Acute and Chronic Gastrointestinal Manifestations Associated With *Yersinia enterocolitica* Infection

A Norwegian 10-year Follow-up Study on 458 Hospitalized Patients

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The aim of the present study was to elucidate the gastrointestinal manifestations of yersiniosis. During the period 1974 to 1983, *Yersinia enterocolitica* infection was diagnosed in 458 patients, by isolation from fecal samples or by antibody response. At first admission, 184 patients had abdominal pain; 200, diarrhea; 45, vomiting; and 36, weight loss. Ulcerative colitis was diagnosed in 7 patients, Crohn's disease in 2, and unspecific colitis in 11. Mesenteric lymphadenitis or ileitis were found in 43 of 56 patients at laparotomy. The patients were followed for 4 to 14 years (1987). Thirty-eight patients were readmitted with abdominal pain and 28 with diarrhea; these symptoms were significantly correlated with the corresponding symptoms at first admission. Chronic colitis was diagnosed in 4 patients, chronic weight loss in 12. A follow-up inquiry (380 patients) indicated that patients with right iliac fossa pain during the acute infection less frequently developed chronic abdominal complaints. Gastrointestinal symptoms are common in both the acute and chronic stages of yersiniosis. The correlations between acute and chronic symptoms indicate that yersiniosis is a chronic disease. Immunologically competent individuals may profit by fighting the infection in the right iliac fossa. The relationship between yersiniosis and inflammatory bowel diseases may still not be settled.

YERSINIA ENTEROCOLITICA WAS isolated from a patient with acute terminal ileitis in 1964,[1] and its associations with this condition and with mesenteric lymphadenitis were recognized during the next few years.[2,3]

The most common abdominal manifestation of the acute *Y. enterocolitica* infection apparently is a self-limiting gastroenteritis. Emergency intestinal resections have been performed in some patients, however, and some have died of fulminant disease.[4,5] Other patients have developed chronic intestinal disease.[6]

The aim of the present study was to perform a survey of acute and chronic gastrointestinal manifestations associated with *Y. enterocolitica* infection.

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Materials and Methods

The determination of antibodies to *Y. enterocolitica* was introduced in Norway by the National Institute of Public Health in 1972.

During the 10-year period 1974 to 1983, the institute's laboratory diagnosed *Y. enterocolitica* infection in 553 hospitalized patients. Excluded were 95 patients with insufficient or missing hospital files. Adequate clinical information was obtained on 458 patients (202 men and boys, mean age 33.4 years; and 256 women and girls, mean age 39.6 years) admitted to 52 different hospitals, and these patients constitute the material of the present study.

Clinical Data

Clinical data were obtained from the various clinical departments on the first admission, and from all subsequent admissions. Valuable information was obtained also through general practitioners. The study was terminated June 30, 1987, with observation times of 4 to 14 years. At this time, 46 patients were dead and two could not be located.

Three hundred eighty of the 410 remaining patients replied to a clinical questionnaire on persistence or development of particular abdominal complaints *after* the infection, by checking as appropriate the alternatives "Yes," "No," or "Uncertain." The patients admitted to Bergen University Hospital all underwent a thorough clinical follow-up examination, including endoscopic examinations in patients with severe chronic diarrhea.

Diagnosis of *Y. enterocolitica* infection was based on one or both of the following methods:

A. Isolation of Y. enterocolitica from fecal samples (serotype 0:3, 56 patients; serotype 0:9, 1 patient).
B. Antibody response to *Y. enterocolitica* as evaluated by one of the following methods:
   (i) During the period 1974 through August 1982: bacterial whole cell agglutination using alcohol-treated bacterial cells as antigen. An agglutination titer of at least 640, or a fourfold or greater increase of the titer in two consecutive samples, was recognized as indicative of an actual or recent infection (serotype 0:3, 395 patients; serotype O:9, 2 patients).
   (ii) During the period September 1982 through 1983: enzyme-linked immunosorbent assay (ELISA) using lipopolysaccharide extracted with hot phenol water as antigen.[7] Serum samples were examined for both specific IgG and IgM activity (at follow-up also IgA activity). Net absorbance values (absorbance in the sample minus the absorbance in the negative control) of 0.1 or greater were regarded as significant. A net absorbance of 0.5 or greater, or an increase in the activity of at least 30% in two consecutive serum samples, were considered indicative of an actual or recent infection (serotype 0:3, 33 patients).

Laboratory and Clinical Examinations. Laboratory and clinical examinations were performed according to standard procedures. Their extent varied between hospitals and departments and with seriousness of disease. The reported observations represent minimum numbers.

Statistics

The two-sample Student's t test, the standard error of difference between two proportions, the chi square test with Yates' correction, and Fisher's exact test for 2 × 2 contingency tables (all two-sided) were used for comparison between subgroups of the material.

Results

First Admission

Acute Abdominal Symptoms. Age and sex distribution of patients with acute abdominal symptoms are displayed in Table 1. Patients with particular pain localizations showed significantly different age distributions. The majority of patients with *vomiting,* and every second patient with *diarrhea,* concomitantly had abdominal pain.

Children less than 10 years of age had a significantly higher total frequency of diarrhea than did older patients (17/24 > 183/424; p = 0.015); and a higher relative frequency of macroscopically bloody diarrhea (5/17 > 14/183; p = 0.03). Most children with bloody diarrhea were infants. Children younger than 10 years of age had a significantly higher frequency of vomiting than did older patients (6/24 > 39/424; p = 0.04); all children with vomiting were in fact younger than 5 years of age.

Weight Loss. Weight loss (mean, 7.4 kg) in 36 patients usually took place over a few weeks or months in association with the acute infection. Twenty-four patients concomitantly had diarrhea; 19, acute polyarthritis; 4, liver involvement; 2, acute nephritis; and 1, pulmonary involvement. Four female and 2 male patients lost more than 10 kg of weight. A 26-year-old woman who lost 20 kg over 1 year developed chronic pancreatic insufficiency.

Emergency Operations. Thirty males (14.9%) and 26 females (10.2%) underwent emergency abdominal operations. Perioperative findings and age distribution of patients are displayed in Table 2.

TABLE 1. *Acute Abdominal Symptoms Observed Among 448 Patients Admitted With* Y. enterocolitica *Infection**

	M				F			
		Age (yr)				Age (yr)		
	No.	Range	Mean	SD	No.	Range	Mean	SD
Abdominal pain								
Diffuse	40	2–66	32.6*	17.2	52	3–81	39.1‡	18.5
Low right	36	6–88	27.1†	17.9	38	7–68	30.9‡	16.8
Subcostal right	7	35–60	46.1*†	9.2	8	19–94	41.6	24.2
Left side	2	33–36			1	47		
Total	85				99			
Diarrhea								
Without bleeding	80	1–88	34.0	18.9	101	0–81	41.3	18.3
Bloody	9	0–65	30.7	21.2	10	0–55	23.8	18.0
Total	89				111			
Vomiting	21	2–77	25.4	18.2	24	0–94	40.5	22.9
Weight loss	14	15–68	33.4	14.6	22	6–75	50.9	17.2

Ten patients with previous ulcerative colitis, Crohn's disease, or chronic colitis not included.
* p = 0.05.
† p < 0.01.
‡ p < 0.04.

TABLE 2. *Intra-abdominal Conditions Observed in 56 Patients who Underwent Emergency Laparotomy*

	M				F			
		Age (yr)				Age (yr)		
	No.	Range	Mean	SD	No.	Range	Mean	SD
Mesenteric lymphadenitis	10	6–23	14.6*†	5.0	13	7–47	23.2*‡	11.5
Terminal ileitis/ileitis	14	17–66	31.5†	12.4	6	16–66	38.2‡	21.3
Other conditions (see text)	6				7			

Sex and age distribution, significance of observed mean age differences.
* p = 0.04.
† p = 0.0006.
‡ p = 0.06 (NS).

Mesenteric lymphadenitis was the only finding in 10 male and 13 female patients. Among 13 male patients with acute terminal ileitis, eight also had mesenteric lymphadenitis. One male patient had regional ileitis. Among six female patients with ileal affection, three had terminal ileitis and three had diffuse ileitis. The youngest two (16 and 18 years of age) additionally had mesenteric lymphadenitis. One woman with diffuse ileitis shortly afterward developed acute pancreatitis. The sex differences in frequency of ileitis, and in lymphadenitis/ileitis ratio, were statistically not significant.

In two men (18 and 40 years of age) and one woman (23 years of age), surgery disclosed acute appendicitis, an 88-year-old man suffered from acute cholecystitis, two women (17 and 75 years of age) had acute hepatitis, and a 35-year-old woman had acute colitis. In a 21-year-old man, mesenteric lymphadenitis was associated with a perforated duodenal ulcer. A 41-year-old man presented with monstrous mesenteric lymphadenitis, splenomegaly, and slight liver affection[8]; in another (57 years of age), mesenteric lymphadenitis caused ileocolic intussusception.[9] An ileopsoas muscle hematoma was found in a 22-year-old woman; in another (20 years of age), ample intraperitoneal fluid only was found.

Examinations and Findings in Patients Not Operated On. Thirty-two patients underwent endoscopy, and 137 were radiologically examined. Acute gastroduodenitis was diagnosed in one patient, terminal ileitis in one, acute colitis in seven, acute proctitis in two, and chronic unspecific colitis in two patients.

Abdominal Masses. A boy and a man (14 and 26 years of age) and three women (19, 42, and 80 years of age) were admitted with right iliac fossa inflammatory masses, and a 66-year-old man was admitted with a rectovesical fossa abscess.

Association With Chronic Inflammatory Bowel Disease. A 30-year-old woman was admitted 1 month after the acute onset of severe diarrhea; a 32-year-old man was admitted after 7 months. Both patients later underwent bowel resection. Microscopy of specimens showed changes consistent with ulcerative colitis (UC) in the woman, and Crohn's disease (CD) in the man.

Another four men (19 to 74 years of age) and three women (41 to 62 years of age) had suffered from chronic inflammatory bowel disease for 2 to 20 years. Ulcerative colitis was diagnosed in six; CD, in 1. Some of them had experienced extraintestinal manifestations like eosinophilic pulmonary infiltrate, hepatitis, chronic cholecystitis, rectovaginal or perianal fistulas, arthritis, eye inflammation, or generalized urticaria; one had positive tests for rheumatoid factor. One patient died in hospital, three underwent intestinal resections, and three were still on medical treatment at follow-up. Chronic nonspecific colitis was diagnosed in a 48-year-old woman with chronic diarrhea.

Follow-up

Readmissions. One hundred sixty patients (73 males, 36.1%; and 87 females, 34.0%) were readmitted during the follow-up period; 47 male and 55 female patients were readmitted three or more times. One male and 1 female patient were admitted about 40 times each because of chronic disease affecting several organ systems.

Abdominal symptoms. Among the 160 readmitted patients, 38 suffered from chronic abdominal pain, and 28 from chronic diarrhea. Nine patients suffered from both abdominal pain and diarrhea. Symptoms at readmission were significantly correlated with symptoms at first admission (Table 3).

Weight loss (mean, 9.4 kg) was observed in 12 patients (5 males and 7 females); it was associated in all with some chronic manifestation such as diarrhea, nephritis, hepatitis, or arthritis. Three of these patients had also experienced weight loss in association with the acute infection. A woman who lost 24 kg needed intravenous alimentation.

Examinations and findings. Thirty-three patients underwent endoscopy, and 53 were radiologically examined. Chronic colitis was diagnosed in another four male patients (mean age, 30 years). A 36-year-old man with diffuse abdominal complaints and abnormal stools had low serum levels of iron, cholesterol, and cobalamin. His duodenal biopsies showed low and partly coalesced villi, sug-

TABLE 3. *Patients With and Without Acute Abdominal Pain or Diarrhea at First Admission who Were Readmitted With Chronic Abdominal Pain or Diarrhea*

First admission		Readmission symptoms			
		Abdominal pain		Diarrhea	
Symptom	No.	No.	(%)	No.	(%)
Abdominal pain					
With	184	23	(12.5)*	15	(8.2)
Without	264	15	(5.7)*	13	(4.9)
Diarrhea					
With	200	22	(11.0)	18	(9.0)†
Without	248	16	(6.5)	10	(4.0)†
Total	448	38	(8.5)	28	(6.3)

Ten patients with previous ulcerative colitis, Crohn's disease, or chronic colitis not included.
* $p < 0.015$.
† $p = 0.03$.

gesting celiac disease; gastric biopsies showed chronic inflammation and intestinal metaplasia, and colonic biopsies showed slight chronic inflammation. Two patients had pathologic Schilling's tests, indicating ileal affection.

Reexamination at the Bergen University Hospital. Among 24 reexamined patients, nine complained of diarrhea; they all related the start of their complaints to the *Y. enterocolitica* infection.

Five with severe chronic diarrhea (5 to 15 stools a day) underwent duodenoscopy and colonoscopy; in four of them duodenal biopsies were abnormal with slight edema, moderate inflammation, and some flattened villi. One patient microscopically had minor changes in distal colon. Small bowel series disclosed no abnormality; serum levels of folic acid, cobalamin, calcium, and total protein were normal in all. *Y. enterocolitica* or other pathogenic bacteria were not isolated from their stools. All still had significant specific activity of IgG (net absorbance values: 0.25 to 0.57), three had low but significant IgM activity, and three had IgA activity. One patient had an IgA net absorbance value of 0.25 after 12 years; another, 0.61 after 9 years (ELISA).

Questionnaire. Chronic complaints inquired about were abdominal pain, diarrhea, mucous or bloody diarrhea, voluminous stools floating on water, and weight loss.

The frequencies of "Yes" answers among 371 patients without inflammatory bowel disease (IBD) (see above) are displayed in Table 4. The complaints usually were tolerable and experienced periodically, but several patients (among them 11 with weight loss) had needed hospital admission, and some were socially disabled.

Sex and age. Male and female patients reported comparable frequencies of the particular complaints; the age distributions mirrored the sexes' whole material age distributions. No correlation was found between age at first admission and frequencies of later complaints.

Time of observation. Patients who had been followed for 10 years or more reported higher frequencies of mucous or bloody stools, and of weight loss, than patients admitted later ($38/213 > 17/158$, $p < 0.06$; *viz.* $28/213 > 11/158$, $p < 0.06$).

Relation to first admission symptoms. More patients complained of diarrhea who had been admitted with abdominal pain, than did patients admitted without abdominal pain ($69/158 > 70/213$; $p < 0.035$).

Patients admitted with diffusely located abdominal pain reported higher frequencies of mucous or bloody diarrhea, voluminous stools floating on water, and of unintentional weight loss than did patients with right iliac fossa pain. A high frequency of voluminous stools was reported by pa-

TABLE 4. *Follow-up Results: Chronic Abdominal Symptoms Among 371 Patients Without Previous Inflammatory Bowel Disease*

First admission		Chronic complaints							
		Diarrhea without bleeding		Mucous or bloody diarrhea		Voluminous floating stools		Weight loss	
Symptom	No.	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Abdominal pain									
Without pain	213	42	(19.7)	28	(13.1)	30	(14.1)	18	(8.5)
Diffuse	81	18	(22.2)	19	(23.5)*	16	(19.8)†	15	(18.5)‡
Right iliac fossa	62	17	(27.4)	6	(9.7)*	5	(8.1)†§	4	(6.5)‡
Right subcostal	12	5	(41.7)	1	(8.3)	6	(50.0)§	2	(16.7)
Left side	3	2		1		2		0	
Diarrhea									
None	201	35	(17.4)	26	(12.9)	31	(15.4)	20	(10.0)
Without bleeding	154	48	(31.2)	24	(15.6)	26	(16.9)	18	(11.7)
Bloody	16	1	(6.3)	5	(31.3)	2	(12.5)	1	(6.3)
Total	371	84	(22.6)	55	(14.8)	59	(15.9)	39	(10.5)

* $p < 0.035$
† $p = 0.05$
‡ $p = 0.035$
§ $p = 0.003$

tients with right-sided subcostal pain. More patients complained of diarrhea who had been admitted with diarrhea, than did patients admitted without diarrhea ($78/170 > 61/201$; $p < 0.0025$).

Clinical Course of Patients With Ileal Affections. The 21 patients with verified terminal or regional ileitis all replied to our questionnaire. None had developed CD; neither had this group experienced more abdominal complaints than other patients. Three male patients were examined by small bowel series after 5 years, with normal findings. *Y. enterocolitica* had been isolated from stools in two patients during the acute infection, and antibody titers of 5000 had been recorded in two.

Discussion

Acute Abdominal Manifestations

Previous reports state that abdominal pain is common during acute *Y. enterocolitica* infection. Attention has been paid to "the right iliac fossa syndrome"[2-4,10,11]; and one of us has described "the right subcostal syndrome" mimicking cholecystitis.[12] The present study supports these observations, regarding both frequency and localization of abdominal pain. Diarrhea is a common acute manifestation at all ages,[4,10,11] but macroscopically bloody diarrhea is especially seen in infancy and childhood.[13-15] The present study concurs with the previous ones; and we have been able to show the statistical significance of the age distribution. In accordance with previous reports, "the right iliac fossa syndrome" was the most common indication for emergency surgery, which regularly disclosed mesenteric lymphadenitis or ileal affection.[1-3,10,11] The significant difference between age distributions of male and female patients with mesenteric lymphadenitis has no counterpart in previous reports. Clinical studies indicate that the *Y. enterocolitica* infection may cause acute appendicitis; but it is responsible in only a minor fraction of the total number.[2,16,17] The appendicular inflammation is generally slight.[1,16] We abstain from causative conclusions in our three cases, because isolation of *Y. enterocolitica* was not attempted. Findings of perforated duodenal ulcer and acute cholecystitis possibly may represent coincidences; abdominal masses in unoperated patients may represent conditions like those found in patients who underwent surgery.

Chronic Abdominal Manifestations

At readmission, every third patient complained of abdominal pain or diarrhea; these symptoms were significantly correlated with the corresponding symptoms at first admission. Twelve patients suffered from chronic weight loss. In a few patients, the substrates of these complaints might have been traced by the demonstration of chronic colitis, duodenal microscopic changes, or abnormal Schilling tests.

At follow-up, chronic abdominal complaints were common even among patients who had not consulted a doctor, and significant correlations were demonstrated between pain localization at first admission and frequencies of particular complaints. The higher frequencies among patients with long-time observation might indicate development over several years.

Reexamination of the Bergen University Hospital patients confirmed the frequencies of abdominal complaints claimed by questionnaire responders. Duodenal microscopic changes in four of five patients with severe diarrhea are in accord with findings in one of the readmitted patients (see above), and with a previous report on duodenal affection associated with weight loss and arthritis.[18]

In keeping with our observations are several previous reports of sustained or recurrent diarrhea, or abdominal pain, after *Y. enterocolitica* infection.[4,11,12,18] An association between the *Y. enterocolitica* infection and chronic colitis or UC was suggested from clinical observations 15 years ago[19,20]; later, high frequencies of specific antibodies were observed among patients with UC[21] and CD,[22] and recently persistence of virulent *Y. enterocolitica* has been demonstrated in patients with chronic intestinal inflammations.[23]

Ulcerative colitis had been diagnosed in six of our patients several years before the diagnosis of *Y. enterocolitica* infection. This prevalence of UC significantly exceeds the highest prevalence previously estimated in the Scandinavian countries ($6/458 > 741/807.000$; $p < 0.000001$).[24] Some of our patients with IBD may have acquired *Y. enterocolitica* infection in an already diseased state. Two patients, however, were admitted shortly after the acute onset of diarrhea; they both underwent bowel resection. These observations may support the concept of a connection between the *Y. enterocolitica* infection and IBD.

Patients admitted with right iliac fossa pain had the better prognosis regarding future mucous or bloody stools, voluminous stools floating on water, and unintentional weight loss. It may be supposed that different pain localizations represent involvement of different organs. Given that right iliac fossa pain represents mesenteric lymphadenitis or terminal ileitis, the patients who are immunologically capable of fighting the microorganism at this early line of defense will profit. If a connection between *Y. enterocolitica* infection and IBD exists, the hypothesis also may explain why patients with *Y. enterocolitica* infection and verified acute terminal ileitis infrequently develop CD at a later time[25,26]; and it might be in accordance with the hypothesis that development of IBD involves an interaction between external agents, immunologic genetic influences, and host response.[27] Ulcerative colitis and

Crohn's disease may be prototypes, or polar extremes, of a single disease also comprising indeterminate colitis.[27,28]

Weight loss was experienced by 73 patients, (27 males, 46 females; 16.3%). Forty-five were admitted to hospital; another 28 reported this complaint at follow-up. Correspondingly, a previous report states that 6 of 37 patients (16%) in a gastroenterologic unit lost weight[4]; the symptom also has been noticed by others.[18,29] Weight loss may be associated with bowel affection and diarrhea, but also with extraintestinal or systemic disease without diarrhea.

Conclusion

The present study supports previous observation on gastrointestinal affection during acute *Y. enterocolitica* infection, and indicates that the infection may launch chronic abdominal complaints. The relationship between the *Y. enterocolitica* infection and indeterminate colitis, UC, and CD still may not be definitively settled. Further prospective studies are required to elucidate the role of *Y. enterocolitica* in chronic gastrointestinal disease.

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