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REVIEW ARTICLE

Life-threatening hemorrhagic pneumonia caused by *Stenotrophomonas maltophilia* in the treatment of hematologic diseases

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Abstract Since the late 1990s, *Stenotrophomonas maltophilia* (*S. maltophilia*) has become one of the most common nonfermenting Gram-negative bacilli that cause opportunistic infection. Patients with hematologic diseases are the most risky candidate for *S. maltophilia* pneumonia or sepsis because of chemotherapy-induced neutropenia or immunodeficiency. Frequent exposure to broad-spectrum antibiotics and prolonged insertion of central venous catheter further enhance the risk of *S. maltophilia* infection. One of the most severe *S. maltophilia* infections is hemorrhagic pneumonia. This type of infection is mostly fatal because of pulmonary alveolar hemorrhage that leads to acute respiratory failure. Furthermore, *S. maltophilia* exhibits a high-level intrinsic resistance to conventional antibiotics such as β-lactams and aminoglycosides and, more recently, the increasing acquired resistance to co-trimoxazole and quinolones. According to our experienced and previously reported cases, all of the patients with hemorrhagic pneumonia caused by *S. maltophilia* had a fatal course within a few days after the onset of the pneumonia. In this article, we perform a systematic review on a total 30 cases of hemorrhagic pneumonia induced by *S. maltophilia* from our institutions and the literature, and we describe its early diagnosis, prophylaxis, and recommended therapeutic strategy for the infection in the treatment of hematologic disease.

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Introduction

Infections in patients with hematologic disease who have undergone chemotherapy tend to be serious and are sometimes life-threatening due to severe neutropenia and immunosuppression. The infection-caused mortality, however, has been reduced considerably [1] since the development of standard guideline for febrile neutropenia [2] recommending the prompt and exact administration of broad-spectrum antibiotics. Unfortunately, as a result of the use of such antibiotics, the emergence of multidrug-resistant bacteria and of microbial substitution has become a new problem in the treatment of hematologic diseases in recent years [3-5]. *Stenotrophomonas maltophilia* (*S. maltophilia*) infection is one of these serious microbial substitutions. This infection has multidrug resistance and a high mortality rate [6].

Since the late 1990s, *S. maltophilia* has become one of the most common bacilli, similar to *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Serratia marcescens*, which all cause opportunistic infection [7, 8]. *S. maltophilia* is a nonfermenting Gram-negative bacillus and is widely distributed in the environment [9, 10]. Although *S. maltophilia* usually is an attenuated bacillus, it exhibits marked pathogenicity for immunocompromised individuals, causing pneumonia and sepsis and, less frequently, urinary tract and skin infections, endocarditis, and meningitis [8, 11-15]. *S. maltophilia* produces a protease which is thought to be destructive to fine blood vessels during its proliferation [16]. One of the most severe *S. maltophilia* infections is thus

hemorrhagic pneumonia. This type of infection is usually fatal because pulmonary alveolar hemorrhage leads to acute respiratory failure [17, 18]. Almost all patients die within a few days after the onset of hemoptysis or chest pain. It is quite difficult to start appropriate therapy for hemorrhagic pneumonia caused by *S. maltophilia* because these patients die before the *S. maltophilia* is detected from blood or sputum culture.

Patients with hematologic diseases, especially with acute leukemia, are at risk for *S. maltophilia* pneumonia and sepsis because of chemotherapy-induced neutropenia or immunodeficiency [6]. Frequent exposure to broad-spectrum antibiotics and prolonged insertion of a central venous (CV) catheter further enhance the risk of this infection [19-21]. In particular, rapid-progressing hemorrhagic pneumonia due to *S. maltophilia* infection is the most common complication. In light of these infections, there is a pressing need for improvement in the treatment of hematologic patients in the highly neutropenic state [18, 22, 23].

In this review, we clarify the clinical picture of *S. maltophilia* infection, especially, hemorrhagic pneumonia, and we describe its early diagnosis, prophylaxis, and therapeutic strategy for the infection in the treatment of hematologic diseases, based on our experience and an analysis of cases of this infection in the literature.

S. maltophilia infection in hematologic diseases

In recent years at our institutions, we treated four patients with hemorrhagic pneumonia caused by *S. maltophilia*. The patients, who had been diagnosed with acute myeloid leukemia (AML) or chronic myeloid leukemia in blastic phase (CML-BP), were undergoing chemotherapy and died within 24 h after the onset of hemoptysis or chest pain, which is the typical clinical manifestation of hemorrhagic pneumonia. Figures 1, 2, and 3 provide images of the chest, bronchoscopy, and histologic picture from two of the four patients. We can see a progressing infiltrative shadow accompanied by marked hemorrhage. The culture of the sputum or fluid from bronchoalveolar lavage was turned out to be positive for *S. maltophilia* after the death of these four patients. In two of the four patients, blood culture was also positive for *S. maltophilia.*

Such an unfavorable clinical course not only occurred in our institutions but also appeared frequently in the literature in recent years [17, 18, 22-27]. There is a pressing need to clarify the epidemiology, clinical picture, and therapeutic strategy of *S. maltophilia* infection. For this purpose, we retrospectively analyzed clinical parameters regarding *S. maltophilia* in patients with hematologic diseases in our institutions. We focused on the hemorrhagic pneumonia induced by *S. maltophilia* because of its extremely poor prognosis, and we performed a systematic review on a total of 30 cases of hemorrhagic pneumonia from our institutions and the literature.

Retrospecitve analysis of *S. maltophilia* infection in our institutions

Patients and methods

We reviewed the chart of each patient who produced a positive culture for *S. maltophilia* at either of our institutions from January 2010 to December 2012, and we used the patient charts and medical records to retrospectively analyze the clinical picture of *S. maltophilia* infection. We defined a case as sepsis or bacteremia when more than two blood culture sets were positive for *S. maltophilia* or only a single set was positive in the absence of other microorganisms in patients who had definite infectious lesions such as perianal abscess or cutaneous cellulitis. In addition, sepsis was defined as the presence of a systemic inflammatory response to infection according to the consensus definition of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee [28].

We defined a case as pneumonia when the culture of the sputum or the fluid from bronchoalveolar lavage was positive for *S. maltophilia* in patients who had the clinical signs of cough or sputum with pulmonary infiltration on image analysis. *S. maltophilia* abscess was defined based on a positive result only for this microorganism in a pus culture in patients who had a fever or focal signs of inflammation. The identification of *S. maltophilia* was made on the basis of Gram staining, colony morphology, analysis with NGKG agar (NISSUI, Tokyo), and the MicroScan WalkAway plus System (Siemens, Erlangen, Germany) or the BD Phoenix Automated Microbiology System (Becton Dickinson, Lincoln Park, NY). Antimicrobial susceptibility tests were performed by the broth microdilution method using the same systems.

Results

Patient characteristics

We identified a total of 16 patients as having had *S. maltophilia* infection. The *S. maltophilia* infection occurred sporadically, but not as an outbreak, during the 2-year data collection period. The patient characteristics are shown in Table 1. The median age was 66 years (range 33 to 86) old. Of the 16 patients, 14 were male and 2 were female. As underlying diseases, six patients had AML, two had adult T cell leukemia/lymphoma (ATLL), two had myelodysplastic syndrome (MDS), three had plasma cell myeloma (PCM), and one patient each had acute lymphoblastic leukemia (ALL), CML-BP, and aplastic anemia. As the type of *S. maltophilia* infection, seven patients developed nonhemorrhagic pneumonia, four had sepsis, four hemorrhagic had pneumonia, and one had perianal abscess. Two of the four patients with

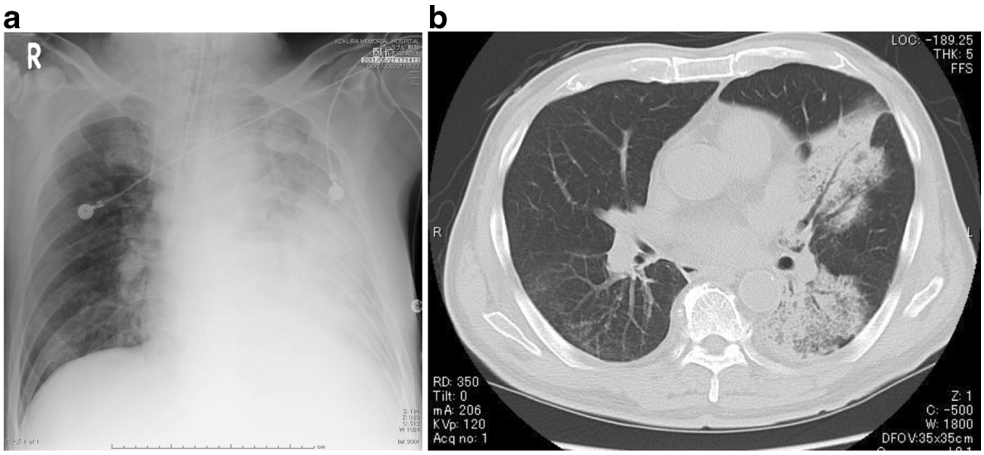

Fig. 1 Images of *S. maltophilia* hemorrhagic pneumonia from case 16. **a** Chest X-ray, and **b** CT scanning

hemorrhagic pneumonia also had sepsis with this microorganism. No patients had coinfection with fungus; fungus growth was not documented in respective cultures performed in all patients, and serum concentration of β-D-glucan was not elevated in four cases with hemorrhagic pneumonia. There was no histopathological evidence of fungal or viral infection, GVHD, and leukemia invasion in one autopsy case (case 15). The median neutrophil counts were 4,554/μL (range 34 to 6,820), 1,700/μL (range 14–4,650), and 6/μL (range 0–31) in seven patients with nonhemorrhagic pneumonia, four with sepsis, and four with hemorrhagic pneumonia, respectively. Leukemic cells were not expanded in four cases with hemorrhagic pneumonia. Severe mucositis was not observed in these four cases. The insertion of a CV catheter was performed in 10 patients; however, sepsis with *S. maltophilia* caused by catheter infection was not observed. Twelve of the 16 patients prophylactically took co-trimoxazole (trimethoprim component 80 mg daily for 7 days per week or three times per week on alternative days) before the development of *S. maltophilia* infection.

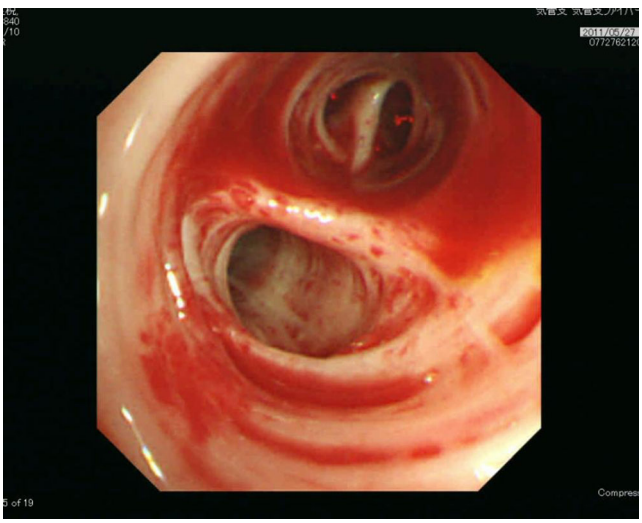

Fig. 2 The bronchoscopical imaging of massive bleeding in the trachea of case 16

Outcomes

Seven of the 16 patients with *S. maltophilia* infection died of this infection itself, and five patients died of other causes including heart failure (two patients), other infection (one patient), graft-versus-host disease (one patient), and cerebral hemorrhage (one patient), while four patients are currently alive. Six of the seven patients who died of *S. maltophilia* infection included four patients with hemorrhagic pneumonia, one with nonhemorrhagic pneumonia, and one with sepsis.

In vitro drug susceptibility of S. maltophilia strains

Antimicrobial susceptibility tests were performed in the 16 patients described above. The results were as follows: 6 of the 11 strains examined were susceptible to co-trimoxazole, 9 of 16 to levofloxacin, 16 of 16 to minocycline, and 4 of 16 to ceftazidime. In addition, antimicrobial susceptibility tests were performed in 9 of the 12 patients who prophylactically received co-trimoxazole. Five of the nine strains were susceptible to co-trimoxazole. In addition, the co-trimoxazole prophylaxis was also for the prevention of *Pneumocystis jirovecii* pneumonia.

Systematic review of hemorrhagic pneumonia based on previously reported cases and ours

Patients and methods

We searched PubMed (http://www.ncbi.nlm.nih.gov/pubmed) for all relevant data regarding *S. maltophilia* and pneumonia up to 2013, and we identified all of the patients with hemorrhagic pneumonia caused by *S. maltophilia*.

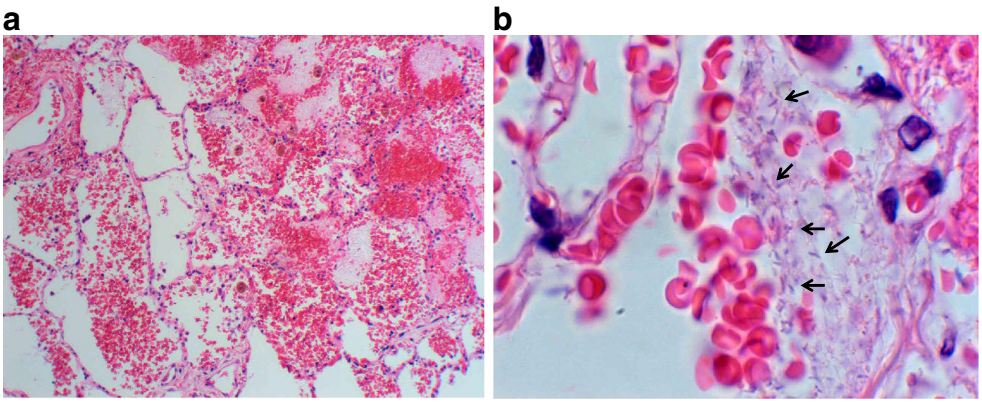

Fig. 3 Histologic picture of the lung necropsied in case 14. **a** Alveolar space is filled with red blood cells, ×100, H-E staining. **b** Many rod-shaped bacilli are seen (*arrows*), ×1,000, H-E staining

Results

Patient characteristics

We found a total of 26 cases of hemorrhagic pneumonia caused by *S. maltophilia* in the literature [17, 18, 22-26] and summarized the clinical information of a total of 30 cases including our four in Table 2 [27]. Nineteen of the 30 patients were male and 11 were female, with a median age of 51.5 years (range 0 to 63). Underlying diseases included AML in 19 patients, ALL in 4, MDS in 2, CML-BP in 2, non-Hodgkin's lymphoma (NHL) in 2, and myelofibrosis (MF) in 1. Interestingly, no case of hemorrhagic pneumonia associated with diseases other than hematologic disorders has been reported. The hemorrhagic pneumonia manifested itself after intensive chemotherapy (12 cases) or as a complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT) (18 cases). The median neutrophil count at the onset of hemorrhagic pneumonia was 0/μL (range 0 to 1,720). At least 12 patients prophylactically took co-trimoxazole or new quinolones before the onset of the pneumonia. Ciprofloxacin was administered as the infection prophylaxis after allo-HSCT in some patients (cases 20 to 26). As the treatment for hemorrhagic pneumonia, high-dose co-trimoxazole combined with fluoroquinolones was administered in eight patients, high-dose co-trimoxazole was administered in three patients and fluoroquinolones in two patients, and broad-spectrum antibiotics such as carbapenems or vancomycin (in combination in most cases) were used for the remaining 18 patients. The proportions among *S. maltophilia* strains that were susceptible to co-trimoxazole and fluoroquinolones were 80–90 and 50–70 %, respectively.

Outcomes

All 30 patients died of hemorrhagic pneumonia within 1.5 days (median, range 0–16). Only two patients survived more than 1 week; for both patients, high-dose co-trimoxazole and fluoroquinolones were promptly administered after the onset of the pneumonia. Interestingly, one of the two patients (case 12) had a neutrophil count over 1,000/μL, and the other (case 26) received a granulocyte transfusion. Granulocyte transfusion was performed 38 h after the onset of hemoptysis, because pulmonary hemorrhage due to *S. maltophilia* was strongly suspected based on a typical clinical course.

Characteristics of S. maltophilia infection in patients with hematologic diseases

In general, *S. maltophilia* infection mostly manifests itself as pneumonia and bacteremia [6, 8]. The exact clinical course of *S. maltophilia* infection in hematologic diseases, however, has not been reported. The database that we created in the present study revealed that the most frequent type of *S. maltophilia* infection in patients with hematologic disease was pneumonia, followed by bacteremia and then soft-tissue infection. Regarding the *S. maltophilia* infection in the patients who underwent allo-HSCT, a retrospective analysis of a 4-year period in a single center revealed 17 of 19 patients to be bacteremia [29]. The remaining two patients had nonhemorrhagic pneumonia. The overall mortality was 32 %. The high incidence of CV catheter insertion and long-term insertion (median 4.5 months) may have contributed to this high proportion of bacteremia.

Another retrospective analysis of *S. maltophilia* pneumonia for a 5-year period at a single institution identified 10 cases of this pneumonia [18]. All 10 of the patients were post-allo-HSCT and developed hemorrhagic pneumonia, with 100 % mortality. In light of the present and previous findings, it is apparent that pneumonia and bacteremia are the most common clinical manifestation in patients with hematologic diseases, similar to those with nonhematologic disorders.

Severe neutropenia is the most important risk factor for S. maltophilia hemorrhagic pneumonia

In our institutions, 4 of the 11 patients with *S. maltophilia* pneumonia developed hemorrhagic-type pneumonia.

Table 1 Patient characteristics and clinical data of *S. maltophilia* infection at our institutions (Kokura Memorial Hospital, Kitakyusyu, Japan and Shinko Hospital, Kobe, Japan)

Case	Age/sex	Disease	Disease status/treatment	ANC, cells/μl	CV catheter	Prophylactic ST	Antibiotics administered before SM infection	Type of SM infection	Outcome
1	33/M	AA	ATG + CsA	1,984	+	−	CFPM	Bacteremia	Alive
2	67/F	ATLL	Allo-PBSCT day 48	4,650	+	+	CAZ + MINO	Bacteremia	Alive
3	75/M	MDS	Azacitidine	14	−	+ (R)[a]	CAZ + LVFX	Bacteremia	Recovery ⇒ died (heart failure)
4	61/M	PCM	Refractory (lenalidomide + Dex)	1,415	+	+ (S)[b]	LVFX + DAP + MINO	Bacteremia	Died (PCM, SM sepsis)
5	65/M	AML	Refractory (CAG)	10	−	+ (S)	LVFX	Anorectal abscess	Alive
6	82/M	AML	Refractory (no chemotherapy)	34	−	−	MEPM + CVA	Pneumonia	Recovery ⇒ died (other sepsis)
7	80/F	PCM	MP	4,554	+	+	MEPM	Pneumonia	Died (heart failure)
8	86/M	AML	Refractory (no chemotherapy)	744	+	+ (S)	CPFX + ABK	Pneumonia	Recovery ⇒ died (cerebral hemorrhage)
9	67/M	MDS	Allo-PBSCT day 93	5,233	+	+ (R)	MEPM + MINO	Pneumonia	Recovery ⇒ died (cGVHD)
10	58/M	ATLL	Allo-PBSCT 2 years before, cGVHD	6,820	+	+ (R)	CPFX	Pneumonia	Alive
11	86/M	Ph + ALL	Refractory (Hyper CVAD + imatinib)	810	+	+ (R)	MEPM + MINO	Pneumonia	Died (SM pneumonia)
12	75/M	PCM	Refractory (CyBorD)	5,249	−	+ (S)	CPFX	Pneumonia	Died (SM pneumonia)
13	37/M	AML	Refractory (FAM)	0	−	+	CPFX + VCM	Hemorrhagic pneumonia	Died (SM hemorrhagic pneumonia)
14	47/M	CML-BP	Refractory (nilotinib + HU)	0	+	+ (S)	TAZ/PIPC + VCM	Hemorrhagic pneumonia	Died (SM hemorrhagic pneumonia)
15	59/M	AML	Allo-BMT day70, azacitidine	31	+	-	CPFX	Hemorrhagic pneumonia, Bacteremia	Died (SM hemorrhagic pneumonia)
16	63/M	AML	Reinduction chemotherapy (MEC)	11	−	−	TAZ/PIPC + VCM	Hemorrhagic pneumonia, Bacteremia	Died (SM hemorrhagic pneumonia)

AA aplastic anemia, *ABK* arbekacin, *allo-PBSCT* allogeneic peripheral blood stem cell transplantation, *AML* acute myeloid leukemia, *ANC* absolute neutrophil counts, *ATG* antithymocyte globulin, *ATLL* adult T cell leukemia/lymphoma, *CAG* cytarabine, aclarubicin, and G-CSF, *cGVHD* chronic graft-versus-host disease, *CAZ* ceftazidime, *CFPM* cefepime, *CML-BP* chronic myelogenous leukemia in blastic phase, *CPFX* ciprofloxacin, *CSA* cyclosporine A, *CVA* clavulanic acid, *CVAD* cyclophosphamide, vincristine, doxorubicin and dexamethasone, *CV catheter* central venous catheter, *CyBorD* cyclophosphamide, bortezomib, and dexamethasone, *DAP* daptomycin, *DEX* dexamethasone, *FAM* fludarabine, cytarabine, and mitoxantrone, *HU* hydroxyurea, *LVFX* levofloxacin, *MDS* myelodysplastic syndrome, *MEC* mitoxantrone, etoposide, and cytarabine, *MEPM* meropenem, *MINO* minocycline, *MP* melpharan and prednisolone, *PCM* plasma cell myeloma, *Ph + ALL* BCR-ABL1 associated acute lymphoblastic leukemia, *SM S. maltophilia*, *ST* trimethoprim-sulfamethoxazole, *TAZ/PIPC* tazobactam/piperacillin, *VCM* vancomycin

[a] *S maltophilia* strain examined in the patient was resistant to co-trimoxazole

[b] *S. maltophilia* strain was susceptible to co-trimoxazole

Table 2 Reported cases of hemorrhagic pneumonia due to *S. maltophilia*

Case	Age/sex	Disease	Treatment	ANC, cells/μL	SM bacteremia	Prophylaxis for infection	Treatment for pneumonia	Time of death after pneumonia onset (days)	Reference
1	52/M	AML	Reinduction chemotherapy	<200	+	CPFX	IPM + CAZ + TOB	3	[23]
2	28/F	ALL	Induction chemotherapy	<200	−	−	IPM + CAZ + VCM	2	[23]
3	46/M	AML	Reinduction chemotherapy	<200	−	CPFX	IPM + TOB	3	[23]
4	0/F	B-ALL	Induction chemotherapy	100	+	−	IPM + AMK	3	[25]
5	3.5/F	B-ALL	Induction chemotherapy	100	+	ST	IPM + AMK + TEIC + ST	1	[25]
6	11/F	B-ALL	Induction chemotherapy	100	+	ST	CAZ + AMK + VCM + ST	2	[25]
7	63/F	AML	Consolidation chemotherapy	100	+	OFLX	TAZ/PIPC + TOB + VCM	2	[22]
8	63/F	MDS	Induction chemotherapy	100	−	LVFX (resistant)	IPM	2	[26]
9	57/F	NHL	Salvage chemotherapy	100	+	ST	DRPM	2	[17]
10	45/M	AML	2nd allo-SCT (CB)	0	+	−	N.A.	1	[18]
11	62/M	AML	Allo-SCT (CB)	0	+	CPFX	ST + quinolone + broad-spectrum antibiotics	3	[18]
12	57/M	AML	Allo-SCT (PB)	1,720	+	CPFX	ST + quinolone + broad-spectrum antibiotics	10	[18]
13	36/M	AML	2nd allo-SCT (CB)	0	+	−	Quinolone + broad-spectrum antibiotics	2	[18]
14	59/M	NHL	Allo-SCT (CB)	0	+	−	Broad-spectrum antibiotics	1	[18]
15	60/M	AML	Allo-SCT (CB)	0	+	−	ST + quinolone + broad-spectrum antibiotics	2	[18]
16	56/F	AML	2nd allo-SCT (CB)	0	+	−	Broad-spectrum antibiotics	1	[18]
17	42/F	CML-BP	Allo-SCT (CB)	0	+	−	ST + quinolone + broad-spectrum antibiotics	4	[18]
18	59/F	AML	2nd allo-SCT (CB)	78	+	CPFX	ST + quinolone + broad-spectrum antibiotics	3	[18]
19	62/F	MDS	Allo-SCT (CB)	0	+	−	ST + quinolone + broad-spectrum antibiotics	1	[18]
20	27/M	AML	Allo-SCT (CB)	0	+	CPFX?	Broad-spectrum antibiotics	0	[24]
21	37/M	MF	Allo-SCT (BM)	0	+	CPFX?	Broad-spectrum antibiotics	0	[24]
22	54/M	AML	Allo-SCT (BM)	0	+	CPFX?	Broad-spectrum antibiotics	1	[24]
23	58/M	AML	2nd allo-SCT (CB)	0	+	CPFX?	CAZ	0	[24]
24	43/M	AML	2nd allo-SCT (CB)	0	+	CPFX?	ST + PZFX + CAZ	1	[24]
25	24/M	AML	Allo-SCT (PB)	0	+	CPFX?	ST	1	[24]
26	51/M	AML	Allo-SCT (BM)	0	+	CPFX?	ST + PZFX + granulocyte transfusion	16	[24]
27	63/M	AML	Reinduction chemotherapy	11	+	−	MEPM + VCM	1	Our case [27]
28	37/M	AML	Salvage chemotherapy	0	−	ST + CPFX	DRPM + AMK	1	Our case
29	47/M	CML-BP	Nilotinib + HU	0	−	ST	TAZ/PIPC + VCM	1	Our case
30	59/M	AML	Allo-SCT (BM), azacitidine	31	+	−	CPFX	1	Our case

ALL acute lymphoblastic leukemia, *allo-SCT* allogeneic hematopoietic stem cell transplantation, *AMK* amikacin, *AML* acute myeloid leukemia, *ANC* absolute neutrophil counts, *BM* bone marrow, *CAZ* ceftazidime, *CB* cord blood, *CML-BP* chronic myelogenous leukemia in blastic phase, *CPFX* ciprofloxacin, *DRPM* doripenem, *HU* hydroxyurea, *IPM* imipenem, *LVFX* levofloxacin, *MDS* myelodysplastic syndrome, *MF* myelofibrosis, *MEPM* meropenem, *NHL* non-Hodgkin's lymphoma, *OFLX* ofloxacin, *PB* peripheral blood, *PZFX* pazufloxacin, *SM S. maltophilia*, *ST* trimethoprim-sulfamethoxazole, *TAZ/PIPC* tazobactam/piperacillin, *TEIC* teicoplamin, *TOB* tobramycin, *VCM* vancomycin

Importantly, the neutrophil counts in these four patients were below 100/μL. Twenty-five of 26 patients with *S. maltophilia* hemorrhagic pneumonia, whose cases are described in the literature, were also severely neutropenic. Although the remaining one patient had a neutrophil count of 1,720/μL, this patient developed hemorrhagic pneumonia on day 27 after allo-HSCT and appeared to be severely neutropenic before day 27. The manifestation of *S. maltophilia* infection in AML patients with severe and long-lasting neutropenia appears to almost exclusively be hemorrhagic pneumonia. Further, the prognosis of this hemorrhagic pneumonia was extremely poor; the mortality of the 30 patients including our four was 100 %, and 90 % of them died within 3 days after the onset of the pneumonia.

The mechanism underlying pulmonary hemorrhage

Although the exact mechanism of alveolar hemorrhage is unclear, a protease produced by *S. maltophilia* has been proposed to play an important role in this type of hemorrhage [16, 30]. This protease, coded by StmPr1 gene, promotes the degradation of collagen and fibronectin in the connective tissue and that of fibrinogen in the plasma, ultimately causing the destruction of fibroblasts in vitro [16]. This function of the protease might lead to the destruction of alveolar microvessels.

The mortality of *S. maltophilia* bacteremia is considerably low

Regarding *S. maltophilia* bacteremia, a retrospective analysis in a single center revealed the mortality rate to be 7.5 % in 40 patients with hematologic disease whose cases were complicated by *S. maltophilia* bacteremia and 29 % in 24 allo-HSCT recipients who developed the bacteremia [24, 31]. The former group included neutropenic patients (<500/μL, 23 of the 40 patients); nevertheless, the mortality was low when compared to that of the patients with hemorrhagic pneumonia. At our institutions, a patient who developed *S. maltophilia* sepsis during the neutropenic period (case 3, Table 1) recovered from the sepsis without severe complications. In general, the prognosis of *S. maltophilia* bacteremia thus appears to be fairly favorable. However, prolonged neutropenia beyond 10 days and the association of pneumonia with another microorganism or enterococcus infection have been reported as unfavorable factors for the prognosis of *S. maltophilia* bacteremia [24, 32, 33].

Therapeutic strategies for *S. maltophilia* infection

In patients with hematologic diseases with risk factors such as long-lasting severe neutropenia, long-term exposure to broad-spectrum antibiotics, and severe sepsis [34], the risk of *S. maltophilia* infection should always be borne in mind, because the antibiotics that are active for this microorganism differ markedly from those used for febrile neutropenia. When patients with hematologic diseases with these risk factors develop hemoptysis or chest pain with infiltrative shadow on chest X-ray, antibiotics treatment should be started soon after the initiation of blood and sputum cultures. It takes a few days to obtain a result from the culture. Gram-staining of the sputum is useful to approximately identify the microorganism and enables an early start to therapeutic intervention. Although imaging of *S. maltophilia* pneumonia is nonspecific [18], blood culture is mostly positive for this microorganism in hemorrhagic pneumonia. Combined antibiotics treatment is reasonable because of the possibility of both intrinsic and acquired resistance of *S. maltophilia* to antibiotics [6, 35]. It is also important to put stress on the local resistance pattern of *S. maltophilia* due to the increasing incidence of acquired resistance to co-trimoxazole and quinolones.

Mechanism of the resistance of *S. maltophilia* to antibiotics

S. maltophilia is constitutively resistant to broad-spectrum cephem, carbapenem, and aminoglycoside antibiotics, which are used as empiric therapy for febrile neutropenia [6]. The resistance is caused mainly by the synthesis of β-lactamase, multidrug-efflux pumps, the production of modifying enzymes, outer membrane changes, or target site modification [36]. *S. maltophilia* produces β-lactamases of types L1 and L2, and the L1 type acts as metallo-β-lactamase, resulting in extensive resistance to penicillin, cephem, and carbapenem antibiotics [37-39]. The resistance to aminoglycoside is derived mainly from the production of aminoglycoside-modifying enzyme and outer membrane changes [40-42]. The multidrug-efflux pumping generates the resistance to fluoroquinolone, tetracycline, and macrolide antibiotics [43, 44].

The prophylaxis of hemorrhagic pneumonia by *S. maltophilia*

S. maltophilia hemorrhagic pneumonia is rapidly progressive and mostly fatal; there has been no survivor of this pneumonia regardless of treatment with high-dose co-trimoxazole and fluoroquinolones, for example [18]. The prophylaxis of *S. maltophilia* is thus crucially important. In the present analysis, 12 of the 16 patients who developed *S. maltophilia* infection prophylactically took oral co-trimoxazole (Table 1). Among the 30 patients with hemorrhagic pneumonia, at least eight took oral fluoroquinolones and five took oral co-trimoxazole as the prophylaxis (Table 2). From these

results, prophylactic dose of co-trimoxazole, which was previously described, may be insufficient to prevent *S. maltophilia* infection. Regarding fluoroquinolones as the prophylaxis for this infection, the majority of the patients were treated with ciprofloxacin; therefore, the prophylactic effect of newer fluoroquinolones is worth being studied because the appearance of resistant strains of *S. maltophilia* to ciprofloxacin is increasing [45, 46]. During intensive chemotherapies for hematologic diseases, especially prolonged neutropenia, regular surveillance culture of the sputum is very important. When *S. maltophilia* colonization is suggested, physicians should be aware of minimizing the use of broad-spectrum antibiotics. However, a surveillance culture before the onset of hemorrhagic pneumonia gave a positive result of colonization in only three of 10 patients in the neutropenic period [18]. Therefore, the administration of moxifloxacin or minocycline is recommended in the situation of prolonged severe neutropenia with a caution of avoiding unnecessary antibiotic usage.

Another means of preventing *S. maltophilia* infection is to maintain a rigorous sterilization program. *S. maltophilia* easily colonizes on medical instruments because of its ability to form a biofilm and make its own surface cationic [47, 48]. This character of *S. maltophilia* makes it difficult to eliminate it from medical instruments. It is also well known that outbreaks of this microorganism can occur more easily in wet areas and equipment in a hospital such as the bathrooms, washstands, inspirators, and artificial respirators [6, 49-51]. When an increased incidence of *S. maltophilia* infection is suspected in a hospital, prompt sampling, identification of colonized site(s), and subsequent thorough cleaning are required.

Recommended antibiotics for the treatment of *S. maltophilia* infection

The first-choice antibiotic in the treatment of *S. maltophilia* infection is co-trimoxazole [52, 53]. The dosage of co-trimoxazole for this purpose should be equivalent to that in the treatment of *P. jirovecii* pneumonia, that is, 15 mg/kg/day, the same as the recommended dosage of trimethoprim [54], although established clinical data is not available regarding this dosage of co-trimoxazole. Ticarcillin-clavulanate, fluoroquinolone, tetracycline, and chloramphenicol can be used as substitutes for co-trimoxazole [6, 52, 53, 55]. Clavulanic acid has an action to suppress the production of L2 type β-lactamase [56].

In recent years, however, the increase of *S. maltophilia* that is resistant to co-trimoxazole and fluoroquinolones has been reported. The proportion of *S. maltophilia* resistant to co-trimoxazole has been reported as approximately 10 %, although the rate varies from institution to institution [57-59]. Regarding the fluoroquinolones, the resistant rate for ciprofloxacin has been reported to be as high as 50 % [45, 46]. The use of moxifloxacin (a newer fluoroquinolone) is therefore recommended [60]. It is important to regularly determine the proportion of *S. maltophilia* strains that are resistant to co-trimoxazole and fluoroquinolones.

Although myelosuppression by co-trimoxazole should be considered in the state of severe neutropenia, the issue of whether co-trimoxazole affects the recovery of hematopoiesis is controversial, and the combined administration of antibiotics is recommended in the treatment of highly neutropenic and severely immunocompromised patients with hematologic diseases [35]. For example, the combination of co-trimoxazole with ticarcillin-clavulanate, co-trimoxazole with fluoroquinolone, or ticarcillin-clavulanate with fluoroquinolone has been recommended based on in vitro synergy testing but not clinical trials [61, 62]; therefore, evidence regarding the efficacy of these combinations has not been established. Other antibiotics that are suggested to be active against *S. maltophilia* when combined with another agent but not as single agent are ceftazidime, aztreonam, polymyxin B, and rifampicin [6, 63-67]. In a study of *S. maltophilia* hemorrhagic pneumonia after allo-HSCT, 6 of 10 patients promptly received combined treatment of co-trimoxazole with ciprofloxacin, with consequent early death [18]. Therefore, the addition of ceftazidime or aztreonam to the above combination may lead to the improved prognosis of *S. maltophilia* hemorrhagic pneumonia.

Conclusion

In recent years, the prevalence of *S. maltophilia* infection has become a serious problem in the treatment of immunocompromised and long-term hospitalized patients. Patients with hematologic malignancies, especially acute leukemia patients, have a risk for *S. maltophilia* infection because of intensive chemotherapy, frequent exposure to broad-spectrum antibiotics, and prolonged insertion of a CV catheter. The most common clinical manifestation of *S. maltophilia* infection is pneumonia being followed by bacteremia or sepsis. More importantly, in patients with hematologic disease with severe and long-lasting neutropenia, *S. maltophilia* infection leads to fulminant and fatal hemorrhagic pneumonia. Fungal or viral infection, however, should be ruled out, because these infections occasionally cause similar clinical pictures.

S. maltophilia is intrinsically resistant to broad-spectrum antibiotics such as cephem, carbapenem, and aminoglycoside, which are empirically used for febrile neutropenia. The recommended first line agent for *S. maltophilia* infection is co-trimoxazole. Alternative agents include ticarcillin-clavulanate, fluoroquinolone, and tetracycline. In recent years, however, the increase of *S. maltophilia* strains that are resistant to co-trimoxazole and fluoroquinolone has been frequently reported. Thus, the combination therapy is recommended in

the treatment of highly neutropenic and severely immnocompromised patients with hematologic diseases. The addition of ceftazidime or aztreonam to the above combination should be considered for acute leukemia patients who have a risk of hemorrhagic pneumonia by *S. maltophilia*. For these patients, regular surveillance culture of the sputum and blood is important for early diagnosis of this infection and prompt initiation of antibiotic therapy as above. Continuous and intensive cleaning of medical instruments and hospital wet circumstances is also important for preventing the colonization and outbreaks of *S. maltophilia*.

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Conflict of Interest The authors declare that they have no conflict of interest.

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