J Infect Chemother 24 (2018) 59–64

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Effect of antibiotics for infectious diarrhea on the duration of hospitalization: A retrospective cohort study at a single center in Japan from 2012 to 2015

Yosuke Sasaki [a, *], Yoshitaka Murakami [b], Hiroaki Zai [a], Hitoshi Nakajima [a], Yoshihisa Urita [a]

[a] Department of General Medicine and Emergency Care, Toho University School of Medicine, Japan
[b] Department of Medical Statistics, Toho University School of Medicine, Japan

ARTICLE INFO

Article history:
Received 3 April 2017
Received in revised form
18 July 2017
Accepted 6 September 2017
Available online 3 October 2017

Keywords:
Antibiotics
Colitis
Empirical therapy
Enteritis
Probiotics

ABSTRACT

Objective: Routine empirical antimicrobial therapy for patients with infectious diarrhea is not recommended in general practice. Conversely, prescription of empirical antibiotics for hospitalized patients remains controversial due to a lack of studies providing evidence for its benefits. Thus, this study aimed to examine whether empirical antimicrobial therapy would shorten the hospitalization duration for infectious diarrhea patients.

Methods: This single-center, retrospective cohort study was performed at the Department of General Medicine and Emergency Care, Toho University Medical Center Omori Hospital, using medical records. Adult patients (aged ≥16 years) hospitalized for infectious diarrhea from 2012 to 2015 were enrolled. The primary outcome was the duration of hospitalization. Risk factors examined in parallel to antibiotic therapy included age, sex, relevant medical history, probiotics use, vital signs, leukocyte count, liver and renal functions, and microbiological data.

Results: We enrolled 138 and 50 patients treated with and without antimicrobial therapy, respectively. The median hospitalization periods were 6.0 days (interquartile range, 4.0–7.0 days) and 5.0 days (interquartile range, 3.25–6.0 days) for patients treated with and without antibiotics, respectively ($p = 0.007$). Multiple regression showed that empiric antimicrobial therapy ($p = 0.017$), advanced age ($p = 0.003$), hematochezia ($p = 0.008$), elevated serum creatinine ($p < 0.001$), and elevated serum C-reactive protein ($p = 0.002$) were significant risk factors of longer hospitalization duration.

Conclusion: Empirical antimicrobial therapy was found to relate to a longer hospitalization duration for infectious diarrhea patients. Although its effects on the patients' symptoms were not evaluated, our results suggest that empirical antimicrobial therapy should be administered cautiously to not only outpatients, but also hospitalized patients.

1. Introduction

Infectious diarrhea (ID) is a heterogeneous disease with various causes, some of which require specific antibiotics, while most cases are self-limiting and thus do not require antibiotics. Hence, antibiotics should be appropriately selected by taking the specific causative agents into account. Even though, except for in cases of traveler's diarrhea and when there is a high suspicion or risk of systemic bacterial infection, the prevailing guidelines recommend against the use of antibiotics for ID, empirical antibiotics are nevertheless initiated in some cases without a diagnosis of the specific cause, because a precise diagnosis of the cause of ID is difficult at the time of the first encounter; it takes several days to obtain the results of stool cultures [1–4]. Some randomized controlled trials have suggested that empirical use of oral quinolones for acute ID shortens the symptom duration by 1–2 days [5–7]. However, these findings cannot justify the empirical use of

* Corresponding author. Department of General Medicine and Emergency Care, Toho University School of Medicine, Omori Hospital, 6-11-1 Omori-Nishi, Ota-Ku, Tokyo 143-8541, Japan.
E-mail address: yousuke.sasaki@med.toho-u.ac.jp (Y. Sasaki).

http://dx.doi.org/10.1016/j.jiac.2017.09.004
1341-321X/

antibiotics, because antibiotics can cause various severe adverse events, including potentially increasing the risk for hemolytic uremic syndrome associated with enterohemorrhagic *Escherichia coli* (EHEC) infection, antibiotic-related diarrhea such as *Clostridium difficile* infection due to the destruction of the normal gut flora, drug allergies, and induction of bacterial drug-resistance such as quinolone-resistant *Campylobacter jejuni* (*C. jejuni*) [2,3,8].

On the other hand, empirical antimicrobial therapy is currently controversial in cases of hospitalization. The Japanese guidelines suggest empirical use of antibiotics before obtaining stool culture results for these cases [2], whereas other guidelines do not clearly provide guidance for these limited situations [1,3,4]. However, to the best of our knowledge, no study has evaluated the effect of empirical antimicrobial therapy for hospitalized patients with ID. Thus, we conducted this study to evaluate whether empirical antimicrobial therapy, initiated prior to obtaining information on the causative agents, would shorten the hospitalization duration for patients with acute ID.

2. Patients and methods

2.1. Design and setting

This was a single-center, retrospective cohort study using medical records from 2012 to 2015. This study was conducted in the Department of General Medicine and Emergency Care, Toho University Medical Center Omori Hospital, which has 948 beds and is located in the southern part of Tokyo, Japan.

2.2. Patients

Patients aged 16 years or older, hospitalized for the following disorders as the main diagnoses, based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision, were selected: A02, other salmonella infections; A03, shigellosis; A04, other bacterial intestinal infections; A05, other bacterial foodborne intoxications, not elsewhere classified; A06, amebiasis; A08, viral and other specified intestinal infections; and A09, infectious gastroenteritis and colitis, unspecified. We excluded patients who met any of the following criteria: patients without diarrhea within 48 h before or after admission; patients who were clinically unlikely to develop infectious gastrointestinal disease; patients who were diagnosed with other diseases after admission; patients who required hospitalization for other complications, except for antibiotic-related adverse events; pregnant patients; participants of clinical trials; and patients who were discharged against medical advice. Furthermore, patients admitted for the treatment of *Clostridium difficile* infection (CDI) due to previously exposed antibiotics were also excluded, because the treatment of CDI generally takes longer than that of other types of community-acquired ID.

2.3. Outcome measures

The primary outcome in this study was the duration of hospitalization. Data regarding the following variables were collected for the analyses: age, sex, presence of associated symptoms/signs (abdominal pain, hematochezia, nausea/vomiting, fever higher than 38 °C), travel history within 3 weeks (if present, the locations), previously reported risk factors (diabetes mellitus, receiving glucocorticoids or other immunosuppressants, hematological diseases, malignancies, inflammatory bowel disorders, chronic heart failure, liver cirrhosis, artificial device implantation, abdominal aortic aneurysm, previous antibiotic exposure or hospitalization within 2 months, staying in nursing homes, and use of proton pump inhibitors), use of probiotics, systolic blood pressure and heart rate on admission, results of stool/blood culture and/or rapid viral antigen testing, and blood test results, including leukocyte counts and levels of C-reactive protein (CRP), urea nitrogen, creatinine, and alanine aminotransferase. We also measured the incidences of subsequently occurring CDI, antibiotic-related adverse events (such as allergy, hepatotoxicity), and death as adverse outcomes.

2.4. Analyses

We divided the patients into two groups for the analyses: patients who were exposed to empirical intravenous or oral antibiotics during hospitalization (group A), and patients managed without antibiotics (group N). We defined antimicrobial therapy as empirical when it was initiated before the stool or blood culture results were obtained.

The following analyses were performed

1) Analysis of the duration of hospitalization

The duration of hospitalization was compared between the two groups using the Mann-Whitney *U* test. To further evaluate the efficacy of empirical antibiotics for bacterial diarrhea, we also evaluated the duration of hospitalization (1) after excluding 26 cases with simple viral enteritis, defined as cases with positive viral antigens and negative stool cultures, (n = 162) and (2) in patients with positive stool cultures (n = 47), separately.

To adjust for confounding factors, we performed multiple regression analysis based on the use of antibiotics, use of probiotics, age, underlying disorders, hematochezia, leukocyte count, serum creatinine, and serum CRP. All explanatory variables were selected based on previous studies on poor prognostic factors of ID and differences in the distributions of the measured factors between groups A and N. While the stool culture and viral antigen test results are also potential important factors for the duration of hospitalization, we did not include these factors in the multiple regression analysis, as data were available in only 78.8% and 42.9% of participants, respectively (Table 1). To evaluate the efficacy of the antibiotics for bacterial diarrhea, we also performed multiple regression analysis after excluding the 26 cases with simple viral enteritis (n = 162) and in the 47 cases with positive fecal cultures.

2) Analysis of factors that motivate empirical antimicrobial therapy

To examine if the cases treated with empirical antibiotics were consistent with the cases presenting with poor prognostic factors, we performed logistic regression analysis comparing groups A and N based on age, underlying disorders, hematochezia, leukocyte count, serum creatinine, and serum CRP as explanatory variables. We did not include the stool culture results as an explanatory variable of antibiotic use, because there were only 47 cases with positive stool cultures and because empirical antimicrobial therapy in the present study was initiated before obtaining the results of the stool cultures in all cases. Thus, information about the causative bacteria should not be included as an explanatory variable that motivate physicians to initiate empiric microbial therapy. We also performed the same logistic regression analysis for the 26 cases with simple viral enteritis to evaluate the factors that motivate empirical antimicrobial therapy for cases with positive viral antigens.

Statistical analysis was performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R3.3.1 (The R foundation for statistical computing, Vienna, Austria) [9].

The institutional review board of Toho University Medical Center Omori Hospital approved this study.

Table 1
Patient characteristics.

Characteristic	All patients (n = 188)	Group A (n = 138)	Group N (n = 50)	p value
Age (years)	35 [24–54]	32.0 [23.0–50.0]	45.5 [25.5–67.8]	0.023
Male sex	99 (51.9%)	78 (55%)	21 (42.9%)	0.098
Abdominal pain	155 (82.5%)	114 (82.6%)	41 (82.0%)	1
Fever	87 (46.3%)	69 (50.0%)	18 (36.0%)	0.100
Hematochezia	30 (16.0%)	25 (18.1%)	5 (10.0%)	0.259
Nausea/vomiting	142 (75.5%)	104 (75.4%)	38 (76.0%)	1
Underlying disease	34 (18.0%)	23 (16.7%)	11 (22.0%)	0.399
Use of proton pump inhibitors	17 (9.0%)	12 (8.7%)	5 (10.0%)	0.777
Diabetes mellitus	9 (4.8%)	7 (5.1%)	2 (4.0%)	1
Chronic heart failure	3 (1.6%)	2 (1.4%)	1 (2.0%)	1
Artificial device implantation	2 (1.1%)	1 (0.7%)	1 (2.0%)	0.462
Abdominal aortic aneurysm	2 (1.1%)	1 (0.7%)	1 (2.0%)	0.462
Use of immunosuppressants	2 (1.1%)	1 (0.7%)	1 (2.0%)	0.462
Liver cirrhosis	1 (0.5%)	0	1 (2.0%)	0.266
Malignant tumors	2 (1.1%)	0	2 (4.0%)	0.070
Hematological disease	1 (0.5%)	0	1 (2.0%)	0.266
Use of probiotics	78 (41.5%)	51 (37.0%)	27 (54.0%)	0.045
Heart rate (beats/min)	80.0 [70.0–90.0]	80.5 [70.0–90.0]	78.0 [68.0–89.5]	0.332
Systolic blood pressure (mmHg)	112 [102–124]	112.0 [102.0–124.0]	112.5 [106.0–124.0]	0.239
Leukocyte count (/mm^3)	9550 [6575–11,750]	10,550 [7150–12,575]	6650 [5150–9575]	<0.01
CRP (mg/dL)	3.4 [0.9–9.0]	3.9 [1.1–9.4]	1.7 [0.4–5.2]	0.007
Creatinine (mg/dL)	0.78 [0.64–0.94]	0.81 [0.64–0.98]	0.70 [0.61–0.83]	0.013
ALT (IU/L)	14 [10–21]	14 [10–21]	13.0 [10.3–19.8]	0.727
Blood culture submission	38 (20.1%)	35 (25.4%)	4 (8.0%)	<0.01
Positive blood culture result	2 (5.0%)	2 (5.7%)	0	1
Stool culture submission	149 (78.8%)	112 (81.2%)	37 (74.0%)	0.311
Positive stool culture result	47 (31.5%)	37 (33.0%)	10 (27.0%)	0.546
Virus antigen test submission	81 (42.9%)	50 (36.2%)	30 (60.0%)	<0.01
Positive virus antigen	29 (36.3%)	15 (30.0%)	14 (46.7%)	0.155

The data are reported as median [interquartile range] or n (%).
Group A: patients managed with empirical antimicrobial therapy. Group N: patients managed without empirical antimicrobial therapy. The percentages of positive results for the blood culture, stool culture, and viral antigen tests were calculated as the number of positive results divided by the number of submitted tests. P values were calculated by Fischer's exact test between groups A and N. Positive stool culture and positive viral antigen results include cases with mixed infection.
CRP, C-reactive protein; ALT, alanine aminotransferase.

3. Results

During the study period, 308 patients were initially enrolled, of whom 120 patients were excluded according to the exclusion criteria. Thus, 188 patients were finally registered in the study (Fig. 1). One hundred thirty-eight patients (73.4%) were treated with antibiotics (Group A), while 50 patients (26.6%) were managed without (Group N). We confirmed that all patients in group A empirically received antibiotics prior to obtaining the stool or blood culture results. The patient characteristics are listed in Table 1. There were no patients with previous hospitalization, staying at nursing homes, or with inflammatory bowel disorders. Information about the causative agents, as identified using stool cultures or viral antigen tests, in 73 cases and the antibiotics used for those 73 cases are listed in Table 2. For the 138 patients in group A, the numbers of patients who received antibiotics and the specific antibiotics used

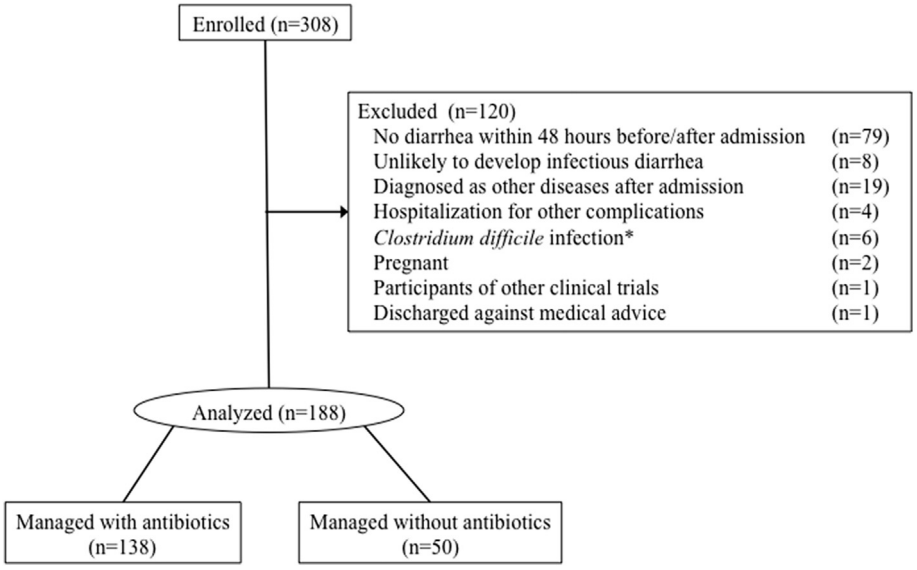

Fig. 1. Flow chart of the study patients. *Cases admitted for treatment for *Clostridium difficile* infection due to previous antibiotics exposure were excluded. There was no case with subsequently diagnosed *Clostridium difficile* infection after admission.

Table 2
Isolated causative agents and the antibiotics used for these cases (n = 73).

Isolated causative agents	Intravenous antibiotics	Oral antibiotics	Number of cases
Bacteria			44
Campylobacter jejuni (*C. jejuni*)			17
	NA	NA	5
	AZM	NA	3
	CMZ	NA	3
	CMZ	FOM	1
	CTRX	NA	1
	CTRX	CPDX-PR	1
	LVFX	LVFX	1
	NA	FOM	1
	NA	AZM + ST	1
Enterotoxic *Escherichia coli* (ETEC)			7
	CMZ	NA	2
	CTRX	LVFX	2
	CMZ	CFDN	1
	LVFX	LVFX	1
	NA	NA	1
Enteropathogenic *Escherichia coli* (EPEC)			4
	CMZ	NA	3
	NA	NA	1
Klebsiella oxytoca			2
	CMZ	NA	1
	ABPC/SBT	NA	1
Salmonella spp.			2
	LVFX	NA	1
	CTRX	NA	1
Yersinia enterocolitica			2
	CMZ	NA	1
	LVFX	NA	1
O-157	CMZ	CPDX-PR	1
O-25	CPZ	NA	1
Shigella sonnei	LVFX	NA	1
C. jejuni + EPEC			3
	CMZ + LVFX	NA	1
	NA	NA	1
	CMZ	STFX	1
C. jejuni + ETEC	CMZ	LVFX	1
ETEC + EPEC	CMZ	LVFX	1
K. oxytoca + *Salmonella*	NA	LVFX	1
O-157 + *C. jejuni*	NA	NA	1
Viruses			26
Norovirus			15
	NA	NA	8
	CMZ	NA	4
	ABPC/SBT	NA	2
	CMZ	CDTR-PI	1
Rotavirus			5
	NA	NA	4
	CMZ	LVFX	1
Norovirus + Rotavirus + Adenovirus			4
	CMZ	NA	2
	CTRX	NA	1
	ABPC/SBT	NA	1
	Rotavirus + Adenovirus		2
	FMOX	NA	1
	AZM	NA	1
Mixed infection			3
C. jejuni + Norovirus	LVFX	NA	1
C. jejuni + Rotavirus + Adenovirus	CMZ	NA	1
EPEC + Rotavirus	CMZ	NA	1
Total			73

Abbreviations: ABPC/SBT, ampicillin/sulbactam; AZM, azithromycin; CAM, clarithromycin; CDTR-PI, cefditoren pivoxil; CEZ, cefazolin; CFDN, cefdinir; CMZ, cefmetazole; CPDX-PR, cefpodoxime proxetil; CPZ, cefoperazone; CTM, cefotiam; CTRX, ceftriaxone; CTX, cefotaxime; FMOX, flomoxef; FOM, fosfomycin; LVFX, levofloxacin; NA; not applicable; ST, sulfamethoxazole-trimethoprim; STFX, sitafloxacin.

are listed in Table 3. The numbers of patients who received intravenous, oral, and combination of intravenous and oral antibiotics were 108 (78.3%), 5 (2.1%), and 25 (18.1%), respectively. Intravenous cefmetazole was the most frequently used antibiotic (Table 3). All patients improved without developing subsequent CDI or drug-related adverse events. Regarding the antibiotics used according to the specific causative agent, antibiotics were empirically used for 17/23 (73.9%) cases of *C. jejuni* infection. In those 17 cases, macrolides or quinolones were used in 9 (52.9%) cases and beta-lactams were used in 8 (47.1%) cases. Antibiotics were also unnecessarily used in 14/26 (53.8%) cases of simple viral enteritis. Finally, beta-lactams were used for 2 of 2 (100%) cases of EHEC infections (Table 2).

Table 3
Antibiotics used in the study patients (Group A).

Antibiotics	Number of cases (%)
Intravenous antibiotics	108 (78.3%)*
CMZ	57 (52.8%)†
CTRX	14 (13.0%)†
LVFX	8 (7.4%)†
AZM	6 (5.6%)†
ABPC/SBT	5 (4.6%)†
FOM	5 (4.6%)†
FMOX	2 (1.9%)†
AZM + MEPM	1 (0.9%)†
ABPC/SBT + AZM	1 (0.9%)†
CEZ	1 (0.9%)†
CMZ_AZM	1 (0.9%)†
CMZ + LVFX	1 (0.9%)†
CPZ	1 (0.9%)†
CTM	1 (0.9%)†
CTX	1 (0.9%)†
IPM/CS	1 (0.9%)†
LVFX + VCM	1 (0.9%)†
MEPM	1 (0.9%)†
Oral antibiotics	5 (2.1%)*
FOM	2 (40%)††
LVFX	2 (40%)††
AZM + ST	1 (20%)††
Combined use of intravenous and oral antibiotics	25 (18.1)*
Intravenous CMZ + oral LVFX	5 (20%)†††
Intravenous LVFX + oral LVFX	4 (16%)†††
Intravenous CTRX + oral LVFX	2 (8%)†††
Intravenous CEZ + oral FMOX	1 (4%)†††
Intravenous CLDM + oral LVFX	1 (4%)†††
Intravenous CMZ + oral AMPC/CVA	1 (4%)†††
Intravenous CMZ + oral AZM	1 (4%)†††
Intravenous CMZ + oral CDTR-PI	1 (4%)†††
Intravenous CMZ + oral CFDN	1 (4%)†††
Intravenous CMZ + oral CPDX-PR	1 (4%)†††
Intravenous CMZ + oral CPFX + oral MNZ	1 (4%)†††
Intravenous CMZ + oral CTM	1 (4%)†††
Intravenous CMZ + oral FOM	1 (4%)†††
Intravenous CMZ + oral STFX	1 (4%)†††
Intravenous CTRX + oral AZM	1 (4%)†††
Intravenous CTRX + oral CPDX-PR	1 (4%)†††
Intravenous LVFX + oral CAM	1 (4%)†††

Abbreviations: ABPC/SBT, ampicillin/sulbactam; AMPC/CVA, amoxicillin/clavulanate; AZM, azithromycin; CAM, clarithromycin; CDTR-PI, cefditoren pivoxil; CEZ, cefazolin; CFDN, cefdinir; CLDM, clindamycin; CMZ, cefmetazole; CPDX-PR, cefpodoxime proxetil; CPFX, ciprofloxacin; CPZ, cefoperazone; CTM, cefotiam; CTRX, ceftriaxone; CTX, cefotaxime; FMOX, flomoxef; FOM, fosfomycin; IPM/CS, imipenem/cilastatin; LVFX, levofloxacin; MEPM, meropenem; MNZ, metronidazole; ST, sulfamethoxazole-trimethoprim; STFX, sitafloxacin; VCM, vancomycin.
Notes: *Percentages were calculated as the number of patients divided by all patients who received antibiotics.
†Percentages were calculated as the number of patients divided by all patients who received intravenous antibiotics.
††Percentages were calculated as the number of patients divided by all patients who received oral antibiotics.
†††Percentages were calculated as the number of patients divided by all patients who received combination of intravenous and oral antibiotics.

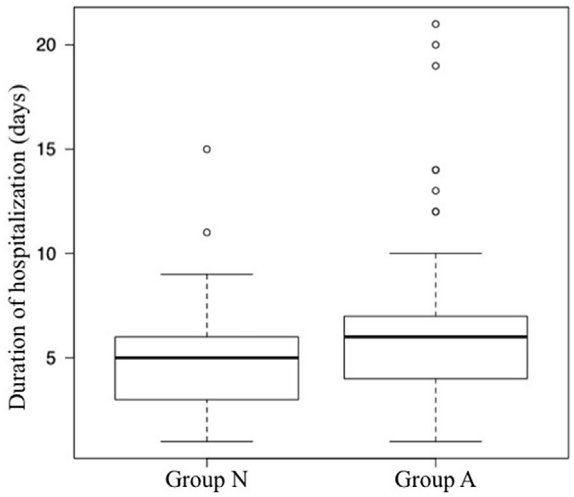

Fig. 2. Distribution of hospitalization duration among the groups. Group A: patients managed with antibiotics during hospitalization. Group N: patients managed without antibiotics.

1) Hospitalization duration

The distributions of hospitalization duration for each group are shown in Fig. 2. The unadjusted median durations of hospitalization were 6.0 days (interquartile range [IQR], 4.0–7.0 days) in group A and 5.0 days (IQR, 3.25–6.0 days) in group N ($p = 0.007$). After excluding 26 cases with simple viral enteritis ($n = 162$), the unadjusted median durations of hospitalization were 6.0 days (IQR, 5.0–7.0 days) in group A and 5.0 days (IQR, 4.0–6.0 days) in group N ($p = 0.028$). In the 47 cases with positive stool cultures, the unadjusted median durations of hospitalization were 6.0 days (IQR, 5.0–7.0 days) in group A and 5.5 days (IQR, 5.0–6.75 days) in group N ($p = 0.854$).

Multiple regression analysis showed that empiric antimicrobial therapy was a significant risk factor of longer hospitalization ($b = 1.173$; $p = 0.017$). For other risk factors, age ($b = 0.031$; $p = 0.003$), hematochezia ($b = 1.435$; $p = 0.008$), serum creatinine ($b = 0.638$; $p < 0.001$), and serum CRP ($b = 0.112$; $p = 0.002$) significantly associated with prolonged hospital duration, whereas the use of probiotics ($b = 0.464$; $p = 0.246$) did not significantly shorten the hospitalization duration (Table 4). After excluding the 26 cases with simple viral enteritis, age ($b = 0.033$; $p = 0.004$), serum creatinine ($b = 0.643$; $p < 0.001$), and serum CRP ($b = 0.102$; $p = 0.006$) remained as significant risk factors, whereas the use of antibiotics was not significant ($p = 0.137$). In the analysis of the 47 cases with positive stool cultures, only serum CRP was a significant risk factor for longer hospitalization ($b = 0.154$, $p = 0.008$).

Table 4
Prognostic factors for the duration of hospitalization for infectious diarrhea.

Variable	Regression coefficient	p value
Empiric antimicrobial therapy	1.173	0.017
Use of probiotics	0.465	0.246
Age (years)	0.031	0.003
Underlying disease	−0.129	0.813
Hematochezia	1.435	0.008
Leukocyte count (/mm^3)	−0.080	0.088
Serum creatinine (mg/dL)	0.638	<0.001
Serum CRP (mg/dL)	0.112	0.002

The above variables were included in the multiple regression analysis, for which the outcome was the duration of hospitalization.
CRP, C-reactive protein.

Table 5
Significant factors that motivate clinicians to use antibiotics.

Variable	Odds ratio (95% confidence interval)	p value
Age (years)	0.98 (0.97–1.01)	0.051
Underlying disease	1.03 (0.313–3.39)	0.857
Hematochezia	1.97 (0.64–6.03)	0.148
Leukocyte count (/mm^3)	1.21 (1.07–1.37)	<0.001
Serum creatinine (mg/dL)	1.72 (0.59–4.97)	0.176
Serum CRP (mg/dL)	1.06 (0.96–1.17)	0.059

The above variables were included in the logistic regression analysis, for which the outcome was use of antibiotics.
CRP, C-reactive protein.

2) Factors that motivate empirical antimicrobial therapy

Logistic regression to detect factors motivating antibiotic use showed that only the leukocyte count was significantly higher in patients who received antimicrobial therapy than in those who did not (odds ratio, 1.21; 95% confidence interval, 1.07–1.37; $p = 0.003$; Table 5). However, multiple regression analysis showed that leukocytosis was not independently associated with longer hospitalization (Table 4), indicating that the cases with antibiotics were not consistent with those with poor prognostic factors. Of note, there were non-significant tendencies of younger patients and patients with higher serum CRP levels to more frequently receive antibiotics ($p = 0.051$ and 0.059, respectively; Table 5). The same logistic regression analysis for the 26 cases with simple viral enteritis revealed that the serum CRP was significantly lower in patients who received antibiotics (odds ratio, 0.46; 95% confidence interval, 0.22-0.96; $p = 0.04$).

4. Discussion

Our study showed that empiric antimicrobial therapy was significantly associated with longer hospitalization due to ID. Our study also showed that advanced age, the presence of hematochezia, and elevated serum creatinine and serum CRP levels significantly associated with a longer hospitalization duration.

The current guidelines do not recommend routine empirical antimicrobial therapy for outpatients with ID, except for patients with traveler's diarrhea, owing to a lack of evidence that the potential benefit outweighs any potential adverse outcomes [2–4]. However, the use of empirical antimicrobial therapy for patients who require hospitalization remains controversial, because these patients tend to have clinically “severe” or “risky” disease, and clinicians prefer to use antibiotics to prevent serious outcomes. Nevertheless, studies limited to hospitalized patients are sparse. Contrary to what was expected, the present study showed that empiric antimicrobial therapy was associated with a longer hospitalization duration. In fact, even after excluding cases with positive viral antigens, antibiotic use did not significantly shorten the hospitalization duration. However, there were no adverse events associated with the use of antibiotics, such as CDI, allergy, or hepatotoxicity. Because the present study could not quantitatively evaluate subjective symptoms such as the severity of nausea, abdominal pain, or diarrhea, we could not deny the potential of selection bias due to symptoms. However, our results at least imply that empirical antimicrobial therapy does not shorten the hospitalization duration, even in hospitalized patients. Accordingly, our results suggest that the cautious attitude for empirical antimicrobial therapy in the prevailing guidelines should also be applied to limited situations such as in hospitalized patients. Our study revealed the following inappropriate antibiotics uses: (1) betalactams were used in 47.1% of *C. jejuni* infections, (2) all cases with EHEC infection were exposed to antibiotics, and (3) antibiotics

were used in 53.8% of simple viral enteritis cases. Retrospectively, these results suggest that empiric antimicrobial therapy results in frequent inappropriate antibiotics use, which subsequently might result in the longer hospitalization duration observed in the present study. Taken together, our results reaffirm the importance of culture-guided and causative agent-targeted antimicrobial therapy.

The present study also analyzed age, the presence of hematochezia, elevated serum creatinine and CRP levels, and the use of probiotics as prognostic factors. Advanced age and hematochezia have been previously established as poor prognostic factors suggestive of severe bacterial infection [2,4]. On the other hand, elevated serum creatinine is not an established poor prognostic factor. However, it is assumed that elevated serum creatinine, a parameter of renal impairment, is associated with longer hospitalization duration for the following reasons: (1) serum creatinine elevation due to acute renal failure is a major poor outcome associated with ID, and such cases require more aggressive fluid administration or even hemodialysis, especially in cases of hemolytic uremic syndrome associated with EHEC infection [1,3]; and (2) patients with chronic renal failure, especially those who require hemodialysis, are immunocompromised [8]. Furthermore, this is, to our knowledge, the first report of serum CRP as a risk factor of prolonged hospitalization in ID patients. This new knowledge could be obtained owing to the unique Japanese practice of commonly using CRP as a biomarker of acute inflammation or bacterial infection. Given that CRP is not an established poor prognostic factor of ID, the possibility of physicians' over-reliance on CRP should be considered; the CRP value itself might affect their judgment of the need for hospitalization.

In terms of probiotics, their benefit for ID patients is controversial, and their use as treatment for ID is discouraged by the current American College of Gastroenterology practice guidelines [4]. However, some systematic reviews have demonstrated that probiotics reduce the duration of symptoms, especially for pediatric cases [10,11]. In the current study, use of probiotics did not affect the hospitalization duration; this provides evidence regarding the use of probiotics in hospitalized adult patients in this controversial area.

Previous studies have shown that underlying diseases or hematochezia are poor prognostic factors that may justify empirical use of antibiotics [1,2,4]. However, the factors that motivate clinicians to administer antibiotics in practice are not well known. Our study revealed that antibiotics are more frequently used in cases with leukocytosis, as opposed to in cases with previously established risk factors. This result implies that clinicians prefer to use antibiotics for patients with leukocytosis, rather than based on established poor prognostic factors, indicating an important evidence-practice gap in the management of ID. Clinicians should reconsider laboratory data-dependent management, because our study indicated that leukocytosis was not associated with longer hospitalization duration.

Our study has three major limitations. First, we did not evaluate symptoms such as abdominal pain or frequency of diarrhea. The effects of antibiotics can be underestimated in this study by ignoring their effects on the patients' symptoms. However, we consider the hospitalization duration an appropriate primary outcome, because our participants were limited to hospitalized patients. Our study is significant at least in the viewpoint of medical economics; cost due to hospitalization is an important economic issue. Second, we could not evaluate the factors associated with the attending physicians such as their preference or experience, which may affect the selection of antibiotics. As mentioned above, inappropriate laboratory data-dependent practice might result in longer hospitalization of cases with elevated CRP levels. Third, the single-center retrospective cohort study design did not allow us to evaluate the variance in practice styles between facilities or any guideline-practice gaps. Multi-center and prospective interventional studies are warranted to further evaluate the effect of empirical antimicrobial therapy for hospitalized ID patients.

In summary, empirical intravenous and oral antimicrobial therapy related to a longer hospitalization duration for ID patients. Although the effects on the patients' symptoms were not evaluated, our study could not establish a clinical benefit of empirical antimicrobial therapy, even for patients who required hospitalization. Failure of empirical antimicrobial therapy to provide appropriate antimicrobial therapy for specific causative agents may explain the negative results. Our study reaffirms the importance of culture-guided antimicrobial therapy. However, further studies on the significance of antibiotic use for cases of ID requiring hospitalization are warranted.

Conflicts of interest

None.

Acknowledgements

We would like to thank Dr. Chiaki Nishimura (emeritus professor of Toho University) and the members of the Center for Innovative Research for Communities and Clinical Excellence, Fukushima Medical University, for their valuable advice. Moreover, we thank Editage (www.Editage.jp) for English language editing.

References

[1] Farthing M, Salam MA, Lindberg G, Dite P, Khalif I, Salazar-Lindo E, et al. Acute diarrhea in adults and children: a global perspective. J Clin Gastroenterol 2013;47:12–20.
[2] Ohnishi K, Ainoda Y, Imamura A, Iwabuchi S, Okuda M, Nakano T. The JAID/JSC Guidelines to Clinical Management of Infectious Diseases (Intestinal infection). J Jpn Assoc Infect Dis 2016;90:31–65 [in Japanese].
[3] Guerrant RL, Van Gilder T, Steiner TS, Thielman NM, Slutsker L, Tauxe RV, et al. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis 2001;32:331–51.
[4] Riddle MS, DuPont HL, Connor BA. ACG Clinical Guideline: diagnosis, treatment, and prevention of acute diarrheal infections in adults. Am J Gastroenterol 2016;111:602–22.
[5] Dryden MS, Gabb RJ, Wright SK. Empirical treatment of severe acute community-acquired gastroenteritis with ciprofloxacin. Clin Infect Dis 1996;22:1019–25.
[6] Goodman LJ, Trenholme GM, Kaplan RL, Segreti J, Hines D, Petrak R, et al. Empiric antimicrobial therapy of domestically acquired acute diarrhea in urban adults. Arch Intern Med 1990;150:541–6.
[7] Wiström J, Jertborn M, Ekwall E, Norlin K, Söderquist B, Strömberg A, et al. Empiric treatment of acute diarrheal disease with norfloxacin. A randomized, placebo-controlled study. Swedish Study Group. Ann Intern Med 1992;117:202–8.
[8] Barr W, Smith A. Acute diarrhea in adults. Am Fam Physician 2014;89:180–9.
[9] Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transpl 2013;48:452–8.
[10] Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea in children. Cochrane Database Syst Rev 2010;11, CD003048.
[11] Bernaola Aponte G, Bada Mancilla CA, Carreazo NY, Rojas Galarza RA. Probiotics for treating persistent diarrhoea in children. Cochrane Database Syst Rev 2013;8, CD007401.