

A sequential study of the relationship between faecal *Klebsiella aerogenes* and the common clinical manifestations of ankylosing spondylitis

C. J. EASTMOND,¹ M. CALGUNERI,^{1*} R. SHINEBAUM,²
E. M. COOKE,² AND V. WRIGHT¹

From the ¹Rheumatism Research Unit, University Department of Medicine, General Infirmary at Leeds, and ²Department of Microbiology, Medical School, University of Leeds

SUMMARY An 8-month sequential study at 4-weekly intervals of faecal *Klebsiella aerogenes* and clinical activity of ankylosing spondylitis is described. Similar frequencies of faecal *K. aerogenes* were found in the 44 patients and 36 healthy controls studied. Eighteen patients on 19 occasions had *K. aerogenes* cultured from their faeces, when the preceding specimen had been negative. Six (31.6%) of these occasions were associated with a deterioration in clinical state compared with a similar deterioration associated with only 17 (9.8%) of the remaining 174 faecal culture sequences ($p < 0.02$). These results suggest that clinical deterioration in ankylosing spondylitis may be associated with the acquisition of faecal *K. aerogenes*.

Genetic factors are known to be important in the aetiology of ankylosing spondylitis.¹⁻³ Circumstantial evidence for the necessity of additional environmental factors for the final expression of this disease has come from studies of identical twins⁴ and from the work of Ebringer *et al.*,^{5,6} who demonstrated an association between the faecal carriage of *Klebsiella aerogenes* and active ankylosing spondylitis, though subsequent reports suggested that the presence of faecal *K. aerogenes* was most strongly associated with the presence of acute anterior uveitis in patients with ankylosing spondylitis.^{7,8} This latter feature has been used as part of the definition of ankylosing spondylitis by Ebringer *et al.*,^{5,6} though the justification for its inclusion has been questioned.⁹ Our early studies in which patients with ankylosing spondylitis were studied clinically and bacteriologically on a single occasion showed that 87% of patients with ankylosing spondylitis had, early in an attack of acute anterior uveitis, recoverable *K. aerogenes* in their faeces, compared with 30% of similar patients not having acute anterior uveitis.⁷ In addition a higher proportion of patients with active peripheral

synovitis had recoverable *K. aerogenes* in their faeces, compared with similar patients who did not have this feature. No association was found between the presence of clinically active spinal disease and the faecal carriage of *K. aerogenes*.

The present study was designed to study the same group of patients over an 8-month period to determine if any change in their clinical features was associated with the appearance of recoverable *Klebsiella aerogenes* in their faeces.

Patients and methods

A total of 49 patients (42 males) and 44 healthy controls (39 males), most of whom were not employed in hospitals, were asked to co-operate in the study. Each subject was sent a letter explaining the nature and aims of the study, together with a questionnaire and containers for the collection and return of a faecal specimen in a stamped addressed package. Identical criteria for spinal disease activity were used as in our initial study.⁷ Each patient was asked to indicate the duration of his morning stiffness, the severity of his back pain on a 4-point scale, and the dose of his current medication. In addition they were asked about peripheral joint swelling, ocular inflammation, recent infections, antibiotics, and hospital admissions. Questionnaires and containers

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Correspondence to Dr C. J. Eastmond, Department of Rheumatology, City Hospital, Urquhart Road, Aberdeen.

* Present address: Etiler A-I Blok Daire: 3, Ankara, Turkey.

were sent out on 6 occasions to each subject at monthly intervals, and a further 2 questionnaires were sent to the patient group on 2 successive months following the last specimen received. Faecal samples were cultured as previously described.¹⁰

Results

A total of 44 patients (37 male) and 36 controls (33 male) representing completion rates of 89.8% and 81.8% respectively returned samples and questionnaires on at least 3 successive months. Only these subjects have been included in the analysis. A total of 252 and 199 questionnaires and samples were received from the patients and controls respectively. A further 74 questionnaires were received from patients in the 2 months following the last faecal specimen received.

Klebsiella aerogenes was not grown from the faeces of 16 (36.4%) patients and 11 (30.6%) controls throughout the period of study. Of the 4 possible sequences between any 2 monthly specimens the patients and controls had similar frequencies of each (Table 1). Two patients and 3 controls, initially positive for faecal *K. aerogenes*, became negative and in the next succeeding specimen again positive for this organism. Serotyping in these 5 subjects indicated that the 2 positive specimens were the same serotype. These subjects have been considered to be positive on the 3 relevant occasions for the purposes of analysis. A further 2 patients and 7 controls had a change in serotype of their faecal *K. aerogenes* in 2 successive specimens. These subjects have also been considered to be persistently positive for the respective 1-month periods.

Seventeen patients indicated the presence of ocular symptoms during the course of the study. All were sent a further questionnaire inquiring about previous uveitis (alternative names were given), the similarity of any of the recent episodes to previously diagnosed uveitis, and whether this diagnosis had been made during any of the episodes recorded during the study. In addition inquiry was made concerning grittiness, pain in the eye, redness of the eye, and disturbance of vision. Fourteen patients (82.4%) replied, and in

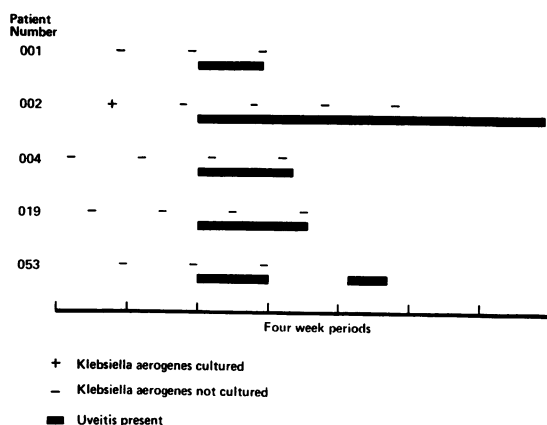


Fig. 1 Relationship between episodes of acute anterior uveitis and faecal cultures in 5 patients. Onset of acute anterior uveitis has been synchronised for convenience.

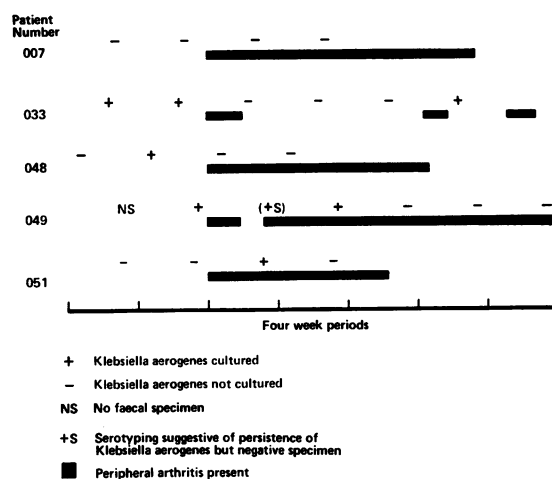


Fig. 2 Relationship between episodes of peripheral synovitis and faecal cultures in 5 patients. Onset of peripheral synovitis has been synchronised for convenience.

Table Summary of faecal culture of *Klebsiella aerogenes* in patients and controls

Group	Total number of subjects	Total number of specimens submitted	Number (percent) of subjects with each culture sequence in successive specimens				Number (percent) of subjects positive on 1 specimen
			- - -	+ + +	- - +	+ - -	
Patients	44	252	121 (62.7)	27 (14.0)	19 (9.8)	26 (13.5)	28 (63.6)
Controls	36	199	75 (48.7)	23 (14.9)	26 (16.9)	30 (19.5)	25 (69.4)

5 of these a diagnosis of acute anterior uveitis could be confidently made on a single occasion in 4 and on 2 occasions in 1. Self-diagnosis of acute anterior uveitis was accepted only when a previous similar attack had been medically diagnosed. No relationship between the onset of any of these episodes of acute anterior uveitis and a change in faecal *Klebsiella aerogenes* could be demonstrated (Fig. 1).

A further 5 patients gave a clear history of the onset of peripheral synovitis during the course of the study. Four patients (033, 048, 049, 051) had

faecal *Klebsiella aerogenes* recovered in the specimen immediately prior to or succeeding the onset of the peripheral synovitis (Fig. 2).

Thirteen patients were noted to have an increase in spinal activity during the course of the study (Fig. 3). In 3 (014, 045, 054) of these inactive spinal disease became probably active, and in the remainder probably active disease became definitely active. One patient (014) who developed active spinal disease, having been previously inactive, had faecal *Klebsiella aerogenes* coincident with this change in spinal

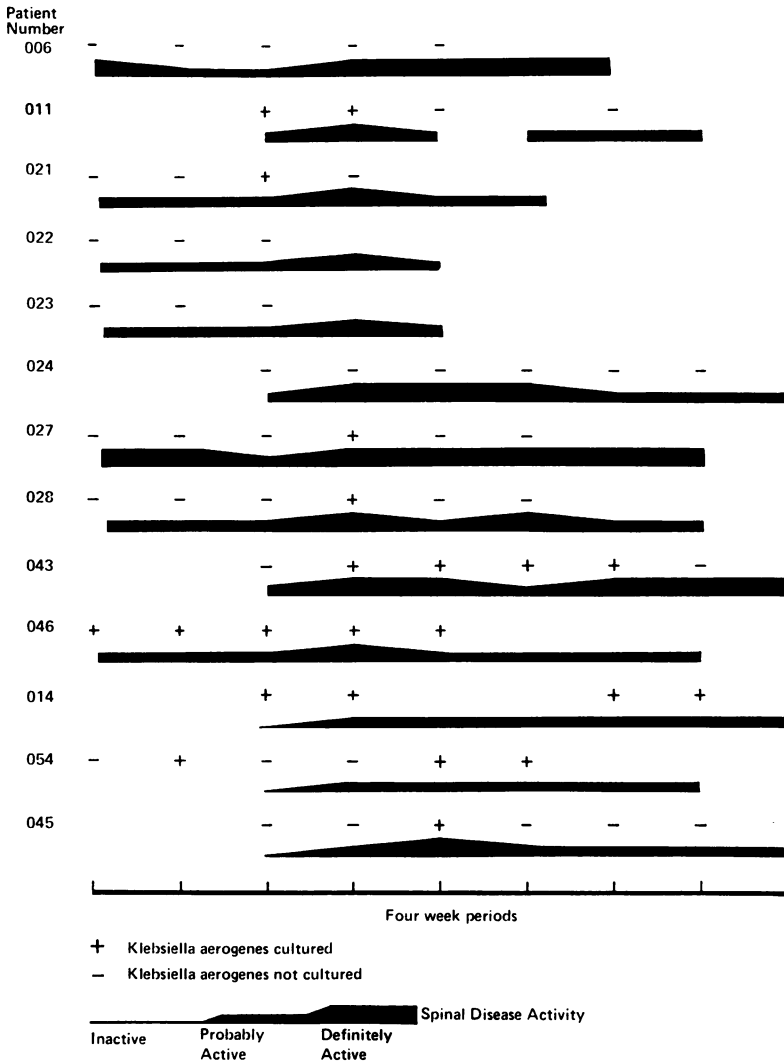


Fig. 3 Relationship between increases in spinal disease activity and faecal cultures in 13 patients. Period of increase in spinal disease activity has been synchronised for convenience.

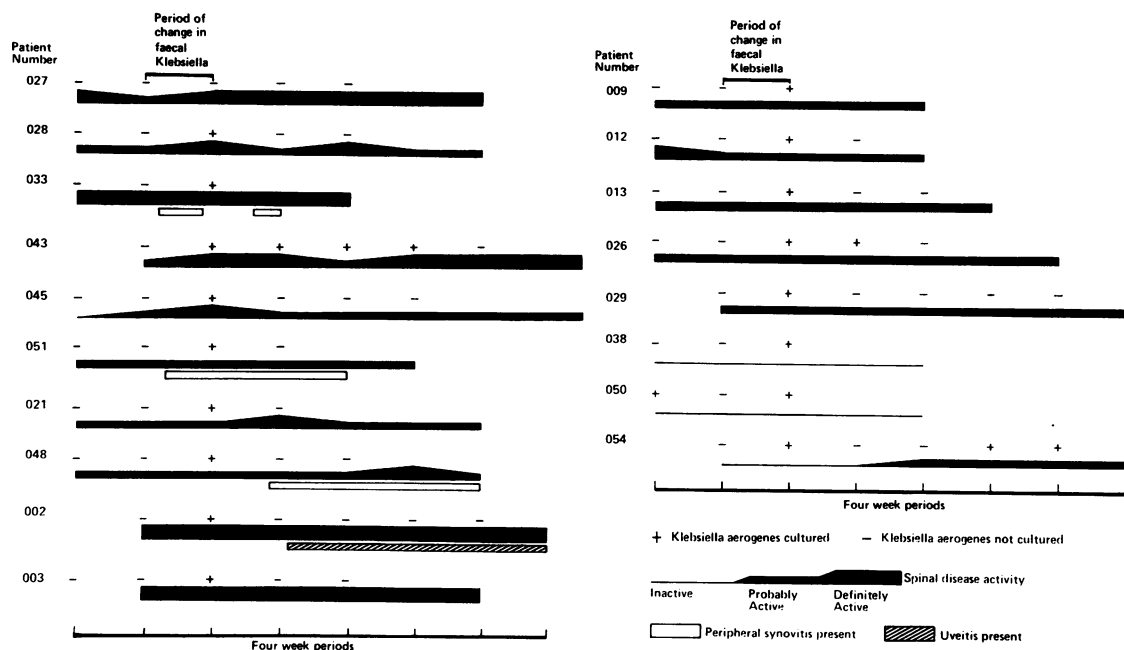


Fig. 4 Relationship between the appearance of faecal *Klebsiella aerogenes* and changes in disease activity in 18 patients. Patient no. 054 acquired faecal *K. aerogenes* on 2 occasions. The periods of change in faecal culture have synchronised for convenience.

activity, though preceding specimens were not available to indicate whether this was a change. A further patient (045) who initially had inactive spinal disease and subsequently developed definitely active disease had faecal *K. aerogenes* when the disease was definitely active but not in the 2 preceding months when the disease was inactive and probably active respectively. The third patient's (054) faeces became positive 1 month after the change in spinal disease activity. Of the 10 patients whose spinal disease activity increased from probably active to definitely active 3 (027, 028, 043) were found to have the appearance of faecal *K. aerogenes* in specimens collected when their spinal disease was active when cultures had previously been negative. A further 2 patients (011, 046) had faecal *K. aerogenes* on both occasions and 2 (006, 024) on neither occasion. One patient's (021) faeces became negative during this period. Two patients (022, 023) developed an increase in spinal disease activity after the 6-month period of faecal specimen collection.

Klebsiella aerogenes could be recovered from the faeces when the immediately preceding specimen had been negative in 18 patients on 19 occasions. The clinical activity of their spinal disease and the presence of peripheral synovitis and iritis have been

analysed in relation to this bacteriological change (Fig. 4). On 6 (027, 028, 033, 043, 045, 051) occasions (31.6%) this change in faecal bacteriology was associated with a coincidental worsening of the clinical status. In 4 instances (027, 028, 043, 045) this was an increase in the spinal symptoms and in 2 (033, 051) the development of peripheral synovitis. In 174 similar instances in which an alternative change in bacteriological status occurred (-/-, +/-, or +/+), 17 (9.8%) were associated with a deterioration in clinical disease ($\chi^2_c = 5.8$; $p < 0.02$). In 3 instances (021, 033, 048) the appearance of *K. aerogenes* in the faeces was associated with a deterioration in the clinical disease in the succeeding month. In 2 instances (033, 048) this was due to the development of peripheral synovitis and in 1 (021) to an increase in clinical spinal disease activity.

Discussion

The results of the present study show a significant increase in the number of clinical events represented by deterioration in spinal disease activity or peripheral synovitis in patients with ankylosing spondylitis, occurring in a period when faeces initially negative for *Klebsiella aerogenes* subsequently

became positive, when compared with other similar 4-week periods where this change in faecal *K. aerogenes* did not occur. No association between the occurrence of acute anterior uveitis with similar changes in faecal *K. aerogenes* was found.

These results contrast with those of our previous study⁷ and those of Ebringer *et al.*⁸ in which the presence of *Klebsiella aerogenes* was found to be particularly associated with episodes of acute anterior uveitis. In our earlier study the faecal specimens were obtained at the time the patient presented to the Ophthalmology Department with an attack of uveitis, whereas in the present study the faecal specimens were collected at regular 4-week intervals irrespective of the occurrence of individual clinical events. It is possible that *K. aerogenes* needs to be present for only a relatively short period in sufficient numbers to be detected in order to precipitate an attack of uveitis in a susceptible individual. The method of timing the bacteriological specimens in the present study, together with the small number of episodes of uveitis, could easily result in specimens being taken at an inappropriate time to detect the precipitating organism.

In a study of similar design recently reported by Warren and Brewerton¹¹ a similar low frequency of episodes of acute anterior uveitis occurred, and they were unable to associate these episodes with any change in faecal bacteriology.

Warren and Brewerton¹¹ could not demonstrate any association between changes in faecal *Klebsiella aerogenes* and any clinical changes in their patients. This contrasts with our own results and those of Ebringer *et al.*^{5,6} The reason for this discrepancy is not certain, but it is possible that the limited number of patients whose faeces grew *K. aerogenes*, having been previously negative, together with the infrequency of clinical events representing a deterioration in the patient's medical condition, makes it difficult to demonstrate an association between these 2 events. In addition serotyping has shown that it is possible for culture results alone to suggest persistence of *Klebsiella* species when one serotype is lost and another acquired. In the present study such a sequence has been analysed as persistence of the organism, since there is currently no evidence to suggest any particular serotype having a pathogenic role. On other occasions serotyping has suggested the persistence of the organism even though it could not be cultured. Our inability to culture the organism on these occasions is likely to be due to a fall in the number of organisms or their patchy distribution in the faeces. It is possible that the same serotype was lost and subsequently acquired, though this seems unlikely.

Unless the difficulties associated with patchy distribution of organisms in the faeces or temporary falls in the number of organism present can be further resolved, it is unlikely that further clinical studies of the types already carried out by ourselves and others will lead to further elucidation of the possible role of cross-reactivity between HLA B27 and *Klebsiella aerogenes* in the pathogenesis of ankylosing spondylitis.^{12,13} It is possible that further information could be gained on a relationship between *K. aerogenes* and acute anterior uveitis in patients with ankylosing spondylitis by even more frequent collection of faecal specimens from patients known to have recurrent but completely resolving attacks of anterior uveitis.

As *Klebsiella* spp. are liable to be multiply antibiotic resistant, the use of antibiotics in therapy is unlikely to be successful in their eradication from the bowel. This, together with the problems of defining active inflammatory disease of the vertebral joints, would be a major drawback to any controlled trial of antibiotics in ankylosing spondylitis.

The present study suggests an association between the appearance of faecal *Klebsiella aerogenes* in patients with ankylosing spondylitis and increases in spinal and peripheral joint disease activity. No association was found between acute anterior uveitis and similar changes in faecal *K. aerogenes*. This latter finding may be a consequence of the study method rather than a true reflection of the biological events.

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