

CONCISE REPORT

Reactive arthritis following an outbreak of *Salmonella typhimurium* phage type 193 infection

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Objectives: To determine the occurrence and the clinical picture of reactive arthritis (ReA) following an outbreak of *Salmonella typhimurium*.

Methods: An outbreak of *S typhimurium* phage type DT 193 occurred in several municipalities in Finland in 1999. A questionnaire which had a specific emphasis on musculoskeletal symptoms was mailed to all 78 subjects with a positive stool culture. Based on the answers, all subjects with recent joint complaints were clinically examined or interviewed by telephone.

Results: Sixty three of 78 subjects (81%) returned the questionnaire. Of these 63 subjects, five (8%) fulfilled the criteria for ReA. All the five subjects with ReA were adults with oligo- or polyarthritis. The antigen HLA-B27 was positive in two of the four subjects tested. In two of five subjects with ReA, the duration of acute arthritis was over six months. Subjects who had received antimicrobial drugs developed acute musculoskeletal symptoms significantly ($p=0.013$) less often than those without such treatment. None of the subjects with ReA had received antimicrobial drugs before the onset of joint symptoms.

Conclusions: The occurrence of ReA following an outbreak of *S typhimurium* was at the same level as in outbreaks due to other salmonella serotypes reported previously by us, indicating that the frequency of ReA after various outbreaks is ~10%. Early use of antimicrobial drugs may prevent the development of musculoskeletal symptoms.

Reactive arthritis (ReA) is a non-purulent joint inflammation which can be triggered by bacterial infections in the gastrointestinal or urogenital tracts. Among these triggering agents are different serotypes of *Salmonella enterica*, of which the most common serotypes causing ReA are Typhimurium and Enteritidis.¹

During outbreaks of *S enterica* infections, ReA has been reported to occur in 1–15% of subjects.^{2–13} We have previously reported two salmonella outbreaks with rheumatological surveys: one due to *S enterica* serotype 4,5,12:b:-,⁸ and the other due to serotype Bovismorbificans 6.8:r:1,5.¹² In these outbreaks, the occurrence of ReA was 6.9% and 11.5%, respectively.

We recently had the opportunity to study another outbreak of salmonellosis. We have applied the same methodology in all our studies of outbreaks, and therefore this enabled us to compare the arthritogenicity of various serotypes of salmonella. Furthermore, because of preliminary evidence of the lack of efficacy of early antibiotic treatment in the prevention of ReA,^{7, 12} we set out to evaluate antimicrobial chemotherapy more accurately in the treatment of infection and subsequent development of arthritis.

SUBJECTS AND METHODS

The outbreak

An outbreak of acute gastrointestinal infection caused by a rare definite phage type DT 193 of *S typhimurium* occurred in several municipalities in Finland in the spring of 1999. In all, 78 subjects were verified to have infection caused by this phage type. The origin of the outbreak was unknown.

Questionnaire on musculoskeletal symptoms

The questionnaire was sent to all 78 subjects with a positive stool culture. The mailing was carried out within two months after the outbreak was noticed. Two separate reminders were sent to those who did not respond. The questionnaire was analogous to that used in our earlier studies dealing with ReA in association with other salmonella outbreaks.^{8, 12} In addition, we focused more specifically on the onset and duration of diarrhoea and of musculoskeletal symptoms in order to examine the effect of antimicrobial treatment of diarrhoea on the occurrence of musculoskeletal symptoms.

Diagnostic criteria

ReA was defined as the development of synovitis (both swelling and pain) in a previously asymptomatic joint within the first weeks after a gastrointestinal infection; there could also be signs or symptoms of inflammatory low back pain, tendinitis, enthesopathy, or bursitis. Each affected joint in toes and fingers was counted individually. Any other forms of joint or back pain during or after the acute infection were also recorded.

Clinical examination

From the answers to the questionnaire, all subjects with suspected ReA or other reactive musculoskeletal manifestations were invited to attend a clinical examination performed by the study rheumatologist (TH). Blood was collected for the measurement of erythrocyte sedimentation rate, C reactive protein, rheumatoid factor, and for HLA-B27 analysis at the clinical examination, which was performed a median of six months after the onset of musculoskeletal manifestations. If the subject could not attend for the clinical examination, the musculoskeletal diagnosis was based on interview by telephone or solely on the information obtained by the questionnaire.

Statistical analysis

Data were analysed by the BMDP statistical software system (BMDP Statistical Software, Inc, Los Angeles, CA, USA). Proportional data were compared by the χ^2 test or with Fisher's exact test. The Mann-Whitney U or Student's *t* tests were applied for comparisons of continuous variables. Statistical significance was set at the 5% level.

Abbreviations: ReA, reactive arthritis

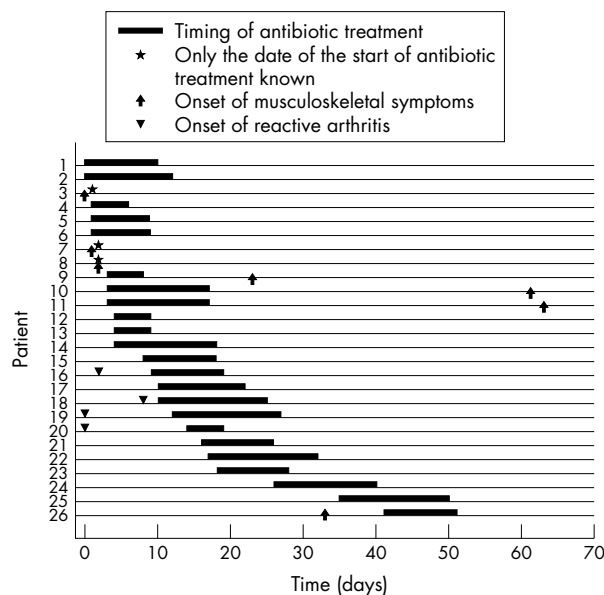


Figure 1 Use of antimicrobial chemotherapy and musculoskeletal complications in the cohort with an outbreak of *Salmonella typhimurium*. Exact data of the onset of antibiotics was available for 26/32 subjects who received antimicrobial drugs. Day 0 = day of the onset of diarrhoea except in subject 24, where it was the day of the positive stool culture.

RESULTS

All subjects

Of the 78 subjects, 63 (81%) returned the questionnaire. The median age of responders was 30.7 years (range 2–66), 50 (79%) were older than 16 years, and 37 (59%) were women. As features of infection, 54/63 (86%) reported diarrhoea, 51/63 (81%) abdominal pain, and 45/58 (78%) fever ($\geq 37.5^{\circ}\text{C}$).

Subjects with musculoskeletal symptoms

Recent joint complaints were reported by 25/63 (40%) subjects. Clinical examination was performed in 13 and telephone interview in nine subjects; in three subjects, the musculoskeletal diagnosis was based solely on the information obtained by the questionnaire. Five subjects (8%) fulfilled the criteria for ReA. Twelve additional subjects (19%) had acute postinfective arthralgia or lumbar pain. Furthermore, five subjects (8%) had joint or back pain in association with acute salmonella enteritis. The remaining three subjects

had other coexistent joint symptoms not related to the recent salmonella infection (tension neck, distension of ankle, arthralgia due to concurrent hepatitis B infection).

Subjects with ReA

The five subjects with ReA were all adults (three women, two men) with a median age of 34.8 years (range 30–46). The median onset of joint symptoms was two days (range 1–9) after the first symptoms of diarrhoea (or positive stool sample in one subject). The arthritis was oligoarticular in three and polyarticular in two subjects. Besides peripheral arthritis, two subjects had inflammatory low back pain; each of these two subjects also had Achilles tendinitis, and one of them enthesopathy.

All five subjects with ReA had visited a doctor because of arthritis, and two subjects had acute arthritis severe enough to lead to admission to hospital. The joint symptoms lasted from three to five months in three subjects and over six months in two subjects. Two of the four tested subjects with ReA were positive for HLA-B27. The duration and severity of joint symptoms were much the same, irrespective of the HLA-B27 status.

Antimicrobial treatment

Altogether, 32/63 (51%) subjects had received antimicrobial drugs, exclusively fluoroquinolones, for intestinal or extra-intestinal symptoms (fig 1). The causative salmonella strain was sensitive to ciprofloxacin. The average interval time between the onset of diarrhoea (or positive stool sample in one subject who had no gastrointestinal symptoms) and the onset of antibiotic treatment, and the average duration of antibiotic treatment did not differ significantly between subjects with or without musculoskeletal complaints (9.0 v 9.1 days, and 11 v 10 days, respectively). Of the 25 subjects with acute musculoskeletal symptoms, 22 provided detailed information which enabled us to analyse the association between the antimicrobial treatment and the occurrence of musculoskeletal symptoms. Of these 22 subjects, two had received antimicrobial drugs before the onset of joint complaints, whereas 13/31 subjects who had no musculoskeletal symptoms had received antimicrobial chemotherapy (9% v 42%; $p=0.013$). In the ReA group ($n=5$) none had received antimicrobial drugs before the onset of joint disease, whereas in the rest of the subjects who provided sufficient information ($n=57$), 26 subjects had received antimicrobial drugs (0% v 16%; $p=0.056$). No distinct time interval existed within which early intervention with antibiotics would have prevented the development of musculoskeletal symptoms (fig 1).

Table 1 Outbreak cohorts of various *Salmonella enterica* serovars with rheumatological survey*

Reference	Serovar	Source	Number of subjects in the outbreak	Study type	No (%) of subjects who responded to the questionnaire	Number of patients with ReA	Occurrence of ReA† (% (No))
Bengtsson <i>et al</i> , 1955 [2]	Typhimurium	Meat	1800	H	–	9	1.4 (9/654‡)
Häkansson <i>et al</i> , 1976 [3]	Typhimurium	NA	330	H	–	13	3.9 (13/330)
Eastmond <i>et al</i> , 1983 [4]	Typhimurium	Milk	448	H	–	8	1.8 (8/448)
Inman <i>et al</i> , 1988 [5]	Typhimurium	Food	473	QwCE	340 (72)	19	7.3 (19/260§)
Thomson <i>et al</i> , 1992 [6]	Heidelberg	Potato salad	83	QwCE	76 (92)	6	7.2 (6/83)
Locht <i>et al</i> , 1993 [7]	Enteritidis	Food	126	Q	113 (90)	17	1.5 (17/113)
Thomson <i>et al</i> , 1994 [9]	Enteritidis	Turkey	88	QwCE	34 (39)	8	9.1 (8/88)
Mattila <i>et al</i> , 1994 [8]	4,5,12:b:-	Mung bean sprouts	272	QwCE	246 (90)	17	6.9 (17/246)
Samuel <i>et al</i> , 1995 [10]	Typhimurium	Food	919	QwCE	321 (35)	6–23	1.2–4.6 (6/495¶ to 23/495¶)
Thomson <i>et al</i> , 1995 [11]	Typhimurium	Food	423	QwCE	411 (97)	27	6.4 (27/423)
Mattila <i>et al</i> , 1998 [12]	Bovismorbificans	Alfalfa sprouts	210	QwCE	191 (91)	22	11.5 (22/191)
McCull <i>et al</i> , 2000 [13]	Typhimurium	Pork rolls	849	QwCE	424 (50)	19	4.5 (19/424)
Present study	Typhimurium	Food	78	QwCE	63 (81)	5	7.9 (5/63)

*Based on studies with a reliable estimate of the total number of infected subjects; †presented as calculated in the referred study; ‡number of subjects admitted to hospital for salmonellosis; §number of subjects with adequate data; ¶number of subjects with positive stool culture for salmonella. NA, data not available; H, hospital based; QwCE, based on questionnaire followed by clinical examination; Q, based only on questionnaire.

DISCUSSION

For other salmonella outbreaks, in which the size of the epidemic has been adequately estimated, the incidence of ReA varied between 1.2% and 15% (table 1). In our study the occurrence of ReA was 8%. This incidence is compatible with our two earlier studies, in which the occurrence of ReA was 11.5% and 6.9% with the serotypes 4,5,12:b:- and Bovismorbificans, respectively.^{8,12} As we have applied the same methodology in our studies, these observed incidences seem to be reliable and valid. The response rate to the questionnaire has been high, between 81% and 91%, and the diagnostic criteria for ReA has been the same in all our studies. Based on the current study and our previous series, arthritogenicity of the triggering salmonella infections is quite similar, irrespective of the specific serotype.

According to our results, antimicrobial chemotherapy seems to have an impact on the development of acute musculoskeletal symptoms following salmonellosis. To date, unlike gastrointestinal infection, a positive effect of the early use of antimicrobial drugs on the prevention of ReA has been seen only in acute non-gonococcal urethritis.¹⁴ This has been evaluated previously in two studies of salmonella outbreak,^{7,12} but neither study showed that early antibiotic treatment was efficacious. As a modification to our previous study,¹² the use of antibiotic treatment was particularly examined in the present study.

Two recent studies showed that ciprofloxacin had no advantage over placebo on the outcome of acute enteric ReA.^{15,16} The object of these studies, however, was to evaluate the use of antimicrobial drugs in the treatment of ReA rather than in the prevention of it. As prospective controlled studies to assess the effects of antimicrobial drugs in the prevention of ReA in humans are difficult to perform, investigations relying on retrospective analysis of defined study groups are the only clear possibility. This was also the situation in the aforementioned study of Bardin *et al.*¹⁴ According to an experimental animal model, the early use of antimicrobial drugs in the prevention of enteric ReA, is not unreasonable: an early course of ciprofloxacin before the appearance of any signs of arthritis prevented ReA, whereas antibiotic treatment of fully developed arthritis was not effective.^{17,18}

In summary, our study has two important implications. Firstly, the arthritogenicity of the salmonella infections seems to be quite similar, irrespective of the triggering serotype. Secondly, early use of antimicrobial chemotherapy may be effective in preventing the development of acute musculoskeletal symptoms following salmonellosis. Despite this encouraging result the role of antimicrobial drugs in the prevention of ReA triggered by enteric infection is still unsettled and warrants future studies.

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REFERENCES

- Mäki-Ikola O, Granfors K. Salmonella-triggered reactive arthritis. *Scand J Rheumatol* 1992;21:265–70.
- Bengtsson E, Hedlund P, Nisell Å, Nordenstam H. An epidemic due to *Salmonella typhimurium* (Breslau) occurring in Sweden 1953. *Acta Med Scand* 1955;153:1–20.
- Håkansson U, Eitrem R, Löw B, Winblad S. HLA-antigen B27 in cases with joint affections in an outbreak of salmonellosis. *Scand J Infect Dis* 1976;8:245–8.
- Eastmond CJ. Gram-negative bacteria and B27 disease. *Br J Rheumatol* 1983;22(suppl 2):67–74.
- Inman RD, Johnston MEA, Hodge M, Falk J, Helewa A. Post-dysenteric reactive arthritis. A clinical and immunogenetic study following an outbreak of salmonellosis. *Arthritis Rheum* 1988;31:1377–83.
- Thomson GTD, Chiu B, De Rubeis D, Falk J, Inman RD. Immunoepidemiology of post-salmonella reactive arthritis in a cohort of women. *Clin Immunol Immunopathol* 1992;64:227–32.
- Locht H, Kihlström E, Lindström FD. Reactive arthritis after salmonella among medical doctors – study of an outbreak. *J Rheumatol* 1993;20:845–8.
- Mattila L, Leirisalo-Repo M, Koskimies S, Granfors K, Siitonen A. Reactive arthritis following a salmonella outbreak in Finland. *Br J Rheumatol* 1994;33:1136–41.
- Thomson GTD, Alfa M, Orr K, Thomson BRJ, Olson N. Secretory immune response and clinical sequelae of *Salmonella* infection in a point source cohort. *J Rheumatol* 1994;21:132–7.
- Samuel MP, Zwillich SH, Thomson GTD, Alfa M, Orr KB, Brittain DC, *et al.* Fast food arthritis – a clinico-pathologic study of post-salmonella reactive arthritis. *J Rheumatol* 1995;22:1947–52.
- Thomson GTD, DeRubeis DA, Hodge MA, Rajanayagam C, Inman RD. Post-salmonella reactive arthritis: late clinical sequelae in a point source cohort. *Am J Med* 1995;98:13–21.
- Mattila L, Leirisalo-Repo M, Pelkonen P, Koskimies S, Granfors K, Siitonen A. Reactive arthritis following an outbreak of *Salmonella bovismorbificans* infection. *J Infect* 1998;36:289–95.
- McColl G, Diviney M, Holdsworth R, McNair P, Carnie J, Hart W, *et al.* HLA-B27 expression and reactive arthritis susceptibility in two subject cohorts infected with *Salmonella typhimurium*. *Aust NZ J Med* 2000;30:28–32.
- Bardin T, Enel C, Cornelis F, Salski C, Jorgensen C, Ward R, *et al.* Antibiotic treatment of venereal disease and Reiter's syndrome in a Greenland population. *Arthritis Rheum* 1992;35:190–4.
- Sieper J, Feender C, Laitko S, Sörensen H, Gripenberg-Lerche C, Hiepe F, *et al.* No benefit of long-term ciprofloxacin treatment in subjects with reactive arthritis and undifferentiated oligoarthritis. A three-month, multicenter, double-blind, randomized, placebo-controlled study. *Arthritis Rheum* 1999;42:1386–96.
- Yli-Kerttula T, Luukkainen R, Yli-Kerttula U, Mötönen T, Hakola M, Korpela M, *et al.* Effect of a three month course of ciprofloxacin on the outcome of reactive arthritis. *Ann Rheum Dis* 2000;59:565–70.
- Zhang Y, Gripenberg-Lerche C, Söderström K-O, Toivanen A, Toivanen P. Antibiotic prophylaxis and treatment of reactive arthritis. Lessons from an animal model. *Arthritis Rheum* 1996;39:1238–43.
- Zhang Y, Toivanen A, Toivanen P. Experimental yersinia-triggered reactive arthritis: effect of a 3-week course of ciprofloxacin. *Br J Rheumatol* 1997;36:541–6.