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Systemic markers of inflammation in stable bronchiectasis

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Systemic markers of inflammation in stable bronchiectasis. C.B. Wilson, P.W. Jones, C.J. O'Leary, D.M. Hansell, R.B. Dowling, P.J. Cole, R. Wilson. ©ERS Journals Ltd 1998.

ABSTRACT: Patients with bronchiectasis have an active local and systemic inflammatory response during infective exacerbations. Systemic markers of inflammation were investigated during a stable phase of their illness, because continued inflammation could affect their general health and be involved in disease progression.

The relationship between levels of various systemic markers of inflammation and extent of disease on computed tomographic scan, lung function, sputum bacteriology and health related quality of life (HRQoL) was investigated in 87 noncystic fibrosis bronchiectasis patients.

Several markers were elevated and correlated with the extent of disease and poor lung function. The total white cell count, neutrophil count and erythrocyte sedimentation rate correlated with both disease measures. Sputum bacteriology did not correlate with inflammation markers and patients with positive and negative cultures were similar. C-reactive protein and total white cell count correlated with some components of a disease-specific HRQoL questionnaire.

In conclusion, patients with bronchiectasis in a stable phase have raised systemic markers of inflammation. Some markers, particularly the neutrophil count, correlate with disease severity. This result is in keeping with the hypothesis that the level of inflammation determines disease progression and health status.

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Bronchiectasis is a chronic lung condition in which damage to the bronchial wall causes abnormal dilation leading to poor clearance and pooling of mucus in the affected areas [1]. Patients are predisposed to lower respiratory tract infections which stimulate a chronic host inflammatory response. Chronic inflammation causes lung damage which, in turn, facilitates persistent infection. This has been termed a vicious circle and culminates in the progression of bronchiectasis and deterioration in lung function [1–3]. The patient's condition can be monitored by lung function tests and high-resolution computed tomography (HRCT), although the latter requires exposure to radiation.

Several studies have investigated markers of inflammation in the blood as indicators of the intensity of the host inflammatory response to pulmonary infections and used them to evaluate the efficacy of antibiotic treatment in bronchiectasis, cystic fibrosis (CF) and community-acquired pneumonia [4–7]. These studies report a rise in the level of inflammation markers during an acute exacerbation and a subsequent fall with antibiotic treatment. However, possibly because of chronic infection, patients with bronchiectasis and CF continue to have an active local and systemic inflammatory response even if they have mild disease, are in a stable phase of their illness, or have just completed antibiotic treatment [4, 5, 8, 9].

The purpose of the present study was to examine the levels of systemic markers of inflammation in a stable, non-CF bronchiectasis population. The study aimed to investigate the relationship between levels of various systemic markers of inflammation and extent of disease as measured by HRCT, lung function, sputum bacteriology and health-related quality of life (HRQoL). Finally, patients who were on long-term antibiotic treatment were compared with those who were not.

Methods

Study population

One hundred and twenty patients with bronchiectasis diagnosed clinically and by HRCT scan were approached over a four month period to participate in this prospective study in the Host Defence Unit outpatient clinics at the Royal Brompton Hospital, a tertiary referral centre. Of these, nine patients refused to participate and 24 were excluded because of a recent exacerbation within the preceding 6 weeks. The remaining 87 patients (49 females, 38 males) were recruited into the study. Their mean age was 53.6 (SD 12.8) yrs (range 23–77 yrs).

The population covered a wide spectrum of aetiologies, including idiopathic 63%, allergic bronchopulmonary aspergillosis 9%, hypogammaglobulinaemia 7%, postinfective (defined as chronic cough and sputum production directly following pneumonia in childhood, *e.g.* whooping cough or measles, or following adult tuberculosis or pneumonia where bronchiectasis was predominantly localized

to the area affected by the illness) 10%, primary ciliary dyskinesia or Young's syndrome 8% and association with inflammatory bowel disease 2%. All patients had a normal sweat test. Ten patients had previously undergone surgery to remove bronchiectatic lung but had residual bronchiectasis, five patients had coexisting emphysema and one patient had mild pulmonary fibrosis by HRCT criteria, but in all cases bronchiectasis was the predominant pathology.

Study protocol

Patients were excluded from the study if they had suffered a severe exacerbation of their symptoms during the preceding 6 weeks, although some patients were chronically unwell. On the day of testing, blood samples were taken from each patient for measurement of C-reactive protein (CRP), total white blood cell count (WBC), neutrophil count, erythrocyte sedimentation rate (ESR) and immunoglobulins (Ig)A, IgG and IgM. Each patient also had a recent HRCT scan assessed and scored, performed comprehensive lung function tests, which included examination of arterial blood gases by earlobe sampling, and provided a fresh sputum sample during physiotherapy. The sputum was taken directly to the microbiology laboratory and after mechanical homogenization with an equal volume of Ringer's solution, inoculated onto blood (aerobic and anaerobic) and MacConkey (aerobic) agar plates (Oxoid, Basingstoke, UK) which were incubated at 37°C for 24 h, and a chocolate agar plate, which was incubated in 10% CO_2 for 48 h.

Finally, each of the 87 patients completed three HRQL measures: the St George's Respiratory Questionnaire (SGRQ) [10], the SF-36 Health Survey Questionnaire, United Kingdom version (SF-36) [11], and a 14-item Fatigue Scale [12]. The questionnaires were presented to the patients in a randomized order.

High-resolution computed tomographic examination

A recent HRCT scan of 80 of the patients was assessed and scored by the same consultant pulmonary radiologist, who was blinded to all other details concerning the patient. Six scans were unavailable for scoring and these patients were excluded from all analyses involving HRCT scores. Each lobe of both lungs was graded for bronchiectatic changes on a 0–3 scale (the lingula was scored as a separate lobe), giving a maximum of 18 points: 0: no bronchiectasis; 1: one or no bronchopulmonary segment involved; 2: more than one bronchopulmonary segment involved; and 3: gross cystic bronchiectasis. This scoring system has been used in previous studies and is associated with low interobserver variation [13, 14]. In order to adjust the scores of those patients who had lobectomies, the bronchiectasis score was calculated as the sum of all points divided by the maximum points available for the individual ×100. Thus, if an individual had one lobe resected, their maximum score was 15.

Health-related quality-of-life measures

Three questionnaires were used to measure different aspects of HRQoL.

The SGRQ is a disease-specific measure containing 76 weighted responses divided into three domains: Symptoms, Activity and Impacts. This measure was designed to be used in patients with asthma and chronic obstructive pulmonary disease (COPD) [10]. However, it has recently been shown that the scores of bronchiectasis patients fall in the same range as these two populations, their degree of airflow obstruction is similar and the SGRQ has high levels of validity, reliability and responsiveness when used in a bronchiectasis population [15, 16]. Component scores ranging 0–100 are calculated for each domain, as well as a total score summarizing the responses to all items.

The SF-36 [11] is a general measure with 36 items covering functional status, well-being and overall evaluation of health. The responses can be summarized into two component scores, the physical component summary (PCS) and the mental component summary (MCS).

The Fatigue Scale [12] consists of eight items covering physical aspects of fatigue and six items covering mental aspects of fatigue. All three measures are self-administered and a higher score on both the SGRQ and the Fatigue Scale and a lower score on the SF-36 indicates worse HRQoL.

Statistical analysis

Summary results are presented as mean±SD or as median with interquartile range (IQR). All correlations were performed using the Spearman rank correlation. The Kruskal Wallis analysis of variance (ANOVA) and Mann-Whitney U-test were used to compare the characteristics of each of the groups. Measurements from six patients with hypogammaglobulinaemia were removed before any statistical analysis of data correlating immunoglobulin levels was performed. Statistical significance was accepted at $p<0.05$.

Results

The characteristics of the population are summarized in table 1. The population covered a wide range of disease

Table 1. – Clinical characteristics of the 87 bronchiectasis patients enrolled in the study

	All patients*	Range
Sex M/F	39/48	
Age yrs	54±13	23–77
Pulmonary function measures:		
FEV1 % pred	63±27	17–127
FVC % pred	86±22	36–137
PEFR % pred	84±31	26–158
P_{a,O_2} kPa	10±6	6–13
HRCT bronchiectasis score %	42±20	6–94
Infective exacerbations in previous year* n	5.0±4.0	0–16
Hospital admissions in previous year*† n	0.6±1.7	0–10

Values are mean±SD. *: patients were asked to self-report this number; †: visits to hospital for *i.v.* immunoglobulin replacement not included in data. M: male; F: female; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; PEFR: peak expiratory flow rate; P_{a,O_2}: arterial oxygen tension; HRCT: high-resolution computed tomography.

severity, as measured by HRCT bronchiectasis scores, pulmonary function measures and number of infective exacerbations and hospital admissions experienced in the previous year. The number of infective exacerbations, defined as an increase in symptoms thought to be due to infection on the basis of sputum characteristics, was self-reported by the patients.

Systemic markers of inflammation

Normal ranges for each of the systemic markers of inflammation along with median measurement values with IQR of the study population are summarized in table 2. The percentage of patients with measurements above the normal range for each of the systemic markers of inflammation was: CRP 30%, WBC 15%, neutrophil count 14%, ESR 33%, IgA 49%, IgG, 12% and IgM 1%.

High-resolution computed tomographic scores

Correlations between HRCT bronchiectasis scores and systemic markers of inflammation are shown in table 3. Significant associations were found between the HRCT bronchiectasis scores and ESR, CRP, WBC and neutrophil count, but not with any of the three immunoglobulin measurements.

Lung function

Correlations between the lung function measures and the measurements of the systemic markers of inflammation are summarized in table 4. WBC, neutrophil count and IgG were shown to correlate significantly with most of the lung function measures performed. ESR correlated significantly with forced vital capacity (FVC), peak expiratory flow rate (PEFR), alveolar volume and the transfer factor of the lung for carbon monoxide, while IgA correlated significantly with forced expiratory volume in one second, FVC, PEFR and residual volume. The only lung function measure with which CRP significantly correlated was arterial oxygen tension, and IgM did not correlate significantly with any of the lung function measures.

Table 2. – Systemic markers of inflammation in 87 bronchiectasis patients

	Patients	Reference ranges
C-Reactive protein $mg \cdot L^{-1}$	6.0 (8.0)	0–10.0
Total white blood cell count $\times 10^9 \cdot L^{-1}$	7.7 (3.0)	4.0–11.0
Neutrophil count $\times 10^9 \cdot L^{-1}$	4.9 (2.5)	2.0–7.5
Erythrocyte sedimentation rate $mm \cdot h^{-1}$	11.5 (15.0)	1.0–15.0
Immunoglobulin A $g \cdot L^{-1}$	3.3 (1.9)*	0.7–3.2
Immunoglobulin G $g \cdot L^{-1}$	12.5 (3.6)*	6.4–16.0
Immunoglobulin M $g \cdot L^{-1}$	1.1 (0.8)*	0.5–2.8

Values are median (interquartile range). *: six hypogammaglobulinaemia patients excluded from data.

Table 3. – Spearman rank correlations between high-resolution computed tomographic (HRCT) bronchiectasis scores and systemic markers of inflammation in 87 bronchiectasis patients

	HRCT score	p-value
C-Reactive protein $mg \cdot L^{-1}$	0.33	0.003
Total white blood cell count $\times 10^9 \cdot L^{-1}$	0.50	<0.0001
Neutrophil count $\times 10^9 \cdot L^{-1}$	0.45	<0.0001
Erythrocyte sedimentation rate $mm \cdot h^{-1}$	0.22	0.05
Immunoglobulin A $g \cdot L^{-1}$	0.02	NS
Immunoglobulin G $g \cdot L^{-1}$	0.21	NS
Immunoglobulin M $g \cdot L^{-1}$	0.02	NS

NS: nonsignificant.

Bacteriology

In order to assess the effect of bacteriology on systemic markers of inflammation, patients were grouped according to the results of their sputum cultures. Thirty-three patients had no bacterial growth (NG group) at the time of testing, 22 patients cultured *Pseudomonas aeruginosa* (Pa group) and 17 patients cultured *Haemophilus influenzae* (Hi group); 15 patients who grew other species (0 group) were grouped together because of low individual numbers. The 0 group consisted of *Staphylococcus aureus* (n=4), *Moraxella catarrhalis* (n=3), *Streptococcus pneumoniae* (n=5), and coliforms (n=3). The median value with IQR of each of the systemic markers of inflammation for each of the bacteriology groups is summarized in table 5. Analyses showed that there were no significant differences between the four groups for any of the systemic markers of inflammation.

Health-related quality of life

Correlations were performed between each of the systemic markers of inflammation and each of the component and total scores of the three HRQoL measures. ESR, CRP and WBC were all significantly associated with the SGRQ activity score (r_s=0.265, 0.238 and 0.215, respectively, $p<0.05$). CRP and WBC were also significantly associated with the SGRQ total score (r_s=0.215 and 0.218, respectively, $p<0.05$). No significant correlations were found between any of the systemic markers of inflammation and the SGRQ symptoms and impacts scores, the PCS and MCS scores of the SF-36, or the component and total scores of the 14-item Fatigue Scale.

Antibiotics

In order to assess whether patients on long-term antibiotic therapy had significantly different measurements of systemic markers of inflammation to patients not on antibiotics, the patients were divided into three groups: those not on any antibiotics at the time of testing (n=65), those on long-term oral antibiotics (n=15) and those on long-term nebulized antibiotics (n=7). No significant differences were found between any of the three groups, nor between those not on any antibiotics and the other two groups combined.

Table 4. – Spearman-rank correlations between lung function measures and systemic markers of inflammation in 87 bronchiectasis patients

	FEV_1 % pred	FVC % pred	PEFR % pred	RV % pred	V_A % pred	$T_{L,CO}$ % pred	P_{a,O_2} kPa
C-Reactive protein $mg \cdot L^{-1}$	-0.13	-0.14	-0.09	-0.11	-0.17	-0.20	-0.29**
Total white blood cell count $\times 10^9 \cdot L^{-1}$	-0.35**	-0.3**	-0.28**	-0.31**	-0.29**	-0.20	-0.34**
Neutrophil count $\times 10^9 \cdot L^{-1}$	-0.33**	-0.33**	-0.25*	-0.28**	-0.32**	-0.21	-0.36**
Erythrocyte sedimentation rate $mm \cdot h^{-1}$	-0.15	-0.29**	-0.22*	-0.03	-0.39**	-0.39**	-0.17
Immunoglobulin A $g \cdot L^{-1}$†	-0.34**	-0.28**	-0.34**	-0.24*	-0.22	-0.16	-0.23
Immunoglobulin G $g \cdot L^{-1}$†	-0.27*	-0.34**	-0.25*	-0.21	-0.36**	-0.25*	-0.30**
Immunoglobulin M $g \cdot L^{-1}$†	-0.04	-0.00	0.002	-0.05	-0.08	-0.07	-0.23

†: six hypogammaglobulinaemia patients excluded from analyses. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; PEFR: peak expiratory flow rate; RV: residual volume; V_A: alveolar volume; $T_{L,CO}$: carbon monoxide gas transfer factor; P_{a,O_2}: arterial oxygen tension. *: $p<0.05$; **: $p<0.01$.

Discussion

Bacterial infections are a major cause of morbidity and mortality in patients with bronchiectasis. Acute inflammation is an important host defence against bronchial infection, but if it fails to clear the infection and becomes chronic it can cause lung damage and lead to disease progression [1–3]. Both local and systemic markers of inflammation have been used in bronchiectasis patients to measure disease activity during acute and stable phases of illness. Several studies have shown that sputum from bronchiectasis patients in a stable clinical state contains neutrophil chemotactic activity and elastolytic activity [1, 4, 17] and there is a significant increase in both of these levels during clinical exacerbations [4, 5]. Hill *et al.* [5] demonstrated similar results with serum α_1-antichymotrypsin.

Bronchiectasis patients in a stable phase of their illness have elevated levels of systemic markers of inflammation. At least one-third of the present patients had elevated levels of CRP and ESR and almost half the study population had an elevated serum IgA level. Similar findings have also been reported in CF patients, even with mild disease [8]. However, despite being the most commonly elevated marker, IgA was not significantly correlated with the HRCT bronchiectasis score (table 3). This was also true of the other immunoglobulin measures, IgG and IgM. However, WBC, neutrophil count, CRP and, to a lesser extent, ESR were all positively correlated with the HRCT bronchiectasis score. This may simply reflect more widespread infection, but is also in keeping with the vicious circle hypothesis [1–3].

WBC, neutrophil count, ESR and, to a lesser extent, IgA and IgG were all correlated with several measures of poor lung function (table 4). Ip *et al*. [18] also showed that higher serum globulin levels were associated with worse lung function in a bronchiectasis population [18]. Interestingly, while CRP correlated significantly with the HRCT bronchiectasis score it was very poorly correlated with lung function measures. The opposite was found with IgA and IgG. Therefore, some markers of inflammation correlate more closely with the anatomical extent of disease, while others correlate more closely with poor lung function. WBC, neutrophil count and ESR correlated with both disease measures.

The bacteriology results in this study were similar to other published work [1], with *P. aeruginosa* and *H. influenzae* being the major pathogens. However, there were no significant differences between the three infected groups, so the type of bacterial infection did not affect the systemic markers of inflammation. Sputum bacteriology may not accurately reflect infection in the lower airways in chronic bronchitis [19], but bronchiectasis patients produce sputum more easily and the sputum sample was obtained during physiotherapy. Therefore, a negative culture is more significant and the lack of a difference in systemic markers of inflammation between infected and noninfected patients suggests that inflammation can be present with-out current infection.

Only a few of the markers of inflammation were found to be associated with HRQoL. CRP and WBC correlated significantly with the activity and total scores of the SGRQ, while ESR correlated significantly with only the SGRQ activity score. None of the measures correlated significantly with the symptoms and impacts scores of the SGRQ, the SF-36 or the Fatigue Scale. It is very interesting that the significant correlations were with the SGRQ activity component, which is concerned with physical

Table 5. – Comparative analysis of systemic markers of inflammation between 87 bronchiectasis patients grouped according to bacteriology

	Pa group n=22	Hi group n=17	0 group n=15	NG group n=33
C-Reactive protein $mg \cdot L^{-1}$	7.5 (7.0)	10.0 (11.8)	6.0 (9.3)	6.0 (9.5)
Total white blood cell count $\times 10^9 \cdot L^{-1}$	8.4 (5.1)	8.7 (2.9)	7.3 (3.2)	7.2 (2.5)
Neutrophil count $\times 10^9 \cdot L^{-1}$	5.2 (4.0)	5.7 (2.6)	4.1 (2.4)	4.5 (2.2)
Erythrocyte sedimentation rate $mm \cdot h^{-1}$	9.0 (22.3)	13.0 (16.5)	10.0 (8.0)	12.0 (11.8)
Immunoglobulin A $g \cdot L^{-1}$†	3.7 (1.6)	3.5 (1.6)	2.7 (2.9)	2.5 (2.1)
Immunoglobulin G $g \cdot L^{-1}$†	12.9 (3.1)	12.2 (3.4)	13.7 (2.8)	11.5 (4.3)
Immunoglobulin M $g \cdot L^{-1}$†	1.3 (0.7)	1.0 (0.5)	1.0 (0.9)	1.1 (0.8)

Values are median (interquartile range). Pa: *Pseudomonas aeruginosa*; Hi: *Haemophilus influenzae*; 0: other; NG: no growth. †: six hypogammaglobulinaemia patients excluded from analyses.

activities that cause or are limited by breathlessness, but not the symptoms component, which includes questions about cough and sputum production. Previous studies have shown that HRQoL of bronchiectasis patients is poorly correlated with other clinical features such as extent of disease as measured by HRCT bronchiectasis scores and lung function measures [15, 20]. A weak association between HRQoL, and clinical markers of disease activity has also been shown to exist in COPD and asthma, where lung function measures are very poor predictors of HRQoL [16, 21].

No evidence was found that long-term antibiotic treatment reduced systemic markers of inflammation in the stable phase. The results of this study showed no significant difference in levels of inflammation between those patients on long-term antibiotics and those not on antibiotics. In fact, patients on long-term antibiotics consistently had the higher measurements. However, since no comparison was made of levels of systemic markers of inflammation of these patients before and after commencing long-term antibiotic treatment, one cannot justly comment on the efficacy of this treatment strategy. It is possible that the patients on long-term antibiotics in this study had significantly elevated markers of inflammation before commencing long-term antibiotics, which have subsequently been lowered to a similar level to those not on antibiotics. Several other studies have examined the effect of antibiotics on markers of inflammation and have shown that antibiotics effectively reduce the amount of inflammation during an exacerbation towards a basal level, but that they are inadequate in dealing with persistent airway inflammation [4, 5].

In conclusion, patients with bronchiectasis in a stable phase have raised systemic markers of inflammation and this is not dependent on the presence of infected sputum. Some of the markers, particularly while blood cell and neutrophil counts, correlate with disease severity. Overall, there was weak correlation between markers of inflammation and health-related quality of life, although some, particularly white blood cells and C-reactive protein correlated with some of the components of the St George's Respiratory Questionnaire. This suggests that the level of inflammation, as measured by systemic markers, affects patients' overall health status, but that the relationship is indirect and, as such, poorly correlated. Future studies should investigate whether markers of inflammation in the lung correlate more closely with measures of disease severity and health-related quality of life. These studies could use either lung secretions [4, 5, 19] or an imaging technique [22]. In addition, a high-resolution computed tomographic scoring system that incorporated bronchial wall thickness may correlate more closely with the level of inflammation than the simple extent of bronchiectasis.

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