronchiectatic subjects. This could be performed by means of conventional gastroscopy and gastric biopsies but this is impractical for a cohort of 100 bronchiectatic and 94 control subjects. Spectrophotometry can also be used, to detect $^{13}CO_2$ production by *H. pylori* urease after ingestion of ^{13}C-urea [15]. This widely adopted breath test can demonstrate the presence of *H. pylori* in the stomach of infected individuals, but was not performed in the present study as many patients with bronchiectasis frequently require antibiotic therapy, which suppresses *H. pylori* urease production [17]. This was also the reason that *H. pylori* IgG was examined as a marker of *H. pylori* infection, rather than using the breath test, in the initial studies as antibody levels are not rapidly affected by antibiotic therapy [10].

The expression of CagA by a strain of *H. pylori* generally indicates a high probability of production of vacuolating toxin, ulcerogenic virulence [11] and pro-inflammatory capabilities in the stomach [11]. The present results show that anti-*H. pylori* CagA-positive and -negative bronchiectatic patients showed no difference in their clinical parameters. This suggests that, even if *H. pylori* plays a significant pathogenic role in bronchiectasis, it probably acts *via* a non-CagA- and nonvacuolating toxin-mediated mechanism(s). Indeed, this is distinctly possible as *H. pylori* produces a wide range of other toxins including urease, catalase, phospholipidases, alcohol dehydrogenase, haemolysin, platelet-activating factor and mucolytic factor [18]. Whilst these toxins are harmful to the stomach and duodenum *via* generation of intense submucosal neutrophil and lymphocyte infiltration, they could also potentially interact with other tissues in the body [19]. *H. pylori*-induced gastric pathology also shares similar pro-inflammatory mediator profiles with many other systemic diseases such as bronchiectasis and asthma [9, 20, 21]. For example, tumour necrosis factor-α, interleukin (IL)-1β and IL-8 levels are all raised in the gastric mucosa of patients with *H. pylori* infection [22]. *H. pylori* also inhibits epithelial cell growth, possibly *via* the action of nonvacuolating and non-CagA-related factor(s) [23].

Gastro-oesophageal reflux (GOR) typically presents as heartburn and acid regurgitation and is a commonly encountered condition in the general population. Indeed, it has recently been reported that ~19% of the general population suffer from symptoms of GOR at least once monthly [24]. The finding of acid regurgitation in 24% of the bronchiectatic patients is of clinical significance as this had an inverse relationship with lung function parameters. Although the association between GOR and respiratory diseases, particularly asthma, has received much attention recently, little is known about the association between noncystic fibrosis bronchiectasis and GOR [25]. Whilst the presence of acid regurgitation or heartburn correlates well with acid reflux [26], the absence of symptoms does not exclude the occurrence of GOR. Although the current gold standard in the investigation of GOR is 24-h oesophageal pH monitoring, which allows accurate assessment of reflux frequency, severity and duration in both the upper and lower oesophagus, this would have been invasive and impractical for assessing the entire cohort [27]. Over one-third of the population in the USA suffer from symptoms of GOR, and probably 10% of these subject suffer from respiratory symptoms due to the reflux process [28]. GOR has been implicated as the cause of many respiratory diseases, particularly asthma, chronic bronchitis, pulmonary fibrosis and bronchiectasis [25–29]. The chronic aspiration of stomach contents could cause airway damage *via* an acidity-mediated erosive process in addition to the chronic inflammation triggered by aspirated substances.

The recently reported lack of association between gastro-oesophageal reflux and *H. pylori* seroprevalence [30] helps clarify the situation, indicating that the high *Helicobacter pylori* immunoglobulin G seroprevalence is unlikely to be due to a high incidence of gastro-oesophageal reflux amongst these patients. It is possible that aspiration of acid as well as *Helicobacter pylori* toxins-containing gastric contents into the bronchiectatic airways leading to further damage could be an underlying mechanism of the pathogenic role of *Helicobacter pylori* in bronchiectasis. This speculation is further supported by the present finding that patients who suffered acid regurgitation and were *Helicobacter pylori* immunoglobulin G-positive yielded significantly worse spirometry results than their counterparts. Further studies should be performed on the potential interactions between *Helicobacter pylori* and the respiratory mucosa in order to determine whether *Helicobacter pylori* truly plays a role in the pathogenesis of this common respiratory disorder amongst Oriental subjects.

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References

1. Marshall J, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; i: 1311–1314.
2. Isaacson PG, Spencer J. Is gastric lymphoma an infectious disease? *Hum Pathol* 1993; 24: 569–570.
3. Parsonnet J, Friedman GD, Vandersteen DP, *et al*. *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med* 1991; 325: 1127–1131.
4. Whincup PH, Mendall MA, Perry IJ, Strachan DP, Walker M. Prospective relations between *Helicobacter pylori* infection, coronary heart disease and stroke in middle aged men. *Heart* 1996; 75: 568–572.
5. Rebora A, Drago F, Picciotto A. *Helicobacter pylori* in patients with rosacea. *Am J Gastroenterol* 1994; 89: 1603–1604.
6. Wedi B, Wagner S, Werfel T, Manns MP, Kapp A. Prevalence of *Helicobacter pylori*-associated gastritis in chronic urticaria. *Int Arch Allergy Immunol* 1998; 116: 288–294.

7. Gasbarrini A, Franceschi F, Tartaglione R, Landolfi R, Pola P, Gasbarrini G. Regression of autoimmune thrombocytopenia after eradication of *Helicobacter pylori* (letter). *Lancet* 1998; 352: 878.
8. Reinauer S, Megahed M, Goerz G, *et al*. Schonlein Henoch purpura associated with *Helicobacter pylori* infection. *J Am Acad Dermatol* 1995; 33: 876–879.
9. Tsang KW, Tsang KWT, Ho PL, *et al*. Fluticasone reduces sputum inflamrnatory indices in bronchiectasis. *Am J Respir Crit Care Med* 1998; 158: 723–727.
10. Tsang KWT, Lam SK, Lam WK, *et al*. High seroprevalence of *Helicobacter pylori* in active bronchiectasis. *Am J Respir Crit Care Med* 1998; 158: 1047–1051.
11. Cover TL, Cao P, Lind CD, *et al*. Correlation between vacuolating cytotoxin production by *Helicobacter pylori* isolates *in vitro* and *in vivo*. *Infect Immun* 1993; 61: 5008–5012.
12. Peura DA. *Helicobacter pylori* and ulcerogenesis. *Am J Med* 1996; 100: 19S–26S.
13. Talley NJ, Phillips SF, Melton LJ, Wiltgen CM, Zinsmeister AR. A patient questionnaire to identify bowel disease. *Ann Intern Med* 1989; 111: 671–674.
14. McGuniness G, Naidich DP, Leitman BS, McCauley DI. Bronchiectasis: CT evaluation. *Am J Radiol* 1993; 160: 253–259.
15. Ching CK, Wong BCY, Kwok E, Ong L, Covacci A, Lam SK. Prevalence of CagA-bearing *Helicobacter pylori* strains detected by the anti-CagA assay in patients with peptic ulcer disease and in controls. *Am J Gastroenterol* 1996; 91: 949–953.
16. SAS Institute Inc. SAS user′s guide (statistics version). 5th ed. Cary, North Carolina: SAS Institute; 1995.
17. Cutler AF. Testing for *Helicobacter pylori* in clinical practice. *Am J Med* 1996; 100: 35S–41S.
18. Megraud F. 1994. Toxic factors of *Helicobacter pylori*. *Eur J Gastroenterol Hepatol* 1994; 6: Suppl. 1, S5–S10.
19. Goodwin CS, Armstrong JA, Marshall BJ. *Campylobacter pyloridis*, gastritis, and peptic ulceration. *J Clin Pathol* 1986; 39: 353–365.
20. Schleimer RP, Benenati SV, Friedman B, Bochner BS. Do cytokines play a role in leukocyte recruitment and activation in the lung? *Am Rev Respir Dis* 1991; 143: 1169–1174.
21. Yamaoka Y, Kita M, Kodama T, *et al*. Role of chemokines in gastric mucosa with *Helicobacter pylori* infection. *Gut* 1996; 39: A60.
22. Noach LA, Bosma NB, Jansen J, Hoek FJ, van Deventer SW, Tytgat GN. Mucosal tumour necrotic factor-α, interleukin-1β, and interleukin-8 production in patients with *Helicobacter pylori* infection. *Scand J Gastroenterol* 1994; 29: 425–429.
23. Wagner S, Beil W, Nietart M, *et al*. Anti-proliferative role of *Helicobacter pylori* on human gastric epithelial cells. *Gut* 1996; 110: A1040 (abstract).
24. Hu WHC, Hui WM, Lam CLK, Lam SK. Anxiety and depresssion are co-factors determining health care utilisation in patients with dyspepsia: a Hong Kong populationbased study. *Gastroenterol* 1997; 112: A153.
25. Ayres JG, Miles JF. Oesophageal reflux and asthma. *Eur Respir J* 1996; 9: 1073–1078.
26. Shi G, Brurley de Varannes S, Scarpignato C, Le Rhun M, Galmiche J. Reflux related symptoms in patients with normal oesophageal exposure to acid. *Gut* 1995; 37: 457–464.
27. DeMeester TR, Wang C, Wesley JA, *et al*. Techniques, indications, and clinical use of 24 hour oesophageal monitoring. *J Thorac Cardiovasc Surg* 1980; 79: 656–670.
28. Barish CF, Wu WC, Castell DO. Respiratory complications of gastro-oesophageal reflux. *Arch Intern Med* 1985; 45: 1882–1888.
29. Cole PJ. Bronchiectasis. *In*: Brewis RAL, Corrin B, Geddes DM, Gibson GJ, eds. Respiratory Medicine. London: Saunders, 1995; 1286–1317.
30. O′Connor HJ, Cunnane K. *Helicobacter pylori* and gastro-oesophageal reflux disease - a prospective study. *Iri J Med Sci* 1994; 163: 369–373.