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ORIGINAL ARTICLE

Management of infection in patients with acute leukemia during chemotherapy in Japan: questionnaire analysis by the Japan Adult Leukemia Study Group

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Abstract Guidelines for the management of febrile neutropenia (FN), deep fungal infection or use of granulocyte colony-stimulating factor (G-CSF) published in the US and Europe cannot be directly applied in other countries. In this study, we undertook a questionnaire survey of member institutions of the Japan Adult Leukemia Study Group to investigate the status of, and problems with, the management of infectious complications in patients with acute leukemia. The questionnaire consisted of 52 multiple-choice questions covering therapeutic environment, antibacterial, and antifungal prophylaxis, empirical therapy (ET) for FN, and use of G-CSF. The results were compared to a previous survey performed in 2001. Usable responses were received from 134 of 184 (71.7%) institutions. With regard to antibacterial prophylaxis, fluoroquinolones and sulfamethoxazole-trimethoprim were most commonly used. Regarding antifungal prophylaxis, the most frequently used agent was fluconazole, followed by itraconazole. In ET for FN, monotherapy with cephems or carbapenems accounted for almost all of the responses. Most respondents indicated that they used micafungin (MCFG) in ET. Prophylactic use of G-CSF during remission induction therapy in acute myeloid leukemia was reported by only 4% of respondents. Strategies for antibacterial and antifungal prophylaxis or treatment of FN should be reviewed and updated as needed.

Keywords JALSG · Febrile neutropenia · Prophylaxis · G-CSF · Leukemia

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1 Introduction

Recent advances in chemotherapy and transplantation have improved the treatment of adult acute leukemia. The major complication during chemotherapy for acute leukemia is infection, such as sepsis and pneumonia, highlighting the clinical importance of preventing and treating infection in these patients. Guidelines for the management of febrile neutropenia (FN) or deep fungal infection or use of colony-stimulating factors (CSFs) published in the US and Europe cannot necessarily be applied in other countries due to differences in national health systems and in climate, especially humidity. For this reason, a guideline specific to Japanese settings was released in 1998 [1], and subsequently revised in 2004 [2]. A barrier to the development of such guidelines is the lack of domestic information on the actual management of infectious complications. The Japan Adult Leukemia Study Group (JALSG) was established in 1987 and is the largest adult leukemia study group in Japan. Although the identical chemotherapeutic regimen is administered by all JALSG-member institutions, supportive care is decided by each institution. A fact-finding questionnaire on the management of infectious complications in patients with acute leukemia, developed by the Supportive Care Committee of the JALSG, was distributed to all 196 and 187 member institutions in 2001 and 2007, respectively. In this report, we evaluate the results of the follow-up 2007 questionnaire. In particular we investigated

the current status of, and problems with, the management of infectious complications according to members of the JALSG, especially focusing on current antibiotic regimens. The results were compared to the previous analysis performed in 2001 [3, 4].

2 Methods

A questionnaire on infectious complications in patients with acute leukemia was mailed to all members of the JALSG in July 2007, and the results were collected by the end of September 2007 and analyzed. The questionnaire consisted of 52 multiple-choice questions covering the therapeutic environment, antibacterial prophylaxis, antifungal prophylaxis, empirical therapy (ET) for FN and treatment in patients unresponsive to ET, therapy for deep fungal infection, the use of anti-methicillin-resistant *Staphylococcus aureus* (MRSA) drugs, and the use of granulocyte colony-stimulating factor (G-CSF). Responses were calculated as percentage of respondents. For all questions, multiple answers were allowed giving the possibility of scores greater than 100%. Respondents were instructed to complete the questionnaire as follows: in principle, they should assume the development of neutropenia during remission induction therapy for acute myeloid leukemia (AML), as it is a frequent complication of infection; answers should reflect actual practice rather than literature knowledge or goals; each JALSG institution should answer according to its own practice, and whenever possible the questionnaire should be completed by a physician involved in daily practice. Approval for the study was obtained from the JALSG. The results of the current survey were compared with those from the 2001 survey.

3 Results

Usable responses were received from 134 out of 184 institutions (Appendix 1), giving a response rate of 71.7% for the 2007 survey (compared with a response rate of 63.8% for the 2001 survey). Answers to the main questions are summarized below.

3.1 Therapeutic environment

Overall, 98% of respondents indicated that their institution had a single- or multi-patient rooms with high efficiency particulate air filtration and laminar airflow (HEPA/LAF) units, and 76% said that a HEPA/LAF unit room was often used during AML remission therapy (vs. 37% in the survey of 2001). Given the fact that the same facility may use a variety of different ward settings for the management of neutropenia during AML remission induction, the respondents were allowed to select two alternative settings used at their institution, if applicable. On this basis, it was found that 66% used a single-patient room with HEPA/LAF unit, 27% used a multi-patient room with HEPA/LAF unit, 44% used a single-patient conventional isolation room with a portable HEPA/LAF system, and 19% used a multi-patient conventional isolation room with a portable HEPA/LAF system.

3.2 Prophylaxis

Oral drugs commonly used for antibacterial and antifungal prophylaxis are listed in Table 1. With regard to antibacterial prophylaxis, fluoroquinolones (58%), sulfamethoxazole-trimethoprim (ST, 37%) and polymixin-B (26%) were most commonly used, while 13% of respondents indicated that they did not use prophylaxis against bacterial infection. In contrast, in the 2001 survey the three most frequently used prophylactic drugs for bacterial infection

Table 1 Comparison of survey results regarding the drugs used for antibacterial and antifungal prophylaxis in Japanese hospitals in 2007 (134 institutions) and 2001 (125 institutions)

	2007 (%)	2001 (%)
Antibacterial agent		
1. PL-B	26	42
2. ST	37	30
3. Fluoroquinolones	58	52
4. Combinations of 1,2 and/or 3 above	3	5
5. Did not respond	3	2
6. No approved policy[a]	7	4
7. Did not use prophylaxis	13	6
Antibacterial agent		
1. FLCZ 100-200 mg	64	47
2. FLCZ 400 mg	1	3
3. MCFG 50 mg	1	NA
4. MCFG 75 mg	0	NA
5. ITCZ cap/os	25	14[b]
6. AMPH-B syrup	5	50[c]
7. Combination of AMPH-B and FLCZ	2	0
8. Did not respond	1	4
9. Did not use prophylaxis	8	3

Percentages exceed 100% since respondents could tick more than one box if applicable

NA not available in 2001, *PL-B* polymixin-B, *ST* sulfamethoxazole-trimethoprim, *MCFG* micafungin, *FLCZ* fluconazole, *ITCZ* itraconazole, *cap* capsule, *os* oral solution, *AMPH-B* amphotericin B

[a] Treatment policy not finalized by the hospital and thus no approved recommendation available, and decision was on a case by case basis

[b] Only capsules (200 mg/day) were available in 2001

[c] 300–2,400 mg/kg (2001)

were fluoroquinolones (52%), polymixin-B (42%) and ST (30%), and 6% of respondents gave no prophylaxis. Regarding antifungal prophylaxis, the most frequently used agent was fluconazole (FLCZ, alone or in combination) (67%) followed by itraconazole (ITCZ) (oral solution and capsule, 25%), and amphotericin B (AMPH-B, alone or in combination) syrup (7%), compared with FLCZ (50%), AMPH-B syrup (50%), and ITCZ (14%) in 2001. No prophylaxis for fungal infection was given by 8% of respondents (3% in 2001 survey). ST was used in remission induction therapy (32%) and consolidation therapy (32%) in patients with AML, and also in remission induction therapy (63%) and consolidation therapy (59%) in acute lymphoblastic leukemia (ALL).

3.3 Empirical antibiotic therapy

With regard to FN, intravenous treatment with antibiotics in patients with FN was given prophylactically before the onset of fever by 3% of respondents, and after the onset of fever at ≥37, ≥37.5, and ≥38°C by 4, 37, and 53%, respectively. Drugs used in ET for FN are listed in Table 2. Monotherapy with either cephems (77%) or carbapenems (31%) accounted for the majority of responses. Dual therapy which included aminoglycosides was used by 31%, including combinations with cephems (20%) or carbapenems (5%). Results from the 2001 survey showed that cephems plus aminoglycoside were used by 37% of respondents, cephems alone by 29%, and carbapenems alone by 21%.

The timing of anti-MRSA drug administration was investigated, and the results showed that administration was started by 12% of respondents if the first-line antibacterial therapy was ineffective, and by 41% if second-line or subsequent therapy was ineffective. Thirty-four percent of respondents started administration of anti-MRSA drugs if any gram-positive strain was detected in culture, while 7% said it was not used until a definite diagnosis of MRSA infection was made, and 12% said it was used as first-line therapy if the patient was at a high risk according to the US guidelines. Among anti-MRSA drugs, the initial drug prescribed was most frequently vancomycin (80%), followed by teicoplanin (13%), arbekacin (5%), or linezolid (2%).

Table 2 Comparison of survey results regarding empirical antibacterial therapy for febrile neutropenia in Japanese hospitals in 2007 (134 institutions) and 2001 (125 institutions)

Antibacterial agent	2007 (%)	2001 (%)
1. Cephems	77	29
2. Cephems + AG	20	37
3. Carbapenems	31	21
4. Carbapenems + AG	5	16
5. Antipseudomonal penicillins	5	1
6. Antipseudomonal penicillins + AG	5	14
7. Cephems + Antipseudomonal penicillin	0	4
8. Cephems + Antipseudomonal penicillin + AG	0	1
9. AntiMRSA[a] + Cephems	1	1
10. AntiMRSA[a] + Carbapenems	0	2
11. AntiMRSA[a] + Cephems + AG	0	0
12. AntiMRSA[a] + Carbapenems + AG	0	0
13. Others	1	10
14. None	0	0

Percentages exceed 100% since respondents could tick more than one box if applicable

AG aminoglycoside

[a] With regard to anti-MRSA, the 2001 questionnaire only enquired about vancomycin

3.4 Empirical and targeted antifungal therapy

With regard to antifungal therapy, standard ET and a pre-emptive/presumptive approach using β-glucan/galactomannan or CT-scan was adopted by 54 and 42% of respondents, respectively. The timing of initiation of antifungal therapy was selected empirically by 54% of respondents, while 20% said it was preemptive and 22% said it was done presumptively. Among respondents who used an empirical approach for antifungal treatment, 88% prescribed micafungin (MCFG) either with or without antifungal prophylaxis. The percentage of each antifungal agent is shown in Table 3. In targeted therapy for *Candida albicans*, *Candida glablata*, and *Candida parapsilosis*, the

Table 3 Drugs used for empirical antifungal therapy in respondents of the 2007 survey of Japanese hospitals who used an empirical approach ($n = 73$)

Antifungal agent	Patients with febrile neutropenia	
	Without antifungal prophylaxis 2007 (%)	With antifungal prophylaxis 2007 (%)
1. FLCZ	4	8
2. MCFG	11	77
3. VRCZ	3	12
4. ITCZ	0	4
5. L-AMB	1	3
6. AMPH-B	1	0
7. Others	0	0

Percentages exceed 100% since respondents could tick more than one box if applicable

FLCZ fluconazole, *MCFG* micafungin, *VRCZ* voriconazole, *ITCZ* itraconazole, *L-AMB* liposomal amphotericin B, *AMPH-B* amphotericin B

three most commonly used drugs were FLCZ, MCFG, and voriconazole (VRCZ). The rates of FLCZ use for these organisms were 57, 2, and 7%, respectively; rates for MCFG use were 28, 50, and 26%, and for VRCZ were 7, 27, and 36%, respectively. In the treatment of invasive pulmonary aspergillosis (IPA), VRCZ and L-AMB were used by 69 and 21% of respondents, respectively. This was markedly different from the 2001 survey, in which the main treatments used for IPA were AMPH-B (80%) and combination treatment (18%) (Table 4).

In fungemia, susceptibility to antimycotic drugs was tested by only 28% of responders. ß-D-glucan measurement was used for monitoring or early diagnosis of fungemia by 99% of facilities, and most respondents (53%) reported that the frequency of ß-D-glucan testing was once a week. It was performed either by an outside contractor (46%, including Biochemical Seikagaku 45% and Wako 1%) or in-house using a Wako test kit (34%) or using a biochemical method such as Fungitec (9%). With regard to galactomannan antigen, 75% of facilities used this method for the purpose of diagnosis of IPA, compared with 57% in 2001. Most responders (71%) did not perform genetic diagnosis.

3.5 Use of G-CSF

Because the use of G-CSF in the treatment of AML and ALL may differ, questions were asked separately for AML remission induction therapy (disappearance of blasts in peripheral blood), AML consolidation therapy (with or without high dose cytarabine), ALL remission induction therapy, and ALL consolidation therapy. The results are shown in Tables 5 and 6. While G-CSF was used primarily in the treatment of life-threatening infections in patients with AML (25–37%; versus 28% in the 2001 survey), prophylactic use of G-CSF before the onset of fever was common in patients with ALL (63–65%), compared with the 2001 survey rates of 52–54%. Only 4% of respondents used prophylactic G-CSF during remission induction therapy in AML.

4 Discussion

This survey adds additional information to the previous 2001 survey on the treatment practices of member hospitals of the JALSG with regard to infectious complications in patients with acute leukemia during chemotherapy in Japan. This is useful because guidelines for the management of FN, deep fungal infection, or the use of G-CSF published in the US and Europe cannot necessarily be applied in other countries.

The proportion of institutions using single- or multi-patient rooms with a HEPA/LAF unit for AML remission therapy increased from 37% in 2001 to 76% in 2007. Of the member institutions of JALSG, 98% have a room with HEPA/LAF unit. The National Health Insurance reimbursement for the treatment of leukemia in a room with HEPA/LAF unit is 30,000 yen (about 300 US dollars) per

Table 4 Comparison of survey results regarding targeted antifungal therapy for fungal infection in Japanese hospitals in 2007 (134 institutions) and 2001 (125 institutions)

Antifungal agent	*Candida albicans* 2007 (%)	*Candida glablata* 2007 (%)	*Candida parapsilosis* 2007 (%)	Candidemia 2001 (%)	Invasive pulmonary aspergillosis 2007 (%)	Invasive pulmonary aspergillosis 2001 (%)
1. FLCZ	57	2	7	26	0	0
2. MCFG	28	50	26	NA	4	NA
3. VRCZ	7	27	36	NA	69	NA
4. ITCZ	1	4	9	0	1	2
5. L-AMB	3	13	16	NA	21	NA
6. AMPH-B	2	4	4	58	3	80
7. MCZ	0	0	0	3	0	0
8. FLCZ + AMPH-B	0	0	0	12	0	0
9. 5FC + AMPH-B	0	0	0	1	0	2
10. ITCZ + AMPH-B	0	0	0	1	0	16
11. MCFG + VRCZ	0	0	0	NA	1	NA
12. No approved policy[a]	1	1	2	0	1	0
13. Others	0	0	0	0	0	0

Percentages exceed 100% since respondents could tick more than one box if applicable

NA not available in 2001, *FLCZ* fluconazole, *MCFG* micafungin, *VRCZ* voriconazole, *ITCZ* itraconazole, *L-AMB* liposomal amphotericin B, *AMPH-B* amphotericin B, *MCZ* miconazole, *5FC* flucytosine

[a] Treatment policy not finalized by the hospital and thus no approved recommendation available, and decision was on a case by case basis

Table 5 Comparison of survey results regarding the use of G-CSF in AML in Japanese hospitals in 2007 (134 institutions) and 2001 (125 institutions)

Clinical status	AML remission induction 2007 (%)	AML remission induction 2001 (%)	AML consolidation high dose Ara-C regimen 2007 (%)	AML consolidation no high dose Ara-C regimen 2007 (%)	AML consolidation 2001 (%)
1. Prophylaxis for neutropenia	4	3	13	7	8
2. FN with ET	7	12	13	10	10
3. FN if refractory to ET	16	20	17	19	19
4. Clinically documented infection	26	23	24	31	21
5. Microbiologically documented infection	11	6	9	10	5
6. Life-threatening infection	37	28	25	30	28
7. Not used	10	7	6	7	7
8. No approved policy[a]	1	3	3	2	3
9. Others	1	3	4	2	2

G-CSF granuloyte-colony stimulating factor, *AML* acute myeloid leukemia, *Ara-C* cytarabine, *FN* febrile neutropenia, *ET* empiric antibiotic therapy

[a] Treatment policy not finalized by the hospital and thus no approved recommendation available, and decision was on a case by case basis

Table 6 Comparison of survey results regarding the use of G-CSF in ALL in Japanese hospitals in 2007 (134 institutions) and 2001 (125 institutions)

Clinical status	ALL remission induction 2007 (%)	ALL remission induction 2001 (%)	ALL consolidation 2007 (%)	ALL consolidation 2001 (%)
1. Prophylaxis for neutropenia	65	52	63	54
2. FN with ET	10	20	10	18
3. FN if refractory to ET	13	14	14	13
4. Clinically documented infection	6	2	6	4
5. Microbiologically documented infection	5	2	6	2
6. Life-threatening infection	6	1	5	1
7. Not used	1	0	1	1
8. No approved policy[a]	2	3	3	4
9. Others	2	5	3	4

G-CSF granulocyte-colony stimulating factor, *ALL* acute lymphoblastic leukemia, *FN* febrile neutropenia, *ET* empiric antibiotic therapy

[a] Treatment policy not finalized by the hospital and thus no approved recommendation available, and decision was on a case by case basis

patient per day in Japan. HEPA/LAF units are quite effective in the management of fungal infection, and this administrative policy did much to help increase the number of institutions in which a room with a HEPA/LAF unit is available, not only for patients receiving hematopoietic stem cell transplantation, but also for patients with leukemia.

The prophylactic use of fluoroquinolones during neutropenia after chemotherapy in patients with AML is controversial. In the current survey, 58% of respondents indicated that they used fluoroquinolones. The Infectious Disease Society of America (IDSA) guideline published in 2002 did not recommend the routine use of antibiotic prophylaxis in afebrile neutropenic patients except for ST, which was used to prevent *Pneumocystis jiroveci*. In contrast, a large-scale meta-analysis published in 2005 reported that all-cause mortality, as well as infection-related mortality, fever and the risk of documented infection, were lower in patients receiving fluoroquinolones compared with a placebo group [6]. A prospective randomized study published in the same year by Bucaneve and colleagues also concluded that fluoroquinolones were effective in the prophylactic treatment of bacterial infections, with the risk of fever, microbiologically documented infection, and bacteremia reduced to a greater extent in a levofloxacin group compared with a placebo group [7]. Since fluoroquinolone use has the potential to increase the risk of producing fluoroquinolone resistant gram-negative bacilli, this may raise some epidemiological concerns; nonetheless, fluoroquinolones can be useful for prophylaxis, particularly in patients with neutropenia of long duration, such as during the chemotherapeutic treatment of leukemia.

With regard to antifungal prophylaxis, the most frequently used agent was FLCZ, at 67%, followed by ITCZ (oral solution and capsule), at 25%. In contrast, use of amphotericin (as AMPH-B syrup) was only 7%. Compared to the previous survey, the use of AMPH-B syrup decreased markedly. Recently, a large-scale meta-analysis comparing anti-fungal prophylaxis with placebo, no treatment, or nonsystemic antifungals in cancer patients after chemotherapy was reported [8]. According to this analysis, the use of antifungal prophylaxis in patients with acute leukemia resulted in the reduction of fungal-related mortality rates and documented invasive fungal infections. There was a reduction in all-cause mortality, which did not reach statistical significance. This meta-analysis also found that ITCZ, posaconazole, and amphotericin (i.e. drugs with anti-mold activity), rather than FLCZ, reduced the risk of documented aspergillus infection and possibly had some effect on all-cause mortality [8]. The incidence of invasive fungal infection and the species of offending organisms varied widely between institutions, and the local epidemiology of fungal infections is very important in making therapeutic choices. If IPA is prevalent at institutions, agents with anti-mold activity, such as ITCZ, are more appropriate than FLCZ for antifungal prophylaxis. On the basis of this background, a nationwide epidemiological investigation of IPA is being undertaken in Japan and the results are awaited with keen interest.

Among patients with fever, treatment of those with neutropenia was primarily symptom-based, with 53% initiating treatment in those with a temperature of 38°C. With regard to empirical therapy for FN, monotherapy with cephems or carbapenems was most common, while in patients unresponsive to empirical therapy, the addition of, or change to, cephems, aminoglycosides, or carbapenems was implemented by 49% of respondents. These results might reflect the influence of reports on mono- and dual-therapy randomized controlled trials published overseas [9] or in Japan [10] since the previous survey. The incidence of infections with gram-positive cocci causing FN has increased in recent years. This change can be accounted for by a relative decrease in the incidence of infections with gram-negative bacilli because of prophylaxis with fluoroquinolones, and an increase in the incidence of intravascular catheter-related infections. The timing of initiation of anti-MRSA agents in the treatment of FN has always been debated. The National Health Insurance system of Japan supports the use of anti-MRSA drugs only for patients with documented MRSA infection. Thus, it is difficult to use anti-MRSA drugs as part of initial empirical therapy and in this survey the proportion of institutions withholding use until MRSA infection was confirmed was 7%. Compared to the results of the 2001 survey, in which the proportion was 30%, this percentage has clearly decreased. The US IDSA guideline suggests that the use of intravenous vancomycin should be limited wherever possible, on account of the potential emergence of vancomycin-resistant organisms [5]. The IDSA guideline also notes that initial empirical therapy with vancomycin is allowed only when the following clinical findings are obtained: (1) clinically suspected serious catheter-related infections, (2) known colonization with penicillin- and cephalosporin-resistant pneumococci or MRSA, (3) positive results of blood culture for gram-positive bacteria before final identification and susceptibility testing, and (4) hypotension or other evidence of cardiovascular impairment. The National Health Insurance of Japan does not cover the use of anti-MRSA agents except for the treatment of documented infections with MRSA. While patients would suffer greatly from such infections, the situation would be more serious if resistant organisms were to appear. From an epidemiological viewpoint we think that the use of anti-MRSA agents should continue to be restricted. Similar concerns have been expressed regarding the use of the carbapenems, although they are included in both the IDSA and Japanese guidelines. Interestingly, carbapenem use (with or without an aminoglycoside) remained relatively constant between the 2001 and 2007 surveys, and perhaps somewhat disappointingly the use of antipseudomonal penicillins remained at a relatively low level.

Among antifungal agents used in empirical therapy for FN, the recent launch of new products has led to marked changes in patterns of administration. MCFG, which was not marketed at the time of the previous survey, was the most frequently prescribed agent, at 88% among respondents who used an empirical approach to antifungal treatment. In contrast, the use of ITCZ and L-AMB was low (each $\leq$4%) in spite of their indication for FN. With regard to strain-specific treatment, FLCZ was most frequently prescribed (57%) for *C. albicans*, followed by MCFG (28%). Among other fungi, MCFG was most frequently prescribed for *C. glablata* (50%), followed by VRCZ (27%), L-AMB (13%), and ITCZ and AMPH-B (4%) while FLCZ was prescribed least often (2%). For *C. parapsilosis*, VRCZ was most frequently prescribed (36%), followed by MCFG (26%), L-AMB (16%), ITCZ (9%), and FLCZ (7%). Invasive aspergillosis was treated with VRCZ in 69% of respondents, probably owing to overseas evidence, particularly the Herbrecht study [11].

With regard to the determination of ß-D-glucan, only 1% failed to perform this test. Determination was contracted out by 46% of institutions, while the Wako kit was most commonly used by those hospitals performing this test in-house (34%). Based on the survey, opinion on the suitability of ß-D-glucan for use as a screening tool for fungi, especially *Candida* or *Aspergillus* appears to vary. In contrast, determination of galactomannan antigen had increased from 57 to 75% in 2007.

The criteria for starting G-CSF therapy differs between the US and Japan. According to the American Society of Clinical Oncology (ASCO) guideline published in 2006, the use of G-CSFs following initial induction therapy for AML is reasonable [12]. The ASCO guideline states that CSFs have no favorable impact on remission rate, remission duration or survival, but have beneficial effects on the incidence of severe infection. However, most Japanese hematologists prefer to use G-CSF for documented infections in patients with AML, because of the possible stimulating activity of G-CSF on AML cells. The results of the 2007 questionnaire showed little change from the 2001 survey with regard to AML induction therapy, AML consolidation therapy, ALL induction therapy, or ALL consolidation therapy.

In conclusion, comparison of the results of the present survey with those from 2001 highlights some significant changes in the use of drugs for the management of infections, including antifungal prophylaxis and empirical therapy. One reason for these changes is the introduction of a number of new antifungal agents since 2001. In addition, anti-MRSA drugs have also been launched, meaning that treatment strategies for FN will change further in the future. Guidelines for FN are currently available, and therapeutic measures should be reviewed and updated as needed, bearing in mind the changing medical environment in Japan, including technical improvements in diagnostic methods and the launch of new antibacterial and antifungal agents. This 2007 questionnaire analysis provides background information which broadens our perspective of current prophylactic practices in the treatment of acute adult leukemia in Japan, and will hopefully help establish guidelines for the management of infections in the fight against FN and leukemia.

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Appendix 1: Institutions responding to the questionnaire

Nihon University School of Medicine, Higashijujo Hospital, Kasukabe Municipal Hospital, Tokyo Metropolitan Komagome Hospital, Nagoya University Graduate School of Medicine, Daido Hospital, Yokkaichi Municipal Hospital, Aichi Cancer Center, Japanese Red Cross Nagoya First Hospital, Fujita Health University School of Medicine, Mie University Graduate School of Medicine, Suzuka Kaisei Hospital, Takeuchi Hospital, Kinki University School of Medicine, Osaka Medical Center for Cancer and Cardiovascular Diseases, Shikoku Cancer Center, Atomic Bomb Disease Institute - Nagasaki University, Graduate School of Biomedical Sciences, Sasebo City General Hospital, National Hospital Organization Nagasaki Medical Center, Kumamoto University School of Medicine, Kumamoto City Hospital, NTT West Kyushu General Hospital, Jichi Medical School, Okayama University Hospital, National Hospital Organization Minami-Okayama Medical Center, Chugoku Central Hospital of the Mutual Aid Association of Public School Teachers, National Hospital Organization Okayama Medical Center, Okayama Rosai Hospital, Kagawa Rosai Hospital, Gunma University Graduate School of Medicine, National Hospital Organization Nishigunma National Hospital, Fukaya Red Cross Hospital, University of Fukui, Kurashiki Central Hospital, Kanazawa Medical Center, Shimada Municipal Hospital, National Cancer Center Hospital, International Medical Center, Saitama Medical University, Hyogo College of Medicine, National Hospital Organization Osaka National Hospital Internal Medicine, Takarazuka Municipal Hospital, Uegahara Hospital, Kawasaki Medical School, Chiba University Hospital, Chiba Aoba Municipal Hospital, Social Insurance Funabashi Central Hospital, Nara Medical University, Jikei University School of Medicine, Dokkyo University School of Medicine, National Hospital Organization Nagoya Medical Center, Kochi Medical School - Kochi University, Shiga University of Medical Science, National Cancer Center East, Anjo Kosei Hospital, St. Marianna University School of Medicine, Yokohama Seibu Hospital, Shinshu University School of Medicine, Nagano Red Cross Hospital, Tokyo Women's Medical University, Tama-Hokubu Medical Center, Hamamatsu University School of Medicine, Fujieda Municipal General Hospital, Kagoshima University Hospital, Tochigi Cancer Center, Kanazawa University Graduate School of Medical Science, Toyama City Hospital, Seirei Numazu Hospital, Hematology, Tokyo Medical, University, Kyorin University School of Medicine, Hokkaido University Graduate School of Medicine, Sapporo Kousei Hospital, Hakodate Central Hospital, Saiseikai Maebashi Hospital, Higashi Municipal Hospital of Nagoya, Tokai University School of Medicine, Yamaguchi University School of Medicine, Yamaguchi Prefecture Central Hospital, Osaka City University, University of Tokyo, Niigata University, Medical and Dental Hospital, Oita University Faculty of Medicine, Oita Prefectural Hospital, Kouseiren Tsurumi Hospital, National Kyushu Cancer Center, National Hospital Organization Kyushu Medical Center, Fukuoka Postal Services Agency Hospital, Aso Iizuka Hospital, Teikyo University School of Medicine, Teikyo University Mizonokuchi Hospital, Sapporo Hokuyu Hospital, Aichi Medical University, Yamagata University Faculty of Medicine, Aomori Prefectural Central Hospital, Hyogo Cancer Center, Kyoto Prefectural University of Medicine, Social Insurance Kyoto Hospital, Social Insurance Kobe Central Hospital, National Hospital Organization Shiga Hospital, National Defense Medical College,

Akita University School of Medicine, NTT Kanto Medical Center, Yokohama City University Hospital, Yokohama City University Medical Center, Kanagawa Cancer Center, Fujisawa City Hospital, Shizuoka Red Cross Hospital, Tohoku University School of Medicine, Osaki Citizen Hospital, Hiroshima University, Kagawa University, Kagawa Prefectural Central Hospital, Sakaide City Hospital, Juntendo University School of Medicine, Kanazawa Medical University, Kobe University Graduate School of Medicine, Jiaikai Imamura Bun-in Hospital, Ehime University Graduate School of Medicine, Metropolitan Bokuto Hospital, Otsu Red Cross Hospital, Yokohama City Minato Red Cross Hospital, Saitama Medical Center Jichi Medical University, Ehime Prefectural Central Hospital, International Medical Center of Japan, National Hospital Organization Kure Medical Center, Nagoya Daini Red Cross Hospital, University of Yamanashi Hospital, Heartlife Hospital, Musashino Red Cross Hospital, Saitama Medical Center, PL Hospital, Toyama Prefectural Central Hospital, Shimane Prefectural Central Hospital, Miyagi Cancer Center.

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