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Epidemiological trends of traveler's diarrhea in Japan: An analysis of imported infectious disease registry data from 2017–2022

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Abstract: Traveler's diarrhea (TD) is a global problem, and identifying the causative organisms of TD is important for adequate treatment. Therefore, this study retrospectively analyzed TD cases in patients who returned to Japan after traveling abroad to determine the causative organisms by travel region. We included patients with a final diagnosis of TD registered in the Japan Registry for Infectious Diseases from Abroad database from September 25, 2017, to September 1, 2022, from 14 medical institutions. A total of 919 patients were analyzed; the causative TD pathogen was identified in 188 cases (20%), of which 154 were caused by diarrheagenic bacteria, the most common being *Campylobacter* spp. (64%). A 2.2 mg/dL C-reactive protein concentration cutoff value had some predictive ability for bacterial TD (negative predictive value, 89%). Therefore, the C-reactive protein level may help rule out bacterial diarrhea and prevent unnecessary antimicrobial administration when patients cannot provide a stool specimen.

***Keywords*:** traveler's diarrhea, epidemiology, travel diseases, C-reactive protein

Introduction

Despite improved hygiene, traveler's diarrhea (TD) is a continuing global issue with frequent occurrence and many potential adverse consequences, including lost time and opportunities, itinerary changes, overseas medical encounters, and hospitalization (*1*). For certain destinations, the TD incidence rate is 20–60% within a two-week period (*2,3*). In Japan, the frequency of TD is estimated to be higher owing to the large number of travelers visiting Asia, which has a high TD risk. Therefore, this study analyzed TD cases diagnosed in Japan.

Study design and data collection

The Japan Registry for Infectious Diseases from Abroad (J-RIDA) was established to clarify the status of imported infectious diseases in Japan (*4*), with 14 Japanese medical institutions contributing to the database. The registry collects information about the patient's age, sex, nationality, travel history, country of residence, departure, return, consultation, onset dates, whether a visit was made to a travel clinic before travel, the prophylactic antimicrobials administered, the final diagnosis, blood collection (yes/no), the TD causative organisms, antimicrobial therapy (yes/no), and outcomes.

Thus, we retrospectively collected data from the J-RIDA database from September 25, 2017, to September 1, 2022, for our analyses.

We included patients with a final diagnosis of TD registered in the J-RIDA database. Patients who developed TD during the trip were included, but those who developed TD more than six days after returning to Japan were excluded because they were likely unrelated to the trip. Similarly, foreign visitors to Japan were included if they were abroad at the time of onset. The destination country was defined as that where the patient stayed at the time of TD onset. However, for patients who developed the disease after returning to Japan, the destination country was defined as the last country the patient traveled to before returning to Japan. Moreover, we analyzed the diagnostic ability of the C-reactive protein (CRP) level for bacterial enteritis. *Campylobacter, Salmonella* spp*., Shigella* spp*., Vibrio parahaemolyticus, V. cholerae,* Enterotoxigenic *Escherichia coli,* Enteroinvasive *E. coli,* Enteropathogenic *E. coli,* Enterohaemorrhagic *E. coli,* and *Plesiomonas shigelloides* were considered causative agents of bacterial enteritis.

Continuous variables were compared by the Mann–Whitney *U* test. A two-sided *p*-value of < 0.05 was considered statistically significant. Cutoff values were assessed by receiver operating characteristic curve analyses based on the area under the curve (AUC) and Youden's index. All statistical analyses were performed using EZR software version 1.61 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is based on R and R Command (R Foundation for Statistical Computing, Vienna, Austria).

This publication was exempt from Institution Review Board (IRB) approval (NCGM-G-002328). The patients' data were anonymized before analysis, and the requirement of individual informed consent was waived by providing an opt-out opportunity because of the study's retrospective design. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Epidemiological trends of TD in Japan

We included 919 patients (average age, 34.3 years; men, 512 [56%]). Furthermore, 870 patients (95%) and 876 (95%) were Japanese and residents of Japan, respectively. Notably, most cases were attributed to destination areas in Southeast Asia ($n = 498$; 54%). By country, most cases were from Thailand ($n = 99$; 11%). Moreover, before traveling, 138 (15%) patients visited a travel clinic, and three patients were prescribed antimicrobial prophylaxis, a standby treatment for TD. Additionally, 815 (89%), 71 (8%), and 33 (4%) patients were treated as outpatients, in a hospital, and had unknown outcomes, respectively. Concurrently, blood tests and antimicrobial prescriptions were administered to 485 (53%) and 129 (14%) patients, respectively (Table 1). Overall, 731 cases (80%) were of unknown origin, and the causative organism was identified in 188 cases (Table 2); of these, most were caused by *Campylobacter* spp. ($n = 93$; 52%).

We obtained the CRP level from 486 patients. The causative organism was bacterial in 102 cases and "other" in 384 cases (including 378 cases where the causative organism was unknown). The bacterial group had a significantly higher CRP level than did the "other" group (median: 3.85 mg/dL [interquartile range: 1.93–7.24] *vs.* 1.36 mg/dL [0.30–3.99], $p < 0.001$) (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=75*). Furthermore, the CRP level had a high AUC (0.67) (Supplemental Figure S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=75*). Thus, several CRP cutoff values were tested for their diagnostic accuracy to distinguish bacterial causative agents from other agents. The optimal cutoff value stood at 2.2 mg/dL, exhibiting a sensitivity, specificity, positive predictive value, and negative predictive value of 73.0% (95% CI: 3.2–81.4%), 60.2% (95% CI: 55.0–65.2%), 33.0% (95% CI: 29.3–37.0%), and 89.2% (95% CI: 85.6–92.1%), respectively. In this study, 72 patients with TD of a non-bacterial cause received antimicrobial prescriptions, and 40 underwent blood testing. Of these, 25 patients had a 2.2 mg/dL or lower CRP level.

Reports indicate that 16.1% of travelers experience TD in Southeast Asia (*5*), and bacterial pathogens are detected in only about 60% of TD cases (*6*). In this study, we found that most TD cases in Japan occurred after traveling to Southeast Asian countries; however, there were more cases with unknown etiologic agents than those previously reported. Importantly, it is unclear whether stool tests were performed in patients with unknown causative organisms, which may explain this result. Many mild TD cases are treated without antibiotics; therefore, stool tests are not conducted, which increases the number of cases with unknown causative agents. We found that 33/188 patients (18%) with confirmed causative organisms required hospitalization, whereas only 38/731 patients (5%) with unknown causative organisms did so, suggesting that cases with unknown causative organisms are less severe. Often, many less severe TD cases only require follow-up observations and no stool test, potentially explaining our results.

In this study, only 3 patients received antimicrobial prophylaxis for TD. Notably, antimicrobial prophylaxis treatment is not routinely recommended for TD (*7*) because it does not protect against non-bacterial pathogens and can harm normal, protective microflora in the bowel, increasing the risk of infection by resistant bacterial pathogens (*8*).

Our analysis suggested that in patients with TD and a CRP level of 2.2 mg/dL or lower, bacteria were likely not the causative agents; thus, the utility of antimicrobial agents appeared to be minimal. Consequently, this

Table 1. Study population characteristics

Characteristics	Total (*n* = 919)	%	Bacterial causative agent (*n* = 154)	%	Other (*n* = 765)	%
Age (median), years	31		27		31	
Male	512	56	87	56	423	55
Nationality						
Japanese	870	95	150	97	720	94
Other	49	5	4	3	45	6
Country of residence						
Japan	876	95	152	99	724	95
Other	43	5	2	1	41	5
Destination area						
Southeast Asia	498	54	104	68	394	52
South Asia	128	14	17	11	111	15
Africa	120	13	8	5	112	15
East Asia	75	8	13	8	62	8
Central and South America	26	3	2	1	24	3
Central and West Asia	20	2	4	3	16	2
Oceania	19	2	4	3	15	2
Europe	17	2	1	1	16	2
North America	16	2	1	1	15	2
Destination country						
Thailand	99	11	25	16	74	10
Indonesia	98	11	24	16	74	10
India	92	10	15	10	77	10
Philippines	88	10	16	10	72	9
Vietnam	76	8	10	6	66	9
Cambodia	51	6	7	5	44	6
China	34	4	5	3	29	4
Myanmar	30	3	7	5	23	3
Malaysia	24	3	7	5	17	2
Singapore	19	2	6	4	13	2
Visited a travel clinic before traveling						
Yes	138	15	13	8	125	16
No	781	85	141	92	640	84
Antimicrobial prophylaxis						
Yes	3	0.3	0	0	3	0.4
No	916	99	154	100	762	99
Outcome						
Outpatient	815	89	115	75	700	92
Hospitalization	71	8	31	20	40	5
Unknown	33	4	8	5	25	3
Blood collection						
Yes	486	53	102	66	384	50
No	433	47	52	34	381	50
Prescribed antimicrobials						
Yes	129	14	57	37	72	9
No	790	86	97	63	693	91

indicator could help reduce the inappropriate use of antimicrobial agents. Furthermore, the relatively high negative predictive value supports the conclusion that the CRP level can rule out bacterial diarrhea, which accounted for approximately 20% of cases in this study. Therefore, unnecessary antimicrobial administration could be avoided in at least 25/72 patients (34.7%) with TD of unknown origin.

Most of the cases in this study pertain to the pre-Coronavirus disease 2019 (COVID-19) era, given that COVID-19 was globally detected in January 2020 (*9*). The COVID-19 epidemic has resulted in significant changes in international travel patterns. Notably, only 51 patients (5.5%) were enrolled in the study subsequent to 2020. Among these, 45% (23/51), 78% (40/51), and 13% (7/51) were attributed to destination areas in Southeast Asia, had an unknown etiological agent, and were caused by *Campylobacter* spp., respectively. Although simple comparisons are difficult due to the small number of post-COVID-19 participants, these data appear to align broadly with the overall study findings.

Our study had some limitations. First, there was considerable bias in the number of TD reports from the medical facilities; thus, reporting bias is possible. In Japan, unlike other travel-related infectious diseases, such as dengue fever and malaria, TD does not have to be reported to public health centers. Additionally, many mild TD cases may not be registered in the J-RIDA database even if encountered in routine medical care. Finally, mild TD cases often do not present in large hospitals with specialized departments and may not be reported.

Table 2. Organisms that caused diarrhea and corresponding travel regions

Organisms	Southeast Asia	South Asia	Africa	East Asia	Central and South America	Central and West Asia	Oceania	Europe	North America
Case Numbers	498	128	120	75	26	20	19	17	16
Pathogenic organism unknown	377 (76%)	102 (80%)	106 (88%)	61 (81%)	24 (92%)	16 (80%)	15 (79%)	15 (88%)	15 (94%)
Bacteria (total cases)	105	17	9	13	2	4	4	1	1
Enterotoxigenic *Escherichia coli*	3	5	2	1	0	1	1	0	0
Enteroinvasive *E. coli*	2	0	0	0	0	0	0	0	0
Enteropathogenic *E. coli*	1	0	0	0	0	0	0	0	0
Enterohaemorrhagic *E. coli*	1	0	0	0	0	0	0	0	0
Plesiomonas shigelloides	2	0	1	0	0	0	0	0	0
Vibrio parahaemolyticus	2	0	0	0	0	0	0	0	0
Vibrio cholerae	0	2	0	0	0	0	0	0	0
Salmonella spp.	11	0	0	5	0	0	1	0	0
Shigella spp.	13	0	1	0	2	0	0	0	1
Campylobacter spp.	70	10	5	7	0	3	2	1	0
Viruses (total cases)	2	3	1	1	0	0	0	0	0
Norovirus	0	2	1	1	0	0	0	0	0
Rotavirus	2	1	0	0	0	0	0	0	0
Protoza (total cases)	14	6	4	0	0	0	0	1	0
Cryptosporidium spp.	1	0	1	0	0	0	0	0	0
Giardia lamblia	5	6	1	0	0	0	0	1	0
Entamoeba histolytica	8	0	2	0	0	0	0	0	0

Second, the low causative organism detection rate may be due to in-hospital testing differences. For instance, polymerase chain reaction methods, such as the FilmArray Gastrointestinal Panel (BioFire Diagnostics, Salt Lake City, UT, USA), may be more sensitive for detecting pathogens than conventional stool cultures (*10*). In the present study, only two facilities reported positive results for viruses. Thus, we suspect that identifying the causative organisms is easier in facilities with such capabilities, whereas facilities with less advanced testing capabilities report a higher percentage of cases with unknown causative organisms. Moreover, patients with unknown organisms included those with stool culture tests that did not reveal diarrheagenic organisms and those who did not undergo stool culture tests. Possibly, most patients for whom stool cultures were not performed may have visited hospitals after their diarrhea had improved, suggesting that they could have surpassed the inflammatory extreme stage. Therefore, CRP levels might be lower in this study's group of patients with unknown bacteria. Importantly, the association between CRP and bacterial enteritis is the same as that previously reported (*11*). These factors may have influenced the study results, and we believe that it is necessary to improve the registry studies in the future to accurately determine the contents and severity of the tests performed.

Third, statistics on the antimicrobial use type and duration were lacking in this study. Thus, collecting antimicrobial therapy data would be beneficial as it could encourage the reduction of unnecessary antibiotic administration in the future, suppressing resistant bacterial strains. Generally, TD is self-limiting without antimicrobial therapy (*1*). In this study, 58/731 patients (8%) with unknown causative organisms were prescribed antimicrobial drugs. Thus, investigating whether antimicrobial therapy is essential may prevent unnecessary prescription of antibacterial drugs. Consequently, in future J-RIDA registry studies, we would like to include the antimicrobial administration type and duration, as well as treatment and prognosis factors.

In conclusion, this study retrospectively analyzed TD cases in patients who returned to Japan after traveling abroad to determine the causative organisms by travel region. The CRP level may help rule out bacterial diarrhea and prevent unnecessary antimicrobial administration when patients cannot provide a stool specimen.

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