

Incomplete recovery of the fecal flora of hematological patients with neutropenia and repeated fluoroquinolone prophylaxis

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Background: Routine fluoroquinolone prophylaxis in neutropenic patients with hematological malignancies is still controversial, because of antibiotic resistance concerns. The recovery of the fecal microbiota to the initial composition in patients receiving multiple courses of quinolone prophylaxis and repeated chemotherapy has not been evaluated.

Methods: We prospectively examined the changes in the fecal bacterial composition before and after levofloxacin prophylaxis. A sequential observation of bacterial resistance in patients receiving multiple prophylactic courses was also conducted.

Results: In this trial, 68 cases, including (35 with the first course and 33 with the second and subsequent courses) were registered. The disappearance of quinolone-susceptible (QS) *Enterobacteriaceae* and dominant emergence of quinolone-resistant (QR) coagulase negative staphylococci (CNS) and QR *Enterococci* were observed after the first prophylaxis. The detection of QS *Enterobacteriaceae* was recovered before the second and subsequent courses to a level of the initial composition (28/35 samples, 80.0% before the first course vs 23/33 samples, 69.7% before the second and subsequent courses, $P=0.41$). In contrast, the detection rate of QR CNS and *Enterococci* significantly increased at the second and subsequent courses, even before prophylaxis (8/35 samples, 22.9% before the first course vs 20/33 samples, 60.6% before the second and subsequent courses, $P=0.003$). The incomplete recovery of the initial bacterial composition was associated with a prophylactic interval of within 30 days. Of the patients receiving multiple prophylactic courses, six had QR *Escherichia coli*, including extended-spectrum β -lactamase (ESBL) producers, at the first course, and four (66.3%) of the six patients had persistent detection of QR *E. coli* at the second course.

Conclusion: In patients receiving multiple courses of prophylactic quinolone, along with a common chemotherapy schedule, newly emergent resistant bacteria could be frequently persistent in their fecal flora.

Keywords: febrile neutropenia, prophylaxis, fluoroquinolone, antibiotic resistance, fecal flora, chemotherapy

Introduction

Febrile neutropenia is one of the most serious adverse events in patients with hematological malignancies and chemotherapy.¹ Bacteremia related to febrile neutropenia often increases infection-related morbidity and mortality. The use of antibiotic prophylaxis, particularly fluoroquinolones (quinolones), has been known to have a positive impact on the frequency of febrile episodes, bacteremia, and even infection-related mortality.²⁻⁴ The latest guideline issued by the Infectious Diseases Society of America (IDSA) stated that the prophylactic use of quinolones is recommended for high-risk patients in

whom chemotherapy-induced neutropenia is expected to last for >7 days.⁵ However, the emergence of bacterial resistance to antibiotics, especially quinolones, has become a critical concern, and routine prophylactic use has been repeatedly questioned to date.^{6–10}

In our previous study, we prospectively examined the incidence of quinolone-resistant (QR) *Escherichia coli* isolates recovered from stool cultures before and after levofloxacin prophylaxis in 68 neutropenic patients with hematological malignancies and analyzed the emergence of QR *E. coli* before and after prophylaxis.¹¹ Patients with hematological malignancies usually receive repeated chemotherapy and, accordingly, repeated quinolone prophylaxis for their neutropenia in many cases. It is not known whether quinolone-susceptible (QS) bacteria in the initial gut flora can be recovered during the administration of multiple courses of prophylactic quinolone. Also, sequential observation of bacterial resistance in patients receiving multiple courses of prophylaxis has not been conducted. In the present study, we used fecal samples collected from the 68 patients who were registered in our previous study to analyze the changes in fecal microbiota before and after quinolone prophylaxis. A significant point of this study was to examine the sequential change of fecal bacterial composition, including the recovery of QS bacteria and persistent detection of QR bacteria, during repeated prophylactic antibiotic exposure. In addition, we examined the detection history of QR *E. coli* at an individual level.

Methods

Patients and ethics statement

From August 2011 to May 2013, 68 cases were recruited from a single hematological unit with 37 beds at Hara-Sanshin Hospital. The protocol was approved, through the ethics review process, by the Institutional Review Board of the Hara-Sanshin Hospital. Written informed consent was obtained from all registered patients not only for publication of these case details but also to participate in this research. Infection control measures including promotion of hand-washing and isolation procedures were maintained throughout the study.

Enrollment

Inpatients with neutropenia were enrolled in the study. Neutropenia was defined as an absolute neutrophil count of <1,000 cells/mm³ or a neutrophil count with a predicted decrease to <1,000 cells/mm³ during the following 48 hours. Exclusion criteria is shown in our previous report.¹¹ Patients

treated for allogeneic hematopoietic stem cell transplantation were excluded from the trial because a confirmative diagnosis of febrile neutropenia is often difficult because of the presence of other causative factors such as graft-versus-host disease and engraftment syndrome. Antimycotic agents were administered for most of the registered neutropenic patients.

Treatment protocol

Antibiotic prophylaxis with levofloxacin (Daiichi Sankyo Co. Ltd., Tokyo, Japan) at a dosage of 500 mg/day was administered to all patients during the study period. Levofloxacin was administered to patients without febrile neutropenia until their neutrophil counts recovered. However, levofloxacin prophylactic treatment was discontinued when the empirical antibiotic therapy for febrile neutropenia was initiated. Febrile neutropenia was defined as: 1) fever, a single axillary temperature of >38.0°C or an axillary temperature >37.5°C lasting 1 hour and 2) neutropenia, defined according to the aforementioned guidelines.

Microbiology

For each patient, 2 stool samples were examined. The first sample was collected before levofloxacin administration, and the second sample after prophylaxis was discontinued. Stool samples were cultured, chiefly using 5% Sheep Blood Agar medium (BD). The species were identified using the Vitek system (bioMerieux Japan Ltd., Tokyo, Japan). Antibiotic susceptibilities were determined by the breakpoints standardized by the Clinical and Laboratory Standards Institute (CLSI).¹² The screening and confirmation tests for extended-spectrum β -lactamase (ESBL) were conducted according to the recommendation of the CLSI.¹² In addition, β -lactamase producers were confirmed using a Cica β test I/MBL kit (Kanto Chemical Co. Ltd., Tokyo, Japan).

Variables and definitions

Clinical data were collected from medical records to evaluate the related risk factors. The variables obtained from the data of the last course of quinolone prophylaxis, which are associated with the detection of QS and resistant bacteria at the second and subsequent courses, included high-intensity chemotherapy, trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis, antimicrobial therapy except for quinolone prophylaxis at the last cycle, duration of quinolone prophylaxis at the last cycle, and duration from the final antimicrobial therapy to sample collection. Of the 33 cases with more than two courses of prophylaxis, 23 cases included relatively high-intensity chemotherapy consisting of a standard

chemotherapy for acute leukemia (ie, daunorubicin plus cytosine arabinoside) and a salvage chemotherapy for malignant lymphoma, for their last chemotherapy. The remaining 10 cases received relatively low-intensity chemotherapy of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or R (rituximab)-CHOP for acute leukemia and malignant lymphoma, for their last chemotherapy. Pneumocystis pneumonia prophylaxis using TMP-SMX was conducted in 18 cases at the last cycle. In the 14 cases of febrile neutropenia at the last cycle, antimicrobial agents recommended for febrile neutropenia, including piperacillin-tazobactam, cefepime, and meropenem, were administered. A protocol for quinolone prophylaxis is mentioned above. The duration of quinolone prophylaxis at the last cycle was examined. The duration from the final antimicrobial therapy to sample collection was defined as the period from the final date of the last quinolone prophylaxis or the last antimicrobial therapy for febrile neutropenia until the date of sample collection before prophylaxis at the second and subsequent courses of prophylaxis.

Statistical analysis

Categorical variables between groups were tested using the Fisher's exact test. $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed using the JMP Pro software, version 11 (SAS Institute, Inc., Cary, NC, USA).

Results

A total of 68 cases were enrolled (Table 1). Patients receiving multiple courses of quinolone prophylaxis were recruited as a different case for every course. Of the 68 cases, 35 cases were applied for the first cycle of chemotherapy and quinolone prophylaxis. Among the 35 cases, 21 cases were applied for the second cycle. Among the 21 cases, 12 cases were applied for the third and subsequent cycles. Accordingly, a total of 33

cases were applied for the second and subsequent cycles. We focused on the decrease of QS *Enterobacteriaceae* and the dominant emergence of QR coagulase negative staphylococci (CNS) and QR *Enterococcus* (QR CNS and *Enterococcus*) species, as a characteristic of the change of bacterial composition in feces before and after quinolone exposure. The *Enterobacteriaceae* detected included *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Citrobacter* spp., *Enterobacter* spp., *Morganella morganii*, and *Raoultella planticola*. As shown in Table 1, QS *Enterobacteriaceae* strains were not detected after the use of quinolones, regardless of the number of cycles. QS *Enterobacteriaceae* strains were detected in 80% of samples before the first cycle of prophylaxis and ~70% of samples before the second and subsequent prophylactic cycles, resulting in no significant decrease of these bacterial species after repeated quinolone exposure (28/35 samples vs 23/33 samples, $P = 0.4055$). QR CNS and *Enterococcus* strains were detected in ~20% of samples before the first prophylaxis (Table 1). In contrast, the detection rate of these bacterial strains significantly increased at more than two cycles, even before quinolone exposure (8/35 samples vs 20/33 samples, $P = 0.0028$). In addition, the detection frequency appeared to increase per the number of cycles (52.4% for cycle 2 and 75.0% for cycle >3), although no statistical significance was shown. QR CNS and *Enterococcus* strains were detected in ~70% of samples after the first prophylaxis, followed by detection in 95.2% of samples for cycle 2 and 100.0% for cycle >3. Vancomycin-resistant Enterococci (VRE) were not isolated in any of the samples.

Of the 33 samples from the cases with more than two courses of prophylaxis, QS *Enterobacteriaceae* strains and QR CNS and *Enterococcus* strains were detected before the prophylaxis in 23 and 20 samples, respectively. Next, we examined the predisposing factors for the detection of these bacteria before the prophylaxis of cycle >2 (Table 2). The duration of >31 days from the final antimicrobial use to

Table 1 Detection of fluoroquinolone-susceptible and/or resistant bacteria in the fecal flora of hematological patients with neutropenia and repeated quinolone prophylaxis

Each cycle	Quinolone-susceptible <i>Enterobacteriaceae</i>		P-value	Quinolone-resistant CNS and/or <i>Enterococci</i>		P-value
	Before prophylaxis	After prophylaxis		Before prophylaxis	After prophylaxis	
	No. of samples / total samples (%)	No. of samples / total samples (%)		No. of samples / total samples (%)	No. of samples / total samples (%)	
Cycle 1, n = 35	28 / 35 (80.0)	0 / 35 (0.0)	< 0.001	8 / 35 (22.9)	25 / 35 (71.4)	< 0.001
Cycle >2, n = 33	23 / 33 (69.7)	0 / 33 (0.0)	< 0.001	20 / 33 (60.6)	32 / 33 (97.0)	< 0.001
Cycle 2, n = 21	14 / 21 (66.7)	0 / 21 (0.0)	< 0.001	11 / 21 (52.4)	20 / 21 (95.2)	0.004
Cycle >3, n = 12	9 / 12 (75.0)	0 / 12 (0.0)	< 0.001	9 / 12 (75.0)	12 / 12 (100.0)	0.217

Abbreviation: CNS, coagulase negative staphylococci.

Table 2 Related factors for the detection of quinolone-susceptible *Enterobacteriaceae* and quinolone-resistant CNS and/or *Enterococci* before the prophylaxis of cycle >2

Variable	Quinolone-susceptible <i>Enterobacteriaceae</i> before prophylaxis (cycle >2)			P-value			Quinolone-resistant CNS and/or <i>Enterococci</i> before prophylaxis (cycle >2)			P-value		
	Detection (n = 23)		No detection (n = 10)	Detection (n = 20)		No detection (n = 13)	Detection (n = 20)		No detection (n = 13)	Detection (n = 20)		No detection (n = 13)
	No. of samples / total samples (%)	No. of samples / total samples (%)	No. of samples / total samples (%)	No. of samples / total samples (%)	No. of samples / total samples (%)	No. of samples / total samples (%)	No. of samples / total samples (%)	No. of samples / total samples (%)	No. of samples / total samples (%)	No. of samples / total samples (%)	No. of samples / total samples (%)	No. of samples / total samples (%)
High-intensity chemotherapy at last cycle	n = 23	16 / 23 (69.6)	7 / 10 (70.0)	1.0	15 / 20 (75.0)	8 / 13 (61.5)	0.4611					
TMP-SMX prophylaxis at last cycle	n = 18	11 / 23 (47.8)	7 / 10 (70.0)	0.2828	13 / 20 (65.0)	5 / 13 (38.5)	0.1686					
Antimicrobial therapy except for quinolone prophylaxis at last cycle	n = 14	12 / 23 (52.2)	2 / 10 (20.0)	0.1312	10 / 20 (50.0)	4 / 13 (30.8)	0.3095					
Duration of quinolone prophylaxis at last cycle												
within 7 days	n = 12	8 / 23 (34.8)	4 / 10 (40.0)	1.0	7 / 20 (35.0)	5 / 13 (38.5)	1.0					
within 14 days	n = 27	21 / 23 (91.3)	6 / 10 (60.0)	0.0534	16 / 20 (80.0)	11 / 13 (84.6)	1.0					
Duration from final antimicrobial therapy to sample collection												
within 30 days	n = 23	13 / 23 (56.5)	10 / 10 (100.0)	0.0148	16 / 20 (80.0)	7 / 13 (53.8)	0.1393					
>31 days	n = 10	10 / 23 (43.5)	0 / 10 (0.0)	0.0148	4 / 20 (20.0)	6 / 13 (46.2)	0.1393					

Abbreviations: CNS, coagulase negative staphylococci; TMP-SMX, trimethoprim-sulfamethoxazole.

sample collection was a factor significantly associated with the recovery of QS *Enterobacteriaceae* strains ($P=0.0148$). All 10 samples without the detection of QS *Enterobacteriaceae* strains were collected within 30 days from the final antimicrobial exposure. There were no significant factors associated with the detection of QR CNS and *Enterococcus* strains. However, these bacterial strains tended to be detected more frequently in the samples collected within 30 days from the final antimicrobial exposure. In fact, the detection frequency significantly decreased when collected after >31 days from the final antimicrobial exposure (16/20 samples vs 4/20 samples, $P=0.0004$).

Table 3 shows the detection history of QR *Enterobacteriaceae* strains at an individual level in seven patients receiving quinolone prophylaxis of cycle ≥ 2 . All the QR *Enterobacteriaceae* strains were *E. coli*. Of the seven patients, six had QR *E. coli*, including QR ESBL-producing *E. coli*, before and/or after the first prophylaxis. Of the six patients, four (registration no. 3 [+4], 14 [+15, 16, and 17], 20 [+21], and 37 [+38]) had a persistent detection of QR *E. coli* before and/or after the second prophylaxis (4/6 patients, 66.3%). In addition, three of the four patients had QR ESBL-producing *E. coli*. In two patients (registration no. 3 and 20), QR ESBL-producing *E. coli* isolated at the first prophylaxis were detected before and after the second prophylaxis. In the patient with registration no. 14, QR *E. coli* which emerged after the first prophylaxis disappeared from the sample after the second prophylaxis, followed by reemergence before the fourth prophylaxis. In the patient with registration no. 37, QR ESBL-producing *E. coli* isolated before the first prophylaxis were not detected after the first prophylaxis, followed by reemergence before the second prophylaxis.

Discussion

In the previous study,¹¹ we concluded that quinolone prophylaxis did not significantly increase QR *E. coli*, while in the current study, a significant increase in quinolone resistance was observed. Although this appears to be contradictory and confusing, this is due to the evaluation of only *E. coli* in the previous study, as compared to that of all detected bacteria including CNS and *Enterococci* in the current study.

The recovery of QS *Enterobacteriaceae* was seen in ~70% of patients with more than two courses of quinolone prophylaxis (Table 1). In the recent report of de Lastours et al,¹³ it has been found that 70.8% (34/48 cases) of the cases exhibited reemergence of QS *E. coli* in the fecal flora after 28 days from final quinolone exposure. In de Lastours et al's study,¹³ quinolones were administered to healthy volunteers

Table 3 Detection history of fluoroquinolone-resistant and/or ESBL-producing *E. coli* in the fecal samples from patients with repeated quinolone prophylaxis.

Registration No.	1st prophylaxis		2nd prophylaxis		3rd prophylaxis		4th prophylaxis	
	Before	After	Before	After	Before	After	Before	After
3, 4	None	ESBL EC ^a	ESBL EC	ESBL EC				
8, 9, 10	QR EC	QR EC	QS EC	None	None	None	ESBL EC, QR EC	ESBL EC, QR EC
14, 15, 16, 17	QS EC	QR EC	QR EC	None	ESBL EC, QS EC	ESBL EC	ESBL EC, QR EC	ESBL EC, QR EC
20, 21	ESBL EC	ESBL EC	ESBL EC	ESBL EC				
32, 33	QS EC	None	None	QR EC				
37, 38	ESBL EC	None	ESBL EC	ESBL EC				
47, 48	QR EC, QS EC	QR EC	QS EC	None				

Note: ^aESBL EC strains were all resistant to quinolone.

Abbreviations: ESBL, extended-spectrum β -lactamase; EC, *Escherichia coli*; QR, quinolone-resistant; QS, quinolone-susceptible; ESBL EC, ESBL-producing EC.

without chemotherapy. In our study, all but one were subjected to chemotherapy for hematological diseases,¹¹ which is expected to result in mucosal injury in the gut. As shown in Table 2, the intensity of chemotherapy was not associated with the reemergence of QS *Enterobacteriaceae*. Thus, original *Enterobacteriaceae* strains in human fecal flora could recover from quinolone exposure, irrespective of chemotherapy. Interestingly, the recovery of QS *Enterobacteriaceae* tended to be unsuccessful upon initiation of the next course of quinolone prophylaxis within 30 days from final antimicrobial exposure (Table 2).

For many cases in our study, QR CNS and *Enterococcus* strains persisted and were detected before receipt of more than two courses of quinolone prophylaxis (Table 1). On the contrary, the detection rate of these strains dramatically decreased when antimicrobials were administered at an interval of >31 days (Table 2). These findings mean that patients with hematological malignancies usually experience repeated chemotherapy with an interval of ≤ 1 month, and accordingly, quinolone prophylaxis also repeats at a similar interval, in many cases. Thus, quinolone prophylaxis for febrile neutropenia might allow QR CNS and *Enterococcus* strains to be detected in the fecal flora before receipt of more than two courses of prophylaxis. It has been reported by metagenome analysis that the composition of human gut microbiota may not completely recover, even after 6 months, from the initial quinolone exposure.¹⁴

In the previous report of this study, we showed the most frequency of 5% in the emergence of QR *E. coli* after quinolone prophylaxis.¹¹ In contrast, in the studies conducted by European institutes, the detection rates of QR *E. coli* after quinolone prophylaxis were $\sim 30\%$.^{15,16} Quinolone exposure in healthy volunteers also showed the new emergence of QR *E. coli* at a frequency of $\sim 20\%$ (9/48 cases).¹³ We have not resolved the mechanism of this difference in detection rates. de Lastours et al demonstrated that quinolone exposure did

not induce resistant mutations on the quinolone-resistance-determining region (QRDR) genes (eg, *gyrA* or *parC*) of the same *E. coli* clones.¹³ The researchers have presumed the two following possibilities based on this result: first, the newly emergent QR *E. coli* strains after quinolone exposure were present at undetectable levels; and second, the exogenous acquisition of QR *E. coli* strains occurred. In our study, the footprint of QR *E. coli* strains at an individual level showed repeated appearance and disappearance in the same gut flora (Table 3). This finding suggests that QR *E. coli* strains always compete with other bacterial strains in the gut environment, resulting in that the acquisition or loss of dominance in the flora is repeated. This also suggests the possibility that the exogenous transmission of QR *E. coli* strains occurs during or at the interval of quinolone prophylaxis. Thus, in any case, the most relevant factor for the detection of QR *E. coli*, including ESBL-producing *E. coli*, seems to be the level of the endemic spread of QR *E. coli*. This claim could resolve the question mentioned above. In fact, QR *E. coli* were detected frequently in the blood isolates after quinolone prophylaxis in the highly endemic area of these bacteria.^{17,18} The detection rates of ESBL-producing *E. coli*, most of which are resistant to quinolones, vary across the world.¹⁹ The prevalence of ESBL-producing *E. coli* has been increasing in Japan, not only in the hospitals but also in the community.^{20,21} Therefore, the emergence of QR *E. coli* after quinolone prophylaxis may be found more frequently in the other regions of Japan than in our region.

Based on the above-mentioned consideration, the emergence of QR *Enterococci* after prophylaxis may be also due to the enrichment of the QR *Enterococcus* subpopulation already present in the initial gut flora. In this case, if VRE are present at undetectable levels in the initial flora, they may be persistently detected by the repeated prophylaxis, as predicted by our study, finally resulting in possible VRE bacteremia. We previously reported that the detection rate of *Enterococ-*

cus strains in bacteremic isolates was significantly higher in patients with quinolone prophylaxis than in those without prophylaxis.²² Interestingly, the increase of bacteremic VRE isolates after quinolone prophylaxis was also reported from an institute in the United States.²³ In the highly endemic areas of VRE, quinolone prophylaxis might affect the detection rates of their bacteremia in patients with febrile neutropenia.

There is a concern that the detection sensitivity of resistant bacteria might be less than ideal in our study. Therefore, a detection sensitivity limit might have affected the results, including the repeated appearance and disappearance of resistant bacteria in the patient's gut flora.

The emergence of QR bacteria after quinolone prophylaxis for neutropenic patients would depend on the environmental spread of them. The previous colonization of QR bacteria before prophylaxis is also likely attributed to the endemic spread of them. Thus, the spread of resistant bacteria, particularly, QR *E. coli* including ESBL-producers and QR *Enterococci* including VRE, as a local factor may influence strategies toward the use of quinolone prophylaxis. Therefore, no conclusion can be made as to whether quinolone prophylaxis should be administered for all patients with neutropenia, from the aspects of the concerns for antibiotic resistance. Continued surveillance for the detection of resistant bacteria in both blood and stool cultures is warranted.

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