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Antimicrobials for the treatment of febrile neutropenia clinical usefulness of antimicrobial cycling

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Abstract

Bacterial or fungal sepsis is one of the leading causes of death in patients with hematological disease. Neutropenia occurs depending on the dose of chemotherapy or radiotherapy and is considered to be an important predictive factor for the incidence and severity of infection in chemotherapy patients. Approximately 40% to 60% of febrile patients who receive chemotherapy are clinically or microbiologically diagnosed with infection, while the remaining patients are diagnosed with fever of unknown origin and treated as such. Along with the routine use of carbapenem antibiotics (which mainly target Gram-negative bacteria) in recent years, multidrug-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), have evolved and have become a serious clinical and social problem, however, no specific strategy for infection control has yet been established. For patients with hematological disease who had fever caused by an unknown pathogen, including febrile neutropenic patients, we performed antimicrobial cycling and assessed changes over time in the isolation rates of MRSA, *Pseudomonas aeruginosa*, etc. For 448 patients admitted to our hospital, the use of carbapenem, penicillin, fluoroquinolone, and cephem antibiotics (all of which were injectable preparations) was rotated in this order at 3-month intervals over a two-year period (antimicrobial cycling). We concluded that cycling of the four classes of antibiotics used in this study was effective in patients with fever of unknown origin, including febrile neutropenic (FN) patients, since it could decrease the isolation rates of MRSA and *P. aeruginosa*.

Key words: antimicrobial cycling, gram-negative bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA), febrile neutropenia

Introduction

Infections associated with neutropenic patient following chemotherapy for hematological disease often become serious and may result in death. Although it has been suggested that bacterial infection plays a role in most febrile episodes in neutropenic patients, it is often difficult to isolate and identify the pathogen.[1] For patients with febrile neutropenia (FN), physicians usually select antibiotics recommended by the guidelines[2-4] and perform the empiric antimicrobial therapy, however, the possibility that drug-resistant strains may be unintentionally selected along with the selective use of antibiotics cannot be ruled out. In fact, the predominant use of fourth-generation cephem and carbapenem antibiotics has resulted in emergence of the drug-resistant bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), posing a serious clinical problem.

On the other hand, antimicrobial cycling has recently been highlighted as a measure to prevent the emergence of drug-resistant bacteria, and its efficacy has been reported, mainly in intensive care units (ICUs) and the department of surgery.[5-10] Although the United States Centers for Disease Control and Prevention (CDC) recom-

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mend antimicrobial cycling for the prevention of drug-resistant bacteria,[11] there have been very few reports of antimicrobial cycling in patients with hematological disease,[12,13] if any, insufficient as supporting evidence.

Thus, we performed antimicrobial cycling for patients with hematological disease who had fever of unknown origin, including FN patients. Specifically, we rotated the use of four different classes of first-line injectable antimicrobials at 3-month intervals, repeated the cycle over two years, and examined changes over time in the isolation rates of MRSA, *P. aeruginosa*, etc. We evaluated the efficacy of antimicrobial cycling by comparing the 2-year study results with the previous 6-month results of the conventional empiric therapy without restriction on antibiotic use, in terms of the isolation rate, and hereby report these results.

Subjects and Methods

1) Subjects

In this study, we included patients with fever of unknown origin, including FN patients, who were hospitalized in the Department of Hematology, and Rheumatology of our hospital. Study subjects, had a neutrophil count of less than 1,000/mm^3 and an axillary temperature of at least 37.5°C, and their fever was not due to cancer, drugs, or graft-versus-host disease (GVHD). We excluded patients with severe infection and those who had undergone bone marrow transplantation, for whom therapeutic effect could not be expected from antibiotic use. Since this study was performed in daily clinical practice, we did not obtain informed consent from the subjects.

2) Antimicrobials

The use of either tazobactam/piperacillin (TAZ/PIPC) or sulbactam/ampicillin (SBT/ABPC) as penicillin antibiotics was designated, and the prescribed dose was 10 g/day. As cephem antibiotics, the attending physician could choose cefepime (CFPM) or another antibiotic expected to be at least equivalent in efficacy, such as ceftazidime (CAZ) and cefozopran (CZOP), and the prescribed dose was 4 g/day. As carbapenem antibiotics, the attending physician could choose imipenem/cilastatin (IPM/CS), meropenem (MEPM), or panipenem/betamipron (PAPM/BP), and the prescribed dose was 2 g/day. As injectable fluoroquinolone antibiotics, the attending physician could choose either ciprofloxacin (CPFX) or pazufloxacin (PZFX), and the prescribed dose was 600 mg/day for CPFX or 1 g/day for PZFX. Concomitant use of only one of the following antibiotics was permitted: vancomycin (VCM: 2 g/day), amikacin (AMK: ≥400 mg/day), tobramycin (TOB: ≥ 180 mg/day), and gentamicin (GM: ≥120 mg/day) [the latter three agents are aminoglycoside antibiotics]. Antibiotics were prescribed in line with instructions given in the insert. In principle, a three-hour infusion period was recommended, and, a period of antibiotic treatment was defined within 14 days.

3) Antimicrobial cycling

We divided one year into four periods of three months and rotated the use of the designated antibiotics in the following order at 3-month intervals (antimicrobial cycling). Specifically, during the first period, a carbapenem antibiotic (IPM/CS, MEPM, or PAPM/BP) was used without concomitant use of other agents in principle. During the second period, TAZ/PIPC or SBT/ABPC was used in combination with an aminoglycosides antibiotic (AMK, TOB, or GM). During the third period, an injectable fluoroquinolones (CPFX or PZFX) was used without concomitant use of other agents in principle. During the fourth period, a cephems (CPFM, CAZ, CZOP, or another agent) was used without concomitant use of other agents in principle. We have determined the order of administration of antibiotics relative to the frequency of prescriptions and antibacterial spectrum. In case of insufficient efficacy was found during the first three days after the start of single-agent therapy, an aminoglycoside antibiotic (AMK, TOB, or GM) was added to the carbapenem or cephem antibiotic during the 1st or 4th period, or VCM was added to the injectable fluoroquinolone antibiotic during the 3rd period. The study period was two years from February 2004 to January 2006, and these antibiotics were rotated four times per year over the two-year period.

4) Duration of the treatment

In principle, all patients received any type of antibiotics (alone or in combination) for at least three days, however, if the neutrophil count returned to the normal range along with the disappearance of all signs and symptoms of infection, the treatment was discontinued. In

case of acute exacerbation of any sign or symptom or any adverse drug reaction (accompanying symptom or laboratory abnormality), the treatment was discontinued immediately at the discretion of the physician.

5) Clinical efficacy assessment

Maximum temperature, white blood cell (WBC) differential count, and C-reactive protein (CRP), blood urea nitrogen (BUN), and serum creatinine were measured before and 4 and 7 days after the start and at the end of treatment, as a rule. Clinical efficacy was comprehensively assessed on the following 4-point scale, based on outcome after the last antibiotic administration. The therapy was assessed as very effective, if fever subsided to 37°C or lower within four days after start of the treatment, and the afebrile state was sustained for at least three days with improvement of symptoms. The therapy was assessed as effective, if the fever subsided to 37°C or lower within seven days after the start of treatment, and the afebrile state was sustained for at least three days with improvement of symptoms. The therapy was assessed as slightly effective, if a body temperature of $\leq$37.5°C was observed for at least two days during the first four days after the start of treatment, and the fever subsided to 37°C or lower within seven days after start of the treatment with improvement of symptoms. The therapy was assessed as ineffective, if fever did not subside within seven days after start of the treatment, with no improvement of or aggravation of symptoms. The therapy was assessed as indeterminate, if the treatment effect was offset by the effect of an underlying disease, making it difficult to assess efficacy, if treatment was discontinued due to an adverse drug reaction, or if the patient died. The efficacy rate was calculated by dividing the numbers of very effective + effective cases assessed at the end of treatment by the total number of cases.

6) Study of isolated microorganisms

Blood, sputum, urine, etc. were collected from each subject, and blood culture and surveillance culture were performed. Isolated microorganisms (bacteria, fungi, etc.) were identified regardless of whether they were causative pathogens or not. Antimicrobial susceptibility testing was performed in accordance with the Clinical Laboratory Standards Institute (CLSI) method (formerly, the National Committee for Clinical Laboratory Standards (NCCLS) method), and the level of resistance was classified as [R (resistant)], [I (intermediate)], or [S (susceptible)]. In this study, MRSA, *Serratia* spp., *P. aeruginosa* (including drug-resistant *P. aeruginosa*), *Stenotrophomonas maltophilia*, and *Acinetobacter* spp. were analyzed as potentially drug resistant pathogens..

Results

1) Patient baseline characteristics

Table 1 shows patient baseline characteristics. In the first year, the number of patients assessed during each 3-month period ranged from 43 to 82, and a total of 253 patients were included in this study. The mean age ranged of the patients from 59.8 to 66.0 years and the mean performance status (PS) was from 0.8 to 1.1. Acute myeloid leukemia (AML), lymphoma, and non-hematological disease were common underlying diseases during all of the four periods. In the second year, the number of patients assessed during each period ranged from 27 to 64, and a total of 195 patients were included in this study. The mean age ranged from 51.9 to 63.0 years, indicating that patients assessed in the second year tended to be younger than those in the first year. The mean PS, on the other hand, ranged from 0.9 to 1.0, with little change from the first year. As underlying diseases, AML and non-hematological disease were as common as in the previous year, but the prevalence of lymphoma varied from one period to another in the second year (Table 1).

2) Compliance rates to the protocol-specified antibiotics for cycling

Table 2 shows compliance rates to the protocol-specified antibiotics for cycling. In the first year, adherence rates to the protocol-specified antibiotics were high during all periods, ranging from 94% to 100%. Single-agent use rates, i.e., ratio of patients who used a carbapenems, cephems, or injectable fluoroquinolone antibiotic alone, ranged from 76% to 90%, and the ratio of patients who used a penicillins concomitantly with an aminoglycoside antibiotic (or concomitant use rates) was 82%. In the second year, the adherence rates ranged from 63% to 92%, lower than during all periods of the first year. During the 3rd period, in particular, the adherence rate to an injectable fluoroquinolone antibiotic was markedly lower in the second year. The concomitant use rates tended to increase in the second year, except when cephem antibiotics were used

Table 1 Patient baseline characteristics

	1st Year				2nd Year			
	1st Period	2nd Period	3rd Period	4th Period	1st Period	2nd Period	3rd Period	4th Period
Antimicrobials	carbapenem	penicillin	quinolone	cephem	carbapenem	penicillin	quinolone	cephem
Number of Patients	82	66	43	62	58	46	27	64
Male/Female	51(62)/ 31(38)	43(65)/ 23(35)	26(60)/ 17(40)	31(50)/ 31(50)	37(64)/ 21(36)	28(60)/ 18(40)	17(63)/ 10(37)	40(63)/ 24(38)
Age (mean)	62.1	59.8	63.1	66.0	61.1	51.9	57.2	63.0
Performance Status (mean)	0.8	0.9	0.8	1.1	0.9	1.0	0.9	1.0
Underlying Disease								
AML	12(15)	11(17)	12(28)	10(16)	13(22)	11(24)	4(15)	9(14)
ALL	8(10)	7(11)	2(5)	1(2)	2(3)	2(4)	1(4)	3(5)
CML	5(6)	3(5)	1(2)	1(2)	2(3)	3(7)	0	1(2)
CLL	0	1(2)	0	1(2)	0	0	0	0
ATL	3(4)	1(2)	2(5)	3(5)	1(2)	0	1(4)	1(2)
Lymphoma	10(12)	15(23)	11(26)	15(24)	3(5)	3(7)	8(30)	18(28)
MDS	5(6)	6(9)	3(7)	4(6)	4(7)	3(7)	1(4)	7(11)
MM	5(6)	4(6)	5(12)	4(6)	3(5)	1(2)	0	4(6)
AA	3(4)	2(3)	0	0	0	1(2)	2(7)	0
Hematological Disease	2(2)	1(2)	2(5)	1(2)	2(3)	2(4)	0	2(3)
Non-hematological Disease	29(35)	15(23)	5(12)	22(35)	28(48)	20(47)	10(37)	19(30)
Comments Please confirm	corrected			corrected	corrected	corrected	corrected	

( ) : %

Table 2 Compliance rates with the protocol-specified antibiotics

	1st Year				2nd Year			
	1st Period	2nd Period	3rd Period	4th Period	1st Period	2nd Period	3rd Period	4th Period
Antimicrobials	carbapenem	penicillin	quinolone	cephem	carbapenem	penicillin	quinolone	cephem
Compliance Rate (%)	100	96	94	96	92	81	63	89
Single Use Rate (%)	90	18	76	80	76	6	38	83
Concomitant Use Rate (%)	10	82	24	20	34	94	62	17

during the 4th period (Table 2).

3) Occurrence of infection

Table 3 shows the occurrence of infection. In the first year, the number of patients diagnosed with infection during each 3-month period ranged from 19 to 66. The incidence of infection was highest (80%) during the 1st period and lowest (30%) during the 2nd period. No specific tendency was found in type of infection during any period. In the second year, the number of patients diagnosed with infection during each period ranged from 11 to 51. The incidence of infection was highest (88%) during the 1st period and lowest (41%) during the 3rd period. No specific tendency was found in the type of infection during any period, throughout first and the

Table 3 Occurrence of infection

	1st Year				2nd Year			
	1st Period	2nd Period	3rd Period	4th Period	1st Period	2nd Period	3rd Period	4th Period
Antimicrobials	carbapenem	penicillin	quinolone	cephem	carbapenem	penicillin	quinolone	cephem
Incidence of Infection Rate*	80	30	44	40	88	59	41	69
Name of Infection								
Unknown**	24(36)	15(75)	6(32)	8(32)	24(47)	12(44)	4(36)	7(16)
Respiratory	12(18)	1(5)	0	3(12)	5(10)	3(11)	2(18)	9(20)
Oral cavity	6(9)	2(10)	6(32)	4(16)	9(18)	4(15)	0	8(18)
GI tract	9(14)	0	0	2(8)	1(2)	2(7)	0	5(11)
Sepsis	10(15)	2(10)	7(37)	6(24)	6(12)	3(11)	3(27)	9(20)
Others	5(8)	0	0	2(8)	6(12)	3(11)	2(18)	6(14)
Total	66	20	19	25	51	27	11	44

*Number of patients diagnosed with infection/Number of total admitted patients in the periods×100 (%)
**Unknown : undetermined infected focus
Others include, nasal cavity, urinary tract,. aspirate fluid, and wounded area.,
( ) : %

Table 4 Clinical efficacy

	1st Year				2nd Year			
	1st Period	2nd Period	3rd Period	4th Period	1st Period	2nd Period	3rd Period	4th Period
Antimicrobials	carbapenem	penicillin	quinolone	cephem	carbapenem	penicillin	quinolone	cephem
Clinical Efficacy								
Excellent	15	13	6	16(6)	11	9	4	14
Effective	4	6	4	6(1)	4	5	1	4
Slightly Effective	8	1	2	3(1)	4	2	3	3
Poor	6	4	7	9(0)	11	5	3	9
Total	33	24	19	34(8)	30	21	11	30
Efficacy Rate (%)	58	79	53	65(88)	50	67	46	60
Duration of Neutropenia (days)	5.2	4.8	7.8	6.4(2.6)	6.9	6.1	8.6	6.4
Change/ Concomitant of Agent	6	4	9	12(2)	15	21	7	17
Administration of Additional Antimicrobials	7	5	8	16(4)	9	10	4	12
Mortality Rate (%)	49	40	41	49	25	33	52	43

( ) : Treatment efficacy by administration of CFPM

second years. The annual (average) incidence of infection in the second year was higher (68.2% ; 133/195 patients) than that in the first year (51.4% ; 130/253 patients) (Table 3).

4) Clinical efficacy

Table 4 shows the clinical efficacy rates of antimicrobial cycling. Clinical efficacy rates during each period of the first year ranged from

53% to 79%. The clinical efficacy rate was highest during the 2nd period (penicillin-treatment period) and lowest during the 3rd period ($p<0.005$). The duration of neutropenia was 4.8 to 7.8 days. Recovery from neutropenia was most rapid during the 2nd period (penicillin-treatment period), during which the highest efficacy rate was achieved. Recovery was slow during the 3rd period (fluoroquinolone-treatment period), during which the efficacy rate was lowest. Mortality rates ranged from 40% to 49%, with no significant differences among the periods. In the second year, efficacy rates ranged from 46% to 67%, lower than in the first year. Efficacy rate tended to be high during the 2nd period and low during the 3rd period, as the first year. The duration of neutropenia was 8.6 days during the 3rd period, with the slowest recovery. During the other periods, it ranged from 6.1 to 6.9 days, with little difference in the speed of recovery. Mortality rates ranged from 25% to 52%, with greater differences among the periods in the second year than in the first year and 55% of death was related with infection (Table 4).

5) Isolation of microorganisms

Table 5 shows changes over time in the isolation rates of PDR pathogens during this antimicrobial cycling. In the first year, the number of strains isolated during each period ranged from 140 to 258. The isolation rates of Gram-positive bacteria ranged from 47.5% to 63.6%, which were higher than those of Gram-negative bacteria (32.9% to 44.7%), except for the 2nd period. The isolation rates of MRSA ranged from 22.3% to 36.4%, which were the highest among all of the target species during all periods. The isolation

Table 5 Isolation of potentially drug-resistant (PDR) pathogens (Isolation status of target species including resistant bacteria)

	Control Period (6 months)	1st Year				2nd Year			
		1st Period	2nd Period	3rd Period	4th Period	1st Period	2nd Period	3rd Period	4th Period
		carbapenem	penicillin	quinolone	cephem	carbapenem	penicillin	quinolone	cephem
Gram-positive B]acteria									
Staphylococcus aureus	ND	93(36.0)	43(24.0)	64(25.7)	52(37.1)	69(37.1)	20(18.5)	21(25.6)	37(40.2)
MRSA	176(36.8)	81(31.4)	40(22.3)	62(24.9)	51(36.4)	59(31.7)	15(13.9)	19(23.2)	34(37.0)
Coagulase negative *Staphylococcus*	ND	29(11.2)	19(10.6)	25(10.0)	13(9.3)	22(11.8)	17(15.7)	14(17.1)	12(13.0)
MRSE	ND	20(7.8)	13(7.3)	17(6.8)	8(5.7)	10(5.4)	13(12.0)	7(8.5)	6(6.5)
Enterococcus spp.	ND	7(2.7)	13(7.3)	26(10.4)	17(12.1)	17(9.1)	11(10.2)	8(9.8)	9(9.8)
Others	ND	8(3.1)	10(5.6)	8(3.2)	7(5.0)	2(1.1)	6(5.6)	6(7.3)	3(3.3)
Subtotal		137(53.1)	85(47.5)	123(49.4)	89(63.6)	110(59.1)	54(50.0)	49(59.8)	61(66.3)
Gram-negative bacteria									
Serratia spp.	ND	1(0.4)	1(0.6)	1(0.4)	0	2(1.1)	0	0	4(4.3)
Pseudomonas aeruginosa	112(23.4)	47(18.2)	48(26.8)	37(14.9)	10(7.1)	16(8.6)	25(23.1)	9(11.0)	16(17.4)
Drug resistant *P. aeruginosa**	24(5.0)	19(7.4)	4(2.2)	15(6.0)	9(6.4)	6(3.2)	6(5.6)	3(3.7)	5(5.4)
Stenotrophomonas maltophilia	ND	6(2.3)	3(1.7)	10(4.0)	4(2.9)	18(9.7)	4(3.7)	1(1.2)	2(2.2)
Acinetobacter spp.	ND	3(1.2)	4(2.2)	9(3.6)	2(1.4)	7(3.8)	2(1.9)	1(1.2)	0
Others	ND	34(13.2)	24(13.4)	29(11.6)	30(21.4)	26(14.0)	18(16.7)	7(8.5)	6(6.5)
Subtotal	ND	91(35.3)	80(44.7)	86(34.5)	46(32.9)	69(37.1)	49(45.4)	18(22.0)	28(30.4)
Fungi (Yeast)	ND	30(11.6)	14(7.8)	40(16.1)	5(3.6)	7(3.8)	5(4.6)	14(17.1)	3(3.3)
Others	ND	0	0	0	0	0	0	1(1.2)	0
Total		258	179	249	140	186	108	82	92

*imipenem, meropenem, cefipime, amikacin resistant

ND : not done

rate of *P. aeruginosa* (7.1% to 26.8%), which was the second highest among the target species, varied from one period to another and was lowest during the 4th period and highest during the 2nd period. Regarding other PDR, i.e., *Serratia* spp., drug-resistant *P. aeruginosa*, *Acinetobacter* spp., and *S. maltophilia*, no specific tendency was determined, since the absolute numbers of strains isolated during each period were small. Compared with the 6-month control period before the start of cycling, during which no restriction was placed on antibiotic use, the isolation rates of MRSA during the 2nd and 3rd periods were significantly low (both $p<0.005$). The isolation rates of *P. aeruginosa* were also lower during the 1st, 3rd, and 4th periods than during the control period. In the second year, the number of strains isolated during each period ranged from 82 to 186, and the number of isolated strains was greatest during the 1st period. The isolation rates of Gram-positive bacteria ranged from 50.0% to 66.3%, which were higher than the isolation rates of Gram-negative bacteria during the 1st, 3rd, and 4th periods (22.0% to 45.4%), as was the case with the first year. The isolation rates of MRSA ranged from 13.9% to 37.0%, which varied greatly from one period to another and were lowest during the 2nd period and highest during the 4th period. The isolation rates of *P. aeruginosa* ranged from 8.6% to 23.1%, which varied greatly from one period to another and were lowest during the 1st period and highest during the 2nd period. Regarding other target species (*Serratia* spp., drug-resistant *P. aeruginosa*, *Acinetobacter* spp., and *S. maltophilia*), no specific tendency was determined, as in the first year, since the absolute numbers of strains isolated during each period were small. The isolation rates of MRSA during the 2nd and 3rd periods were significantly lower than during the control period, as in the first year (both $p<0.005$). The isolation rates of *P. aeruginosa* during the 1st and 3rd periods were also lower than during the control period (Table 5).

Discussion

Neutropenia is one of the most important risk factors for the development of infection in patients with hematological disease. In general, if the neutrophil count is less than 500/mm^3, the patient is at risk for infection, and if it decreases to 100/mm^3, the risk of severe infection is said to further increase[14]. Since it is rare for the pathogen to be isolated and identified in patients who have developed infection in a neutropenic state, empiric therapy is often employed by physicians, usually using fourth-generation cephem antibiotics or carbapenem antibiotics as first-line drugs[15,16]. Since the major pathogen of sepsis in patients with hematological disease is *P. aeruginosa*, we selected penicillin, cephem, carbapenem, and injectable fluoroquinolone antibiotics, all of which have potent antimicrobial activity against *P. aeruginosa*, and performed antimicrobial cycling at 3-month intervals. Efficacy rates during the four periods ranged from 53% to 79% in the first year and from 46% to 67% in the second year. Tamura et al.[17] reported that the efficacy rate of CFPM in FN patients on Day 7 was 50.5% in an empirical study of clinical guidelines for FN treatment in Japan. Sugiyama et al.[18] reported that the efficacy rates of MEPM in FN patients were 51.9% to 65.3%. It may not be appropriate to simply compare our results with their results due to differences in patient baseline characteristics, but we believe that the efficacy results of antimicrobial cycling in our study, although they varied from one period to another, were not inferior to those reported by Tamura et al.[17] and Sugiyama et al.[18] Based on the results of this study, we consider that penicillin antibiotics (TAZ/PIPC or SBT/ABPC in combination with an aminoglycoside antibiotic) and injectable fluoroquinolone antibiotics will also be promising for the treatment of fever caused by an unknown pathogen in FN patients. In this study, efficacy rates in the second year tended to be lower than in the first year. This was probably because adherence rates to the specified antimicrobials decreased in the second year. In both the first and second years, the clinical efficacy rate during the 2nd period (penicillin-treatment period) tended to be higher than during other periods. This was probably because the duration of neutropenia was short during the 2nd period.

It has been reported that as the pathogen of sepsis in FN patients with hematological disease, a shift from Gram-negative to Gram-positive bacteria has occurred in recent years.[19] In a survey performed by our department, Gram-negative bacteria were more frequently isolated as the pathogen from patients with bacteremia/fungemia than Gram-positive bacteria between 1985 and 1996, but we observed an apparent decrease

in the isolation rates of Gram-negative bacteria along with a tendency toward increase in the isolation rates of Gram-positive bacteria between 1997 and 2002. We have previously reported that Gram-negative bacteria are still predominant among strains isolated from blood cultures of general-ward patients, while Gram-positive bacteria are predominant among strains isolated from blood culture of patients with hematological disease.[20] It was confirmed in this study that the isolation rates of Gram-positive bacteria were higher than those of Gram-negative bacteria. One of the reasons for this is considered to be that carbapenem and fourth-generation cephem antibiotics with potent antimicrobial activity against Gram-negative bacteria are routinely used in FN patients. During the 2nd period (penicillin-treatment period), the difference between the isolation rate of Gram-positive bacteria and Gram-negative bacteria was found to be small in both the first and second years. This was probably because both Gram-positive and Gram-negative bacteria could be covered by the combination of a penicillin antibiotic and an aminoglycoside antibiotic. The isolation rates of MRSA, one of the target species, during the 1st (carbapenem) and 4th (cephem) periods did not significantly differ from that during the control period (with no restriction on antibiotic use). During the 2nd (penicillin) and 3rd (injectable fluoroquinolone) periods, however, the isolation rates of MRSA decreased. In addition, the isolation rate of *P. aeruginosa* during the 2nd (penicillin) period did not significantly differ from the control period, while those during the other three periods significantly decreased. Regarding other target species, including drug-resistant *P. aeruginosa*, no specific tendency was identified since the absolute number of strains isolated was small for each species. An increase in the prevalence of infection by MRSA and *P. aeruginosa* (including drug-resistant strains) is a serious problem with a great impact on patient survival in the field of hematological disease as well. The results of our study suggested that antimicrobial cycling was effective in FN patients with hematological disease in that it can prevent the emergence of such PDR patogens. Ikegaya et al.[13] performed retrospective analysis of the efficacy of antimicrobial cycling in FN patients with hematological disease and reported an increase in the efficacy rate, shortening of the febrile period, and decrease in the detection rate of resistant strains. This report and our study results suggest that antimicrobial cycling is effective in FN patients with hematological disease, while Dominguez et al.[12] have reported that antimicrobial cycling is not effective in the field of hematological disease.

Antimicrobial cycling has been studied widely, mainly in surgical and ICU settings, in Japan and elsewhere. There have been many reports that it decreased the incidence of infection and decreased the emergence of drug-resistant bacteria, suggesting its efficacy.[5–10] There are some reports, however, that antimicrobial cycling is not effective.[21–24] We consider that such differences in efficacy results were caused by differences in the baseline characteristics of patients assessed and various conditions of cycling, such as the type (class) and number of antimicrobials used, rotation period, and rotation sequence.

In recent years, the variety of diseases hematologists must treat has tended to expanding, not only leukemia but also malignant lymphoma and multiple myeloma, and the range of age of patients has also been increasing. As a consequence, selective use of potent antimicrobials and long hospital stay, as observed today, will certainly continue for years to come. To succeed in antimicrobial chemotherapy, physicians should perform appropriate "target treatment" only after isolation and identification of the pathogen and measurement of its susceptibility, so that the effectiveness of the antimicrobial used can be maximized in terms of its pharmacokinetics/pharmacodynamics (PK/PD) and mechanism of action. However, if it is difficult to isolate and identify the pathogen, as is often the case with FN patients with hematological disease, we believe that "empirical treatment" with antimicrobial cycling is meaningful in preventing the emergence of drug-resistant bacteria. Based on the results of this study, we have found that the following issues remain to be addressed, and that further research is warranted : 1) the clinical efficacy rate and other parameters should be reassessed by changing the order of use of antimicrobials and especially by alternating the use of antimicrobials with different mechanisms of action ; 2) whether we should use two classes of antimicrobials or more than two classes ; 3) whether we can change the length of a cycling interval mid-course ; and 4) whether it is acceptable to introduce injectable fluoro-

quinolone antibiotics into empirical therapy. We believe that after solving these issues, one by one, by further research, we can establish evidence for the efficacy of antimicrobial cycling in the field of hematological diseases.

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References

1. Pennington JE (1977) Fever, neutropenia and malignancy: a clinical syndrome in evolution. Cancer 39: 1345–1349
2. Hughes WT, Armstrong D, Bodey GP, Brown AE, Edwards JE, Feld R, Pizzo P, Rolston KV, Shenep JL, Young LS (1997) 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Infectious Diseases Society of America. Clin Infect Dis 25: 551–573
3. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, Feld R, Pizzo PA, Rolston KV, Shenep JL, Young LS (2002) 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 34: 730–751
4. Masaoka T (1998) Evidence-based recommendations on antimicrobial use in febrile neutropenia in Japan. Int J Hematol 68 (Suppl 1): S-39–S40
5. Gerding DN (2000) Antimicrobial cycling: lessons learned from the aminoglycoside experience. Infect Control Hosp Epidermiol 21 (Suppl 1): S12–S17
6. McGowan JE Jr (2000) Strategies for study of the role of cycling on antimicrobial use and resistance. Infect Control Hosp Epidermiol 21 (1 Suppl): S36–S43
7. Raymond DP, Pelletier SJ, Crabtree TD, Gleason TG, Hamm LL, Pruett TL, Sawyer RG (2001) Impact of a rotating empiric antibiotic schedule on infectious mortality in an intensive care unit. Crit Care Med 29: 1101–1108
8. Hughes MG, Evans HL, Chong TW, Smith RL, Raymond DP, Pelletier SJ, Pruett TL, Sawyer RG (2004) Effect of an intensive care unit rotating empiric antibiotic schedule on the development of hospital-acquired infections on the non-intensive care unit ward. Crit Care Med 32: 53–60
9. Reluga TC (2005) Simple models of antibiotic cycling. Math Med Biol 22: 187–208
10. Martínez JA, Nicolás JM, Marco F, Horcajada JP, Garcia-Segarra G, Trilla A, Codina C, Torres A, Mensa J (2006) Comparison of antimicrobial cycling and mixing strategies in two medical intensive care units. Crit Care Med 34: 329–336
11. CDC (2002) Campaing to prevent antimicrobial resistance in healthcare settings, The 4 starategies. CDC homepage (on line), Aug 28
12. Dominguez EA, Smith TL, Reed E, Sanders CC, Sanders WE Jr (2000) A pilot study of antibiotic cycling in a hematology-oncology unit. Infect Control Hosp Epidermiol 21 (Suppl 1): S4–S8
13. Ikegaya S, Iwasaki H, Kinoshita K, Urasaki Y, Tsutani H, Ueda T (2004) A pilot study of antibiotic cycling for the treatment of febrile neutropenia patients with hematological diseases. JJA infect Dis 78: 241–247 (in Japanese)
14. Balducci L, Halbrook JC, Chapman SW, Vance RB, Thigpen JT, Morrison FS. (1983) Acute leukemia and infections: perspectives from a general hospital. Am J Hematol 15: 57–63
15. Feld R, DePauw B, Berman S, Keating A, Ho W (2000) Meropenem versus ceftazidime in the treatment of cancer patients with febrile neutropenia: a randomized, double-blind trial. J Clin Oncol 18: 3690–3698
16. Vandercam B, Gérain J, Humblet Y, Ferrant A, Wauters G, Moreau M, Longueville J, Symann M, Straetmans N (2000) Meropenem versus ceftazidime as empirical monotherapy for febrile neutropenic cancer patients. Ann Hematol 79: 152–157
17. Tamura K, Imajo K, Akiyama N, Suzuki K, Urabe A, Ohyashiki K, Tanimoto M, Masaoka T; Japan Febrile Neutropenia Study Group (2004) Randomized trial of cefepime monotherapy or cefepime in combination with amikacin as empirical therapy for febrile neutropenia. Clin Infect Dis 39 (Suppl 1): S15–S24
18. Sugiyama H, Horiuchi A, Hasegawa H, Kitani T, Tagawa S, Masaoka T, Tejima H, Yonezawa T, Take H, Kawagoe H (1992) Therapeutic effects of meropenem against severe infections in patients with hematopoietic disorders. Hanshin study Group of Hematopoietic Disorders and Infection. Jpn J Antibiot 45: 687–696 (in Japanese)
19. Martin GS, Mannino DM, Eaton S, Moss M (2003) The epidemiology of sepsis in the United States from 1979 through 2000. N Eng J Med 348: 1546–1554
20. Kanamaru A, Tatsumi Y (2004) Microbiological data for patients with febrile neutropenia. Clin Infect Dis 39 (Suppl 1): S7–S10
21. Kollef MH, Ward S, Sherman G, Prentice D, Schaiff R, Huey W, Fraser VJ (2000) Inadequate treatment of nosocomial infections is associated with certain empiric antibiotic choices, Crit Care Med 28: 3456–3464
22. Warren DK, Hill HA, Merz LR, Kollef MH, Hayden MK, Fraser VJ, Fridkin SK (2004) Cycling empirical antimicrobial agents to prevent emergence of antimicrobial-resistant Gram-negative bacteria among intensive care unit patients. Crit Care Med 32: 2450–2456
23. van Loon HJ, Vriens MR, Fluit AC, Troelstra A, van der Werken C, Verhoef J, Bonten MJ (2005) Antibiotic rotation and development of Gram-negative antibiotic resistance. Am J Respir Crit Care Med 171: 480–487
24. Merz LR, Warren DK, Kollef MH, Fridkin SK, Fraser VJ (2006) The impact of an antibiotic cycling program on empirical therapy for Gram-negative infec-

tions. Chest 130 : 1672–1678