EXTENDED REPORT

Comparison of rheumatological and gastrointestinal symptoms after infection with *Campylobacter jejuni/coli* and enterotoxigenic *Escherichia coli*

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Objectives: To estimate the incidence of postinfectious joint complaints after *Campylobacter jejuni/coli* enteritis compared with enteritis caused by enterotoxigenic *E coli (ETEC)*. To compare gastrointestinal symptoms, antibiotic treatment, and antibody levels among patients with and without joint symptoms.

Method: Questionnaires were sent to 210 consecutive patients with *Campylobacter* infection and an equal number of patients with *E coli (ETEC)*. Blood samples for anti-*Campylobacter* antibodies were collected after two weeks, three months, six months, and two years.

Results: Twenty seven of 173 (16%) patients with *Campylobacter* and 10/177 (6%) with *E coli (ETEC)* reported joint symptoms (p=0.004). In the *Campylobacter* group duration of diarrhoea was a median of 13 days for patients with arthralgia and seven days for those without joint pain (p=0.0058). Patients with *E coli* had diarrhoea of longer duration than patients infected with *Campylobacter* (14 days *v* seven days; p=0.0005). *E coli* patients had fewer gastrointestinal symptoms than *Campylobacter* patients (p=0.0001). Fifty nine per cent of *Campylobacter* patients with joint pain had received antibiotic treatment because of enteritis compared with 26% with enteritis only (p=0.03). *Campylobacter* species and serotypes were equally distributed in both groups and there was no difference in anti-*Campylobacter* antibody levels between the groups.

Conclusion: There was a significantly increased risk of developing joint symptoms after contracting *Campylobacter* infection compared with *E coli*. *Campylobacter* patients with joint pain had more severe gastrointestinal symptoms and longer duration of diarrhoea. Antibiotic treatment does not seem to prevent reactive joint symptoms. Levels of anti-*Campylobacter* antibodies were the same in both groups.

Reactive arthritis (ReA) after gastrointestinal infections caused by *Salmonella*, *Yersinia*, and *Shigella* has been known for a long time. In the late 1970s it was noted that the same clinical picture could be triggered by infection with *Campylobacter* spp.[1 2] *Campylobacters* are curved, microaerophilic, Gram negative rods with a natural reservoir in animals such as waterfowl and chicken, but can also be found in cattle, pigs, cats, and dogs. Animals may be infected without showing signs of disease.[3] In recent years *Campylobacter* has grown to be the leading cause of bacterial gastroenteritis in many Western countries,[4] and 82 cases per 100 000 inhabitants were registered in 2000 in Denmark.[5] Estimates of the incidence of reactive joint symptoms after *Campylobacter* enterocolitis vary between 0.6% and 24%, with most favouring an incidence around 2–3%.[1 6–9] The estimates are based mostly upon sporadic community outbreaks or on hospital records of culture proven *Campylobacter* diarrhoea.

This study is a retrospective survey focusing on self reported gastrointestinal and rheumatological symptoms in a group of *Campylobacter* infected patients. We used as disease controls an equal number of subjects with diarrhoea caused by *E coli (ETEC)* based on the a priori assumption that infection with *E coli* does not lead to reactive joint problems.

PATIENTS AND METHODS

Patients

The study group comprised 210 patients with *Campylobacter* infection proved by stool culture. Faecal samples from patients seeking medical advice for enterocolitis were submitted from general practitioners from all parts of Denmark. When the diagnosis was confirmed patients were asked to deliver serum samples after approximately two weeks, three months, six months, and two years. This study was conducted between 1997 and 1999 at the Department of Gastrointestinal Infections, Statens Serum Institut (SSI), Copenhagen, for the purpose of evaluating the antibody response against *Campylobacter* spp over time.[10] All patients had given written consent and the relevant ethical committees approved the project. Only people over 18 years were included.

In June 2000 all patients were mailed a questionnaire inquiring about gastrointestinal symptoms (duration of diarrhoea, vomiting, nausea, abdominal pain, and fever), antibiotic treatment, and whether pain in a previously healthy joint or back had been experienced after the infection. Our predefined criteria for categorising a case as probable ReA (which covers the spectrum from reactive arthralgia to overt arthritis) were absence of a pre-existing rheumatological condition, pain ascribed to a distinct anatomical location, joint symptoms which appeared within four weeks from the onset of diarrhoea; diffuse muscular/articular pain during the acute phase of diarrhoea was disregarded as ReA.

To estimate the impact of the rheumatic symptoms on daily life, patients were asked about their use of analgesics, if they had consulted their doctor or stayed at home from work because of joint pain. Furthermore, they were asked to mark on a drawing the location of either painful or swollen joints.

Abbreviations: ReA, reactive arthritis; SSI, Statens Serum Institut

Table 1 Clinical and demographic data for 173 patients with enteritis caused by *Campylobacter* and 177 patients with *E coli (ETEC)*

Clinical and demographic data	*Campylobacter* (n=173)		*E coli ETEC* (n=177)	
	ReA (n=27)	Non-ReA (n=146)	ReA (n=10)	Non-ReA (n=167)
Age (median)	36	34	43	41
Range	(18–65)	(18–76)	(25–63)	(18–76)
Sex, M/F (%)	10/17 (37/63)	65/81 (45/55)	5/5 (50/50)	78/89 (47/53)
Duration of diarrhoea, median (days)	13*	7* p=0.0058 7†	18.5	14 NS 14† p=0.0005
Interquartile range	8–28	5–14	9–28	6–21
Duration of joint symptoms, median (days)	60		165	NS
Interquartile range	29–180		45–835	
Days (median) from start of diarrhoea until onset of joint symptoms	14		7	NS
Interquartile range	7–19		2–11	
Treatment with antibiotics for diarrhoea:				
Yes (%)	16 (59)	39 (26) p=0.03	3 (33)	47 (28)
No (%)	11 (41)	75 (51)	6 (67)	91 (55)
Don't remember (%)	0	33 (23)	1 (10)	29 (17)

*Patients with *Campylobacter* ReA versus non-ReA; †patients with *Campylobacter* non-ReA versus *E coli (ETEC)* non-ReA.

As a control group 210 patients with *E coli (ETEC)* proved by stool culture were randomly selected from the same time period. Only patients with a single infection with either *Campylobacter* or *E coli* were included. The *E coli* patients received the same questionnaire.

No reminders were sent out, but instead non-respondents were sought twice by telephone and asked the same questions.

Identification of bacterial isolates

All faecal isolates were typed according to routine procedures at the department of gastrointestinal infections at SSI. *Campylobacter* were identified as *C jejuni* or *C coli* by conventional phenotypic tests, and serotyping was further undertaken by passive haemagglutination.[10]

E coli were identified by colony hybridisation of the primary cultures using probes directed at the genes encoding the heat labile and heat stable enterotoxins of ETEC (LT and ST). The identification was confirmed by the WHO International Escherichia and Klebsiella Centre at SSI.

Enzyme linked immunosorbent assay (ELISA) for anti-*Campylobacter* antibodies

Detection of antibodies to *Campylobacter* was performed as previously described.[10] Briefly, microtitre plates were coated overnight at 5°C with *C jejuni* O:1.44 and O:53 antigen. After blocking and washing, patient serum samples were incubated for 75 minutes, washed, and horseradish peroxidase labelled rabbit antiserum to human IgG, IgM, or IgA (DAKO, Glostrup, Denmark) were added and incubated for 75 minutes. Tetramethylenebenzidine (Kem-En-Tech, Copenhagen, Denmark) was used as substrate. The 90% centiles among 162 control sera for IgG, IgM, and IgA were 1.49, 0.56, and 0.22 U/ml, respectively.

Statistics

A Mann-Whitney U test was used to compare the duration of diarrhoea and joint symptoms between various groups. Yates's corrected χ^2 test was used to calculate differences in the numbers of patients with joint pain, gastrointestinal symptoms, and antibiotic treatment.

RESULTS

Answers were obtained from 173 patients (82%) with *Campylobacter* and from 177 (84%) with *E coli*. Table 1 shows the age and sex distribution of the patients. Thirty seven patients from the *Campylobacter* group reported joint symptoms, of whom 27 (16%) were considered probable ReA (seven were excluded because of diffuse generalised arthralgia during the acute phase of diarrhoea, two because joint symptoms started more than four weeks after the start of diarrhoea, and one had longstanding fibromyalgia). Among the *E coli* patients 22 reported joint symptoms and 10 (6%) were regarded as probable ReA (six were excluded because of diffuse myalgia/arthralgia, three had arthralgia with onset more than four weeks after diarrhoea, and three had pre-existing chronic knee or shoulder problems). The difference in incidence of ReA between the two groups was significant (p=0.004; risk ratio 2.76; 95% CI 1.38 to 5.53).

The patients with joint complaints had longer durations of diarrhoea than those without. In the *Campylobacter* group the

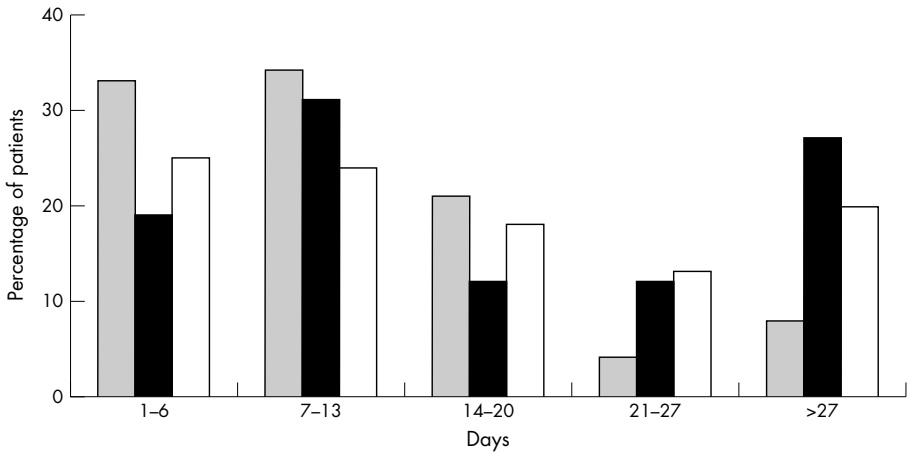

Figure 1 Duration of diarrhoea among 146 patients with *Campylobacter* enteritis (grey columns), 27 patients with *Campylobacter* ReA (black columns), and 167 patients with non-ReA *E coli (ETEC)* enteritis (white columns).

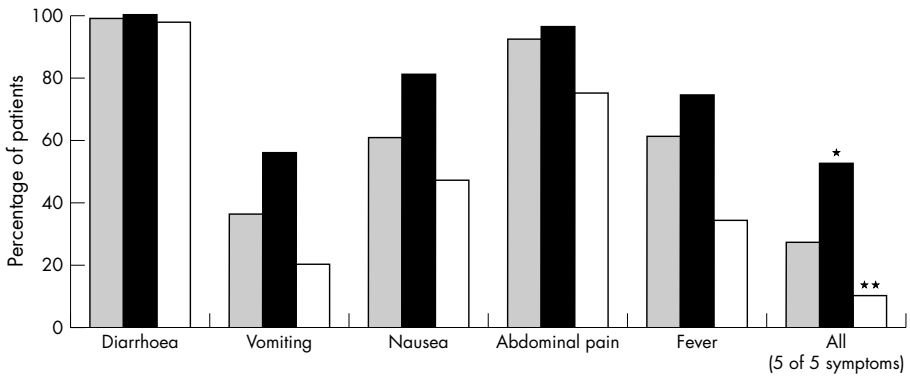

Figure 2 Individual gastrointestinal symptoms among 146 patients with *Campylobacter* enteritis (grey columns), 27 patients with *Campylobacter* ReA (black columns) (*p= 0.02, *Campylobacter* enteritis *v Campylobacter* ReA), and 167 patients with non ReA *E coli (ETEC)* enteritis (white columns) (**p= 0.0001, *Campylobacter* enteritis *v E coli (ETEC)* enteritis).

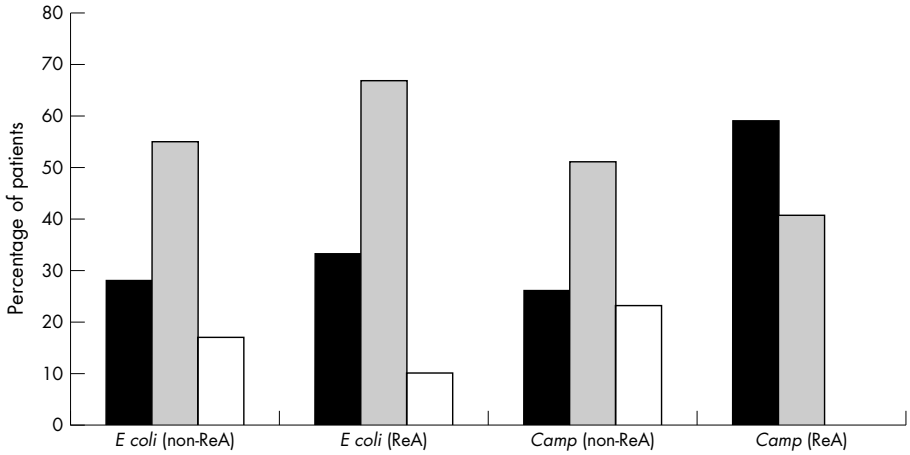

Figure 3 Proportions of patients treated with antibiotics for enteritis after infection with *Campylobacter* or *E coli (ETEC)*. (Black columns, antibiotic treated; grey columns, untreated; white columns, don't remember). *Campylobacter* ReA *v* non-ReA; p=0.03.

median period of diarrhoea was 13 days in the group with joint complaints *v* seven days for those with enterocolitis only (p=0.0058) (fig 1). The same pattern was seen in the *E coli* group, although not statistically significant. When the duration of diarrhoea was compared between non-ReA *Campylobacter* and non-ReA *E coli* the difference was highly significant (seven days *v* 14 days; p=0.0005) (fig 1).

The *Campylobacter* patients had a median period of joint symptoms of 60 days and the time from debut of diarrhoea until the onset of joint symptoms was a median of 14 days. Five patients claimed to have had joint problems for more than a year. Figure 2 shows the incidence of individual gastrointestinal symptoms within the *Campylobacter* group. It is notable that the patients with ReA in general had more symptoms than the patients without ReA. When the total numbers in each group who claimed they had had all five GI symptoms were compared there was a slight but significant difference (27% non-ReA *v* 52% ReA; p=0.02). Although the *E coli* patients had a longer median period of diarrhoea they had fewer gastrointestinal symptoms than the *Campylobacter* patients, when the non-ReA groups were compared (fig 2). All five symptoms was found in 27% of *Campylobacter* patients *v* 10% of *E coli* patients (p=0.0001).

When patients were asked to what extent the joint symptoms had affected their lives and how they had dealt with the problems there was virtually no difference between the *Campylobacter* and *E coli* groups. Forty eight per cent of *Campylobacter* patients had consulted their doctor, 67% took analgesics, and 26% stayed at home from work because of joint tenderness.

The antibiotic treatment for enterocolitis did not differ between the *E coli* and *Campylobacter* groups who had no arthritic complaints, but slightly more patients with *Campylobacter* ReA had received antibiotics (59%) than *Campylobacter* non-ReA patients (26%) (p=0.03, fig 3).

Table 2 Antibodies of IgG, IgA, and IgM isotypes against *Campylobacter* among 146 patients with enteritis and 27 patients with joint symptoms. Results are given as means (SD) in units/ml

Antibodies against *Campylobacter*, units/ml (cut off)	*Campylobacter* ReA (n=27)			*Campylobacter* non-ReA (n=146)		
	IgG (>1.49)	IgA (>0.22)	IgM (>0.56)	IgG (>1.49)	IgA (>0.22)	IgM (>0.56)
Mean after median 18 days	1.667 (0.65)	0.759 (0.87)	0.750 (0.68)	1.804 (0.71)	0.867 (0.77)	1.008 (0.78)
Percentage of sera antibody positive visit 1	63	70	47	70	80	57
Mean after median 114 days	0.984 (0.52)	0.095 (0.09)	0.392 (0.28)	1.189 (0.61)	0.123 (0.14)	0.472 (0.37)
Percentage of sera antibody positive visit 2	15	8	19	32	15	28
Mean after median 208 days	1.026 (0.45)	0.117 (0.07)	0.548 (0.39)	1.160 (0.59)	0.141 (0.12)	0.478 (0.31)
Percentage of sera antibody positive visit 3	13	13	26	31	18	28
Mean after median 599 days	0.909 (0.41)	0.084 (0.07)	0.410 (0.22)	0.899 (0.42)	0.108 (0.12)	0.410 (0.23)
Percentage of sera antibody positive visit 4	11	5	26	10	9	19

Overall, there was great individual variability in antibody response in the *Campylobacter* group; however, no significant differences between patients with and without ReA were noted. In both groups IgA had the highest and IgM the lowest sensitivity to detect infection at the initial visit after two weeks. There was a rapid decline in antibody levels within all isotypes, which was most pronounced, although not significant, in the ReA group (table 2).

The distribution of *Campylobacter* species was equal in both groups with approximately 4% being C *coli* and the rest C *jejuni* Also, there were no differences among serotypes with O:2, O:1.44, and the O:4 complex being the most prevalent. The O:19 serotype commonly associated with Guillain-Barré syndrome[11] was found in five patients, four with enterocolitis and one with ReA.

DISCUSSION

The reported incidence of postinfectious joint symptoms after gastrointestinal infections with arthritogenic bacteria varies considerably throughout published medical reports, not just between individual microbial agents but also between research groups dealing with this issue. In the monumental work by Paronen the incidence of ReA after infection with *Shigella flexneri* was calculated to be one in a thousand.[12] Probably this reflected only the tip of the iceberg, and in a much cited paper by Noer describing a localised outbreak with the same agent on board a battleship the rate of arthritis was 1.2%.[13]

Common to most reports is the fact that only patients with overt arthritis and in many instances only those referred to specialised rheumatological centres were included. As reactive joint symptoms presumably represent a continuum from slight transient arthralgia to longstanding debilitating arthritis a considerable number of cases might have been overlooked.

The bias of counting only those with the most severe symptoms can be overcome by relying on self reported symptoms from questionnaires sent to all exposed. We used this approach in two small outbreaks caused by *Salmonella enteritidis* and found an incidence of reactive joint complaints of between 15% and 19%.[14 15] These estimates, unfortunately, are hampered by the lack of reliable control groups, and there is an obvious risk of including cases where the rheumatological problems were more a consequence of infection itself than a complication of a specific arthritogenic bacterium. Although a number of community outbreaks caused by *Campylobacter* have been described, only a few reports have dealt systematically with postenteric joint pain.

There was an almost three times increased risk of contracting joint symptoms after enterocolitis caused by *Campylobacter* compared with *E coli*. Although a strict set of criteria was used to define ReA, 10 cases fitting our definition were found in the *E coli* group. The possibility cannot be excluded that co-immunisation with arthritogenic pathogens, eventually excreted in such small numbers that they escape diagnosis by routine faecal culture, might have taken place. Another possibility is that *E coli* in fact can lead to reactive joint inflammation, a possibility, however, that must await more substantial proof in clinically confirmed cases.

The duration of diarrhoea was significantly longer among patients with *Campylobacter* ReA than among those with intestinal symptoms only (13 *v* seven days), a difference also found in several *Salmonella* outbreaks,[16–18] but not previously reported for *Campylobacter* infections. This it at variance with findings in *Yersinia* triggered ReA, where patients with arthritis seem to have milder gastrointestinal symptoms and shorter duration of diarrhoea than those with uncomplicated enterocolitis.[19]

The *E coli* patients also had a substantially longer period of diarrhoea than those infected with *Campylobacter*. According to the textbooks, diarrhoea caused by *E coli (ETEC)* usually follows a very short course, with most illness subsiding within five days.[20] The present finding is not necessarily in contradiction to this because people with mild diarrhoea usually do not seek medical attention unless the symptoms have lasted for a long time. Therefore there may be a bias in the *ETEC* group towards illness of longer duration.

In response to questions on how the rheumatological symptoms affected their daily life, 67% had used analgesics, 48% had consulted their doctor, and 26% had been absent from work. Owing to the retrospective design of the study, these figures should be interpreted with caution. There might have been some overlap regarding, for example, absence from work because of either gastrointestinal discomfort or joint tenderness.

Twice as many patients with *Campylobacter* ReA had received antibiotics as those with enterocolitis only. This difference in treatment pattern was probably to some extent because the patients with ReA had more severe gastrointestinal symptoms and prolonged diarrhoea, which might have prompted their doctors to prescribe antibiotics. These figures do not suggest that treating the triggering infection can prevent postinfectious arthritis, a conclusion also reached in a previous report dealing with the same issue in a *Salmonella* outbreak.[14] Several studies with antibiotic treatment have been carried out on patients with manifest ReA[21 22] and besides a slight shortening of the course of *Chlamydia* triggered ReA[23] no substantial effect has been shown. The pathogenic events leading to postinfectious joint symptoms probably take place at such an early time that antimicrobial treatment is without effect.

In contrast with the reports for *Salmonella* and *Yersinia*,[24 25] the *Campylobacter* ReA cohort in this study had slightly lower antibody levels within all isotypes than the non-ReA group. This is rather surprising in view of the longer duration of diarrhoea and more pronounced gastrointestinal symptoms of the former. Most data concerning antibodies in *Salmonella* and *Yersinia* ReA were collected from patients referred to specialist units, and these patients might have had a more aggressive form of arthritis than the self reported cases in this study. The difference in patient sampling may thus explain the discrepancy.

In conclusion, this study shows that a significant proportion (16%) of *Campylobacter* infected patients can develop rheumatological complaints and that the gastrointestinal symptoms in this group are more severe and diarrhoea more prolonged than in those with enterocolitis only. It also raises the question whether *E coli (ETEC)* actually is an arthritogenic bacterium.

As only a minority of patients with diarrhoea seek medical attention and thus will have a stool sample sent for examination,[26] the socioeconomic implications of postenteric joint disease may be larger than previously thought.

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