Clinical Features and Duration of Traveler's Diarrhea in Relation to Its Etiology

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Clinical features of traveler's diarrhea (TD) were studied among 126 adult Finnish tourists who developed this illness during or shortly after a visit to Morocco. Enteric pathogens were identified in 76 (60%) of cases, whereas the etiology remained unidentified in 50 cases (40%). Patients with an identified pathogen did not differ from those with TD of unknown etiology in terms of the time of onset of illness or the median frequency of unformed stools in the first 24 hours. In contrast, the median frequency of unformed stools between 24 and 48 hours (i.e., on the second day) was 1.0 among patients with no pathogen and 2.0 among those with enteric pathogens identified ($P < .001$). A similar difference was evident on the third day (1.0 vs. 2.5). Moreover, a lower proportion of patients with no pathogen identified had watery stools (28% vs. 55%). The durations of diarrhea and concomitant symptoms were significantly shorter and the recovery from TD was significantly quicker among the patients without an identified pathogen. Patients with one or more invasive pathogens had disease that was clearly more severe than that of patients with no pathogen identified; the difference in severity of disease was less marked for patients with invasive vs. noninvasive pathogens. Individuals with diarrhea due to *Campylobacter* species tended to have the most severe disease, whereas diarrhea caused by enterotoxigenic *Escherichia coli* seemed milder than that caused by other agents. Unfortunately, the clinician has only a limited opportunity to predict the etiology of TD and thus to assess the need for antimicrobial therapy at the onset of disease.

Traveler's diarrhea (TD) is a frequent medical problem for tourists in developing countries [1–3] and is costly to both the traveler and the host country. High-risk areas for TD include Africa, Latin America, and Asia [4]. Various infectious agents may cause TD, but bacteria are responsible for ~80% of cases [5, 6]. Although techniques for identifying the bacteria, viruses, and parasites responsible for TD have improved, the etiology remains unknown in 15%–55% (and, in rare instances, up to 75%) of cases [7–12]. The etiology of TD varies both geographically and seasonally [13–16].

Investigators have long attempted to correlate the symptoms and signs of diarrheal diseases with a specific etiology, usually with little success [17–23]. Although adequate comparisons of patients with TD of different etiologies generally have not been possible, a few trends have been noted. *Campylobacter* enteritis has been described as intense diarrhea with abdominal pain and fever in more than 50% of cases. Salmonellosis has been associated with classic enteric fever

or severe diarrhea with abdominal pain, whereas shigella enteritis typically has an abrupt onset with bloody or watery stools, abdominal pain, and fever. Enteritis associated with enterotoxigenic *Escherichia coli* (ETEC) varies considerably but is usually of relatively short duration. Little is known about diarrhea associated with *Aeromonas* species.

A recent study of TD among Finnish travelers to Morocco [24] offered an opportunity to compare the clinical presentation of TD cases according to etiology: no identified pathogen, invasive pathogen(s), or noninvasive pathogen(s).

Patients and Methods

The population studied consisted of 126 individuals from a group of 978 Finnish tourists participating in two packaged tours to Agadir, Morocco [15, 24]. Of the 254 travelers who developed TD during or within 1 week after the tours, 71 were excluded from the study because they had received norfloxacin in a randomized trial of treatment [25]. (The disease was initially as severe in this group as it was in the group that was included in the study.) Follow-up data were available for 126 of the remaining 183 patients with TD. Of these 126 persons, 39 had received B-subunit/whole-cell cholera vaccine. Although that vaccine reduced the risk of TD caused by ETEC alone or in combination with other pathogens [24], it had no effect on the clinical features of the cases that did develop (author's unpublished observation). Thus these patients were not excluded from the study.

The tours took place in January and February 1989 and in October and November 1989 and lasted for 1 or 2 weeks. An office for the study's personnel (two Finnish physicians, a

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This study was approved by the Ethical Committee of the National Public Health Institute, Helsinki. Informed consent was obtained from the patients, and the guidelines for human experimentation of the Declaration of Helsinki were followed.

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nurse, and laboratory staff [15]) was established at a local hotel in Agadir.

Diarrhea was defined as the passage of four or more unformed stools in a period of 24 hours or of three or more unformed stools in a period of 8 hours. In addition to diarrhea, at least one of the following signs or symptoms had to be present for inclusion of a patient in the study: abdominal pain or cramps, nausea, vomiting, or fever [26].

Patients were instructed to contact the study personnel as soon as symptoms developed. One of the study's physicians interviewed and examined the patient within a few hours. Each patient kept a diary during the illness and met with a physician or nurse at least twice before recovery. Individuals who developed gastrointestinal symptoms within a week after returning home were asked to submit a stool specimen and to fill in a questionnaire. If the symptoms fit the case definition, the patient was included in the study. (Twenty-two of the 126 patients were enrolled in this manner.)

Self-medication was not allowed. Five patients received

Table 2. Demographic characteristics of 126 Finnish tourists to Morocco who developed traveler's diarrhea.

Characteristic: unit of measure	Value for indicated group	
	No pathogen identified (n = 50)	Pathogen(s) identified (n = 76)
Median age (range): y	44.1 (20–69)	44.0 (15–71)
Sex: no. male/no. female	11/39	29/47
Season: no. of cases		
Winter	14	29
Fall	36	47
Length of stay in Morocco: no. (%) of patients		
≤1 w	37 (74)	51 (67)
≤2 w	13 (26)	25 (33)
Mean duration of diarrhea ± SD before collection of first stool sample: h	14.5 ± 14.7	14.5 ± 14.4
Previous visits abroad within 1 y: no. of patients (%)	30 (60)	41 (54)

Table 1. Etiology of 126 cases of traveler's diarrhea in Finnish tourists to Morocco.

Pathogen(s) identified*	No. (%) of patients
No pathogen	50 (40)
Single pathogen	54 (43)
<i>Campylobacter jejuni</i>	11
<i>Campylobacter coli</i>	1
ETEC	
ST	10
LT	5
LT and ST	2
EIEC	1
<i>Salmonella enterica</i>	12
<i>Shigella</i> species	1
<i>Aeromonas</i> species	7
Rotavirus	4
Multiple pathogens	22 (17)
ST-ETEC + <i>C. jejuni</i>	1
ST-ETEC + EPEC	1
ST-ETEC + <i>S. enterica</i>	3
ST-ETEC + <i>Shigella</i> species	1
ST-ETEC + <i>Aeromonas</i> species	1
ST-ETEC + <i>S. enterica</i> + <i>C. jejuni</i>	1
LT-ETEC + <i>S. enterica</i>	1
LT-ETEC + EPEC	1
LT/ST-ETEC + <i>S. enterica</i>	3
LT/ST-ETEC + <i>S. enterica</i> + EPEC	1
LT/ST-ETEC + <i>S. enterica</i> + <i>Aeromonas</i> species	1
<i>S. enterica</i> + EPEC	1
<i>S. enterica</i> + <i>C. jejuni</i>	2
<i>S. enterica</i> + <i>Aeromonas</i> species	2
<i>S. enterica</i> + rotavirus	1
<i>C. jejuni</i> + EHEC	1

* ETEC = enterotoxigenic *Escherichia coli*; ST = heat-stable enterotoxin; LT = heat-labile enterotoxin; EIEC = enteroinvasive *E. coli*; EPEC = enteropathogenic *E. coli*; and EHEC = enterohemorrhagic *E. coli*.

metoclopramide, six patients received loperamide, and three patients received metamizole during the course of diarrhea; these medications were given by the physician to alleviate the symptoms of TD during the long flight home or a long day trip. In no other case was the use of a drug for TD reported.

A stool sample collected at the diagnosis of TD was examined macroscopically for mucus, blood, and/or a watery or loose appearance and was cultured by standard methods for *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *Aeromonas*, and *Plesiomonas* species [27]. Standard culture methods were used for detecting enteroviruses or adenoviruses [28] in the first 43 samples, which were collected during the first trip (January and February 1989). As culture of specimens did not yield viruses with these standard methods, the latex agglutination test was used for specimens collected during the second trip (October and November 1989).

Final identification of bacterial pathogens took place in the National Public Health Institute in Helsinki. ETEC was identified by ELISAs for heat-labile and heat-stable enterotoxins, enteropathogenic *E. coli* (EPEC) serogroups and enterohemorrhagic *E. coli* (EHEC) serogroup O157 by serotyping, and enteroinvasive *E. coli* (EIEC) by tissue culture [29–33].

In statistical analyses, proportional data were compared with the χ^2 test. The *t* test or the Mann-Whitney U test was used for the comparison of continuous variables. For multiple pairwise comparison of quantitative variables, analysis of variance was followed by Scheffé's method. For the comparison of variables with highly skewed distributions, logarithmic transformation or nonparametric tests (Kruskal-Wallis analysis of variance or the Kruskal-Wallis test adjusted for multiple comparisons) were employed. The independent dis-

Table 3. Clinical profile of etiologic groups of patients with traveler's diarrhea.

Variable: unit of measure	Two-group comparison			Three-group comparison			P*
	No pathogen identified (n = 50)	Pathogen(s) identified (n = 76)	P	No pathogen identified (n = 50)	Noninvasive pathogen(s) (n = 31)	Invasive pathogen(s) (n = 45)	
Median time (95% CI) from arrival to onset of diarrhea: d	6.0 (5.0, 7.0)	6.0 (5.0, 6.0)	NS	5.0 (5.0, 7.0)	6.0 (5.0, 7.0)	6.0 (5.0, 7.0)	NS
Median frequency of unformed stools (95% CI): no. of stools							
First day (24 h)	7.0 (5.0, 8.0)	8.0 (7.0, 10.0)	NS	7.0 (5.0, 8.0)	6.5 (5.0, 11.0)	10.0 (7.0, 12.0)	NS
Second day	1.0 (0, 1.0)	2.0 (1.0, 4.0)	<.001	1.0 (0, 1.0)	1.0 (1.0, 5.0)	3.5 (2.0, 6.0)	<.001
Third day	1.0 (0, 1.0)	2.5 (1.0, 4.0)	<.001	1.0 (0, 1.0)	1.0 (1.0, 4.0)	3.0 (1.0, 5.0)	<.001
Median duration of symptoms (95% CI): d							
Diarrhea	1.6 (1.0, 3.0)	3.4 (3.0, 4.0)	<.001	1.6 (1.0, 3.0)	3.2 (2.9, 4.0)	4.0 (2.8, 5.0)	<.001
Abdominal pain	1.3 (1.0, 2.0)	3.2 (2.9, 3.7)	<.001	1.3 (1.0, 2.0)	3.1 (2.0, 3.5)	3.2 (2.9, 5.4)	<.001
Nausea	0.4 (0, 1.0)	1.3 (0.8, 2.1)	<.01	0.4 (0, 1.0)	1.3 (0.3, 2.4)	1.3 (0.9, 2.3)	<.01
Fever	0.3 (0, 0.9)	0. (0.3, 1.2)	<.05	0.3 (0, 0.9)	0.3 (0.1, 1.3)	1.0 (0.4, 1.8)	<.05
Description of stools: % of patients			<.05†				<.05†
Watery	28	55		28	49	60	
Loose	58	30		58	29	29	
Mucous	14	12		14	19	9	
Bloody	0	3		0	3	2	
Concomitant symptoms: % of patients							
Abdominal pain	80	76	NS	80	70	80	NS
Nausea/vomiting	32	43	NS	32	45	42	NS
Fever	18	37	<.01	18	29	42	<.05
Other symptoms: % of patients							
Headache	36	39	NS	36	33	43	NS
Myalgia	27	40	NS	27	26	49	NS
Meteorisms	28	31	NS	28	35	29	NS
Sleep disturbances	10	19	NS	10	15	21	NS
Flu-like symptoms	15	13	NS	15	11	14	NS

NOTE. For comparison of continuous variables, the *t* test, the Mann-Whitney U test, or Kruskal-Wallis analysis of variance was used. For comparison of proportional data, the χ^2 test was used. NS = not significant.

* Values refer to overall comparison between the three subgroups.

† As the appearance of stools was roughly classified, only an overall comparison between the subgroups was considered meaningful.

criminary power of each risk factor was assessed by stepwise discriminant analysis. The relation between the number of unformed stools and the duration of diarrhea was expressed as the Spearman-rank correlation. The Kaplan-Meier life-table method was used for the comparison of cumulative proportions of patients recovering from TD.

Results

On the basis of microbiological results, the 126 patients with TD were divided into two groups: those with an identified enteropathogen (76 patients, 60%) and those without an identified pathogen (50 patients, 40%). The pathogens isolated are listed in table 1. The group with identified pathogens was further divided into two subgroups: those with one or more invasive pathogens (45 patients) and those with one or more noninvasive pathogens (31 patients). (The isolation of any invasive pathogen qualified a patient for the former

category.) *Shigella* species, *Salmonella enterica*, *Campylobacter* species, and EIEC were considered invasive pathogens, whereas ETEC, EPEC, EHEC, *Aeromonas* species, and rotavirus were considered noninvasive [34].

ETEC, the most common single pathogen, was identified alone in 17 (31%) of 54 cases. It was followed in frequency by *S. enterica* (22%) and *Campylobacter* species (22%). ETEC and *S. enterica* were also the most common isolates in the 22 cases in which multiple pathogens were identified. Rotavirus was the only viral agent detected; it was found alone in four cases and together with *S. enterica* in one case.

The mean age of the 126 patients was 44.0 years; 86 (68%) were female (table 2). Eighty-eight patients (70%) spent 1 week in Morocco, and the rest spent 2 weeks. No differences in age, sex, or duration of stay in Morocco were documented among the three groups (no pathogen, invasive pathogen, and noninvasive pathogen).

The median time of onset of TD was 6.0 days after the

Figure 1. Percentage of patients with diarrhea and any concomitant symptoms each day from onset of traveler's diarrhea to recovery, by etiologic group. Forty-five patients had at least one invasive pathogen identified, 31 had at least one noninvasive pathogen identified, and 50 had no pathogen identified. The P value was obtained by the Kaplan-Meier life-table method (Mantel-Cox test).

start of the tour (95% confidence interval [CI]: 5.0, 7.0) and did not differ significantly by group (table 3). The frequency of unformed stools on the first day after onset of diarrhea was also the same for all groups. However, the frequency differed significantly on the second and third days, when the median numbers of loose stools were 1.0 and 1.0, respectively (mean numbers, 0.8 and 1.0, respectively) for patients without identified pathogens and were 2.0 and 2.5, respectively (mean numbers, 3.4 and 3.2, respectively) for those with identified pathogens. Watery stools were less common in the latter group than in the former (28% vs. 55%). Bloody diarrhea was documented in only two cases, both of which had an identified etiology (rotavirus in one case and *Campylobacter jejuni* plus *S. enterica* in the other).

Abdominal pain was reported by 98 patients. The type and severity of this pain did not differ in the groups with and without identified pathogens (data not shown). However, abdominal pain tended to occur in a higher proportion of patients with invasive pathogens than of those with noninvasive pathogens (table 3). Fever was documented in 18% of patients with no identified pathogen and in 37% of those with identified pathogens ($P < .01$); it was most common among patients with invasive pathogens (42%). The frequencies of other concomitant symptoms were similar in the various groups. The durations of diarrhea and concomitant symptoms (nausea, abdominal pain, and fever) were significantly shorter among patients without an identified pathogen than among those with identified pathogens (table 3).

Recovery from TD—i.e., the resolution of all symptoms—took significantly longer in cases without an identified etiology ($P < .001$, figure 1). Specifically, diarrhea lasted for <2 days in 50% of cases with no identified pathogen but persisted for at least 4 days in 50% of cases with an identified pathogen. The groups with invasive and noninvasive pathogens did not differ statistically in terms of recovery time.

The number of unformed stools during the first 24 hours of TD correlated with the ultimate duration of diarrhea ($r = 0.3015$; $P < .01$) but not with etiology.

In an evaluation of the clinical features of the etiologic groups, a stepwise discriminant analysis was performed; the presence and severity of abdominal pain, nausea, and fever and the frequency of unformed stools were included in the model. None of these parameters was associated with etiology during the first 24 hours of illness; however, the number of unformed stools on the second day proved a significant independent discriminator among the etiologic groups. Discriminant analysis based on this variable correctly classified 64% of all cases: 92% of those with no pathogen identified and 48% of those with one or more pathogens identified.

The clinical profile of TD caused by single specific pathogens was evaluated (table 4). ETEC was isolated in 17 of these cases, and *Campylobacter* species and *S. enterica* were identified in 12 cases each. Despite these relatively small numbers, some clinical features were significantly associated with each pathogen. On the first day of illness, the clinical features in all groups were quite similar. In cases in which ETEC was identified, diarrhea proved to be quite mild, to be associated with mucous stools in many cases, and to be associated with nausea or vomiting, fever, and other systemic symptoms in few cases. *Campylobacter* species tended to cause the most severe disease, with a large number of unformed stools on the first, the second, and especially the third day and a frequent association with abdominal pain, nausea or vomiting, and fever. *S. enterica* was associated with moderately severe disease. In seven cases, diarrhea was associated with *Aeromonas* species. These cases were quite severe, with a large number of unformed stools and nausea documented on the first day.

Four cases of diarrhea were associated with rotavirus. The clinical features of these cases were not distinguishable from those of cases with a bacterial etiology. All four of the patients involved had nausea and abdominal pain, and three of the four had fever. Three patients had watery stools, and one patient had bloody stools.

Discussion

In this study, the durations of diarrhea and of concomitant symptoms of TD (nausea, abdominal pain, and fever) were significantly shorter among cases without than among those with an identified etiology. The clinical features of TD on the first day of illness were quite similar in these two groups,

Table 4. Clinical profile of TD caused by a single specific pathogen.

Variable: unit of measure	Value for indicated group*					P†
	ETEC (n = 17)	<i>Campylobacter</i> species (n = 12)	<i>Salmonella</i> <i>enterica</i> (n = 12)	<i>Aeromonas</i> species (n = 7)	Other (n = 6)	
Sex: no. male/no. female	4/13	5/7	8/4	2/5	2/4	
Median time (95% CI) from arrival to onset of diarrhea: d	6.0 (4.0, 8.0)	7.0 (5.0, 11.0)	6.0 (5.0, 9.0)	5.0 (2.0, 9.0)	4.0 (2.0, 9.0)	NS
Median frequency of unformed stools (95% CI): no. of stools						
First day (24 h)	5.5 (3.0, 8.0)	9.5 (4.0, 13.0)	7.0 (4.0, 12.0)	11.0 (4.0, 15.0)	12 (7.0, 23.0)	NS
Second day	1.0 (1.0, 3.0)	5.0 (0, 9.0)	2.0 (0, 4.0)	3.0 (1.0, 4.0)	3.5 (0, 9.0)	NS
Third day	1.0 (0, 5.0)	5.5 (1.0, 10.0)	3.0 (0, 4.0)	2.0 (1.0, 4.0)	3.5 (0, 8.0)	NS
Median duration of symptoms (95% CI): d						
Diarrhea	3.1 (1.7, 4.0)	3.8 (2.7, 6.2)	3.5 (1.7, 7.4)	3.8 (2.0, 5.3)	4.1 (3.1, 6.3)	NS
Abdominal pain	3.2 (1.1, 4.2)	4.2 (1.5, 5.8)	2.4 (1.0, 4.0)	2.3 (0, 3.8)	3.3 (2.9, 5.3)	NS
Nausea	0.3 (0, 1.5)	1.1 (0.4, 3.1)	0.7 (0, 1.3)	2.3 (0, 2.8)	3.3 (2.0, 5.3)	<.05
Fever	0.3 (0, 1.5)	2.0 (0.4, 3.0)	1.2 (0, 2.8)	0.3 (0, 2.3)	1.8 (0.1, 4.3)	NS
Description of stools: % of patients						<.05‡
Watery	24	92	59	86	83	
Loose	41	8	33	14	0	
Mucous	35	0	8	0	0	
Bloody	0	0	0	0	17	
Concomitant symptoms: % of patients						
Abdominal pain	71	91	58	33	83	NS
Nausea/vomiting	18	58	8	71	100	<.001
Fever	18	67	33	29	67	<.05
Other symptoms: % of patients						
Headache	24	50	58	29	60	NS
Myalgia	19	64	42	17	100	<.05
Meteorisms	39	10	50	50	0	NS

* ETEC = enterotoxigenic *Escherichia coli*. "Other" includes four cases due to rotavirus, one due to enteroinvasive *E. coli*, and one due to *Shigella* species.

† Quantitative variables were compared by analysis of variance and Scheffe's method or Kruskal-Wallis analysis of variance; proportional data were compared by χ^2 test.

‡ As the appearance of stools was roughly classified, only an overall comparison between the subgroups was considered meaningful.

but the number of unformed stools was significantly smaller on the second and third days in the group without an identified etiology. As in earlier studies [19, 35, 36], disease was less severe in cases without an identified etiology than in those with at least one identified pathogen. The differences between cases due to invasive pathogens and those due to noninvasive pathogens were less marked. *Campylobacter* species caused the most severe disease and ETEC the mildest disease.

Ericsson et al. compared clinical and laboratory features of TD in 56 patients infected with *Shigella* species, 103 patients infected with ETEC, 19 patients with TD due to species other than *Shigella* or ETEC, and 82 patients with TD of unknown etiology [21]. In their analysis, nausea and abdominal cramps were equally common in all etiologic groups, and patients with a mild clinical presentation—regardless of etiology—recovered sooner than those who initially were moderately or severely ill. In our study, ~33% of patients without an identified pathogen and ~43% of those with an identified

pathogen reported nausea. Nausea was common among cases associated with *Aeromonas* species (71%) or *Campylobacter* species (58%) but was uncommon among cases associated with *S. enterica* (8%) or ETEC (18%). Moreover, abdominal pain was frequent both with (76%) and without (80%) an identified etiology.

Kollaritsch studied the clinical features of enteritis among 1,455 Austrian tourists visiting various developing countries between 1986 and 1988 [37]. In this questionnaire-based study, 57% of patients had abdominal cramps, 13% had fever, and 30% had nausea or vomiting. The onset of TD came around the ninth day of travel; in contrast, the median time to onset in our study was 6 days. During the acute illness of the patients in our study, the frequency of stools was about four per day, and the mean duration of diarrhea $\pm$ SD was 3.6 ± 2.7 days. Fever was rather uncommon; it was more common among cases with than among those without an identified pathogen (37% vs. 18%) and was most common among cases due to an invasive pathogen (42%).

What causes cases of TD in which no pathogen is identified? In the present study, the stool specimen for culture was taken after the passage of three or four unformed stools, and the culture methods used were of high quality. Thus major enteropathogens would very likely have been detected. However, the use of methods for the detection of some other potential pathogens (e.g., astroviruses, coronavirus, Norwalk virus, *Hafnia alvei*, *Campylobacter upsaliensis*, *Campylobacter butzleri*, *Cryptosporidium* species, and enteroadhesive *E. coli*) might have revealed the etiology of a few more cases [38–46]. Processing of more than one stool specimen per patient might also have been fruitful. It remains unclear whether TD can be due to changes in the normal flora without the involvement of enteric pathogens.

In conclusion, the first day of TD was fairly similar regardless of etiology, but recovery was significantly quicker among patients without an identified pathogen. In other words, a lower frequency of unformed stools after the first 24 hours distinguished the group with unknown etiology from that with an identified etiology. Fifty percent of patients with fewer than three stools on the second day had no identifiable pathogen. Unfortunately, the clinician has only a limited opportunity to predict the etiology of TD and thus to assess the need for antimicrobial therapy in individual patients at the onset of disease.

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