Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3358-19
Intern Med 59: 193-198, 2020
http://internmed.jp

【 ORIGINAL ARTICLE 】

Clinical Characteristics of Rapidly Progressive Fatal Hemorrhagic Pneumonia Caused by *Stenotrophomonas maltophilia*

Waki Imoto[1-3], Koichi Yamada[1,2], Kazushi Yamairi[1,2], Wataru Shibata[1,2], Hiroki Namikawa[1,4], Satomi Yukawa[1,2], Naoko Yoshii[1-3], Kiyotaka Nakaie[1], Asao Hirose[5], Hideo Koh[5], Tetsuya Watanabe[3], Kazuhisa Asai[3], Hirohisa Nakamae[5], Yukihiro Kaneko[6], Tomoya Kawaguchi[3], Masayuki Hino[5] and Hiroshi Kakeya[1,2]

Abstract:

Objective Hemorrhagic pneumonia due to *Stenotrophomonas maltophilia* (SM) in severely immunocompromised patients has a very poor prognosis. However, the risk factors for hemorrhagic pneumonia are not clear.

Methods This study assessed the predictive factors of hemorrhagic pneumonia caused by SM. The medical records of patients admitted to Osaka City University Hospital with SM bacteremia between January 2008 and December 2017 were retrospectively reviewed.

Patients All patients who had positive blood cultures for SM were included in this study. They were categorized into two groups: the SM bacteremia with hemorrhagic pneumonia group and the SM bacteremia without hemorrhagic pneumonia group. The clinical background characteristics and treatments were compared between these groups.

Results The 35 patients with SM bacteremia included 4 with hemorrhagic pneumonia and 31 without hemorrhagic pneumonia. Hematologic malignancy (p=0.03) and thrombocytopenia (p=0.04) as well as the prior use of quinolone within 30 days (p=0.04) were more frequent in the SM bacteremia patients with hemorrhagic pneumonia than in those without hemorrhagic pneumonia. The mortality of the SM bacteremia patients with hemorrhagic pneumonia was higher than that of those without hemorrhagic pneumonia group (p=0.02).

Conclusion Patients with SM bacteremia who have hematologic malignancy, thrombocytopenia, and a history of using quinolone within the past 30 days should be treated with deliberation.

Key words: bacteremia, hemorrhagic pneumonia, quinolone, *Stenotrophomonas maltophilia*

(Intern Med 59: 193-198, 2020)
(DOI: 10.2169/internalmedicine.3358-19)

Introduction

Stenotrophomonas maltophilia (SM) is a bacterium that can be present in almost any aquatic or humid environment but is not highly virulent (1). It rarely causes infection in a healthy population. When SM is detected upon culture of an airway sample, it is generally judged to be colonization (2). However, SM can cause serious infections, such as pneumonia or bacteremia in immunocompromised patients.

[1]Department of Infection Control Science, Osaka City University Graduate School of Medicine, Japan, [2]Department of Infectious Disease Medicine, Osaka City University Hospital, Japan, [3]Department of Respiratory Medicine, Osaka City University Graduate School of Medicine, Japan, [4]Department of Medical Education and General Practice, Osaka City University Graduate School of Medicine, Japan, [5]Department of Hematology, Osaka City University Hospital, Japan and [6]Department of Bacteriology, Osaka City University Graduate School of Medicine, Japan
Received for publication May 20, 2019; Accepted for publication July 25, 2019
Correspondence to Dr. Hiroshi Kakeya, kakeya-ngs@umin.ac.jp

In addition, it was recently reported that SM can cause fatal hemorrhagic pneumonia in severely immunocompromised patients who have undergone anticancer chemotherapy or stem cell transplantation (2-8). Although some cases of SM hemorrhagic pneumonia have been reported, the exact mechanism by which SM causes hemorrhaging as well as the risk factors involved remain unknown (9). However, due to the very high mortality of SM hemorrhagic pneumonia (2), the urgent detection of the characteristics of the disease is required.

Therefore, we attempted to identify the predictors of SM bacteremia with hemorrhagic pneumonia.

Materials and Methods

Ethics statement

The Ethics Committee of Osaka City University Graduate School of Medicine approved this study, which was performed in accordance with the Declaration of Helsinki. The need for written informed consent was waived owing to the retrospective nature of the study.

Setting and study design

This study was conducted at Osaka City University Hospital, a 980-bed tertiary-care hospital in Osaka, Japan. From January 2008 to December 2017, all patients who had positive blood cultures for SM were included in the study, with each patient being included only once, at the time of the initial blood culture. Data were collected from electronic medical records, and a case-control study design was used.

Variables and definitions

The clinical information acquired from the medical charts included sex; age; baseline disease (hematologic malignancy); hospital stay more than 30 days; polymicrobial bacteremia; neutropenia less than 100/μL at the onset of bacteremia (10); low albumin less than 3.0 g/dL; high C-reactive protein more than 10 mg/dL (10); thrombocytopenia (<5.0/μL) (11); diarrhea; use of a mechanical ventilator, central vein catheter, indwelling catheter, urinary catheter, drainage tube, or artificial dialysis; intensive-care unit stay; history of SM isolation; onset of graft-versus-host disease; history of transplantation (peripheral blood stem cell harvest, cord blood transplantation, bone marrow transplantation); surgery within 30 days; Charlson Comorbidity index; sequential organ failure assessment (SOFA) score; and use of immunosuppression drugs, steroids, antitumor agents, antifungal drugs, or antibacterial drugs within 30 days. Antibacterial drugs included carbapenems, antipseudomonal cephalosporins, non-antipseudomonal cephalosporins, antipseudomonal penicillins, non-antipseudomonal penicillins, quinolones, glycopeptides, aminoglycosides, trimethoprim/sulfamethoxazole, and minocycline.

Patients with SM bacteremia were categorized into 2 groups: the SM bacteremia with hemorrhagic pneumonia group and the SM bacteremia without hemorrhagic pneumonia group. The definition of hemorrhagic pneumonia was as follows: 1) SM isolated from a blood culture, 2) pneumonia developed when the blood culture was positive, 3) pneumonia defined as a new shadow appearing on chest X-ray or computed tomography (CT) with respiratory symptoms such as cough or sputum, 4) continuous appearance of bloody sputum or hemoptysis, and 5) other diseases that manifest as a new shadow on chest X-ray or CT ruled out.

To evaluate the risk factors of hemorrhagic pneumonia, the clinical background characteristcs and treatments were compared between the SM bacteremia with hemorrhagic pneumonia group and the SM bacteremia without hemorrhagic pneumonia group.

Microbiological analyses

Isolate identification and antimicrobial susceptibility were confirmed using the MicroScan WalkAway-96 SI (Beckman Coulter, Brea, USA). The minimum inhibitory concentrations were also determined using the MicroScan WalkAway-96 SI. The results were interpreted according to the 2018 Clinical and Laboratory Standards Institute breakpoints (12).

Statistical analyses

Patient characteristics and outcomes were compared between the SM bacteremia with hemorrhagic pneumonia group and the SM bacteremia without hemorrhagic pneumonia group. Fisher's exact tests were used for univariate comparisons of categorical data, and the Mann-Whitney U test was used for continuous variables. Variables with p values <0.05 in the univariate and nonparametric analyses were assessed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) in order to determine predictors of SM bacteremia with hemorrhagic pneumonia as well as to assess the severity, mortality, and appropriate treatment rate. EZR is a modified version of R commander (version 2.4-0) that includes the statistical functions frequently used in biostatistics. P values <0.05 indicated statistically significant differences.

Results

Patients' clinical characteristics and laboratory findings

The clinical characteristics and laboratory findings of SM bacteremia patients with and without hemorrhagic pneumonia are summarized in Table 1. We identified 36 patients with SM bacteremia, of whom 4 had hemorrhagic pneumonia and 31 did not. One patient was excluded because their information could not be obtained due to the patient being transferred immediately after the blood culture was performed.

The SM bacteremia with hemorrhagic pneumonia group included 3 men and 1 woman, with a median age of 56.2 years. The SM bacteremia without hemorrhagic pneumonia

Table 1. Characteristics of the *Stenotrophomonas maltophilia* (SM) Hemorrhagic Pneumonia Group and Non-SM Hemorrhagic Pneumonia Group.

Variables	with hemorrhagic pneumonia (n=4)	without hemorrhagic pneumonia (n=31)	p value (Fisher's analysis)
Male sex	3 (75%)	19 (61.3%)	1
Age (median)	56.2	59.5	1*
Hematologic malignancy	4 (100%)	12 (38.7%)	0.03
Hospital stay ≥30days	1 (25%)	16 (51.6%)	1
Polymicrobaial bacteremia	2 (50%)	15 (48.4%)	1
Thrombocytopenia (<5.0/μl)	4 (100%)	12 (38.7%)	0.04
Neutropenia(<100μL)	3 (75%)	8 (25.8%)	0.08
Alb <3.0g/dL	3 (75%)	18 (58.1%)	0.6
CRP ≥10mg/dL	3 (75%)	10 (32.3%)	0.1
Use of immunosuppression	2 (50%)	4 (12.9%)	0.1
Use of steroid	2 (50%)	3 (9.7%)	0.09
GVHD	2 (50%)	3 (9.7%)	0.09
Isolation of SM	2 (50%)	12 (38.7%)	1
PBSCH	0 (0%)	1 (3.2%)	1
CBT	1 (25%)	3 (9.7%)	0.4
BMT	1 (25%)	3 (9.7%)	0.4
Antitumor agent	1 (25%)	10 (32.3%)	0.1
Use of antibacterial drugs			
Carbapenems	3 (75%)	18 (58.1%)	0.6
Glycopeptides	3 (75%)	12 (38.7%)	0.3
Antipseudomonal cephalosporins	3 (75%)	15 (48.4%)	0.6
Non-antipseudomonal cephalosporins	0 (0%)	5 (16.1%)	1
Antipseudomonal penicillins	1 (25%)	7 (22.6%)	1
Non-antipseudomonal penicillins	0 (0%)	4 (12.9%)	1
quinolones	3 (75%)	6 (19.4%)	0.04
Aminoglycosides	1 (25%)	6 (19.4%)	1
Trimethoprim/sulfamethoxazole	2 (50%)	7 (22.6%)	0.27
Minocycline	0 (0%)	2 (6.5%)	1
Antifungal drugs	4 (100%)	14 (45.2%)	0.1
Surgery within 30 days	1 (25%)	6 (19.4%)	1
ICU stay	0 (0%)	6 (19.4%)	1
Use of artifical objects			
Mechanical ventilator	0 (0%)	6 (19.4%)	1
Artificial dialysis	1 (25%)	3 (9.7%)	1
Central vein catheter	4 (100%)	16 (51.6%)	0.1
Urinary catheter	2 (50%)	10 (32.3%)	0.6
Indwelling catheter	1 (25%)	10 (32.3%)	1
Drainage tube	0 (0%)	6 (19.4%)	1
Correct empiric antibacterial treatment for SM (in 48 hour)	3 (75%)	6 (19.4%)	0.04
Mortality	4 (100%)	10 (32.3%)	0.02
SOFA score (median)	4.5	3	0.5*
Charlson Comorbidity index (median)	3	2	0.5*
Infection focus			
CRBSI	0 (0%)	9 (29.0%)	
skin and soft tissue	0 (0%)	3 (9.7%)	
pneumonia	4 (100%)	1 (3.2%)	
UTI	0 (0%)	1 (3.2%)	
Intra-abdominal infection	0 (0%)	3 (9.7%)	
undetected	0 (0%)	14 (45.2%)	

*Mann-Whitney U test

Alb: albumin, CRP: C-reactive protein, GVHD: graft versus host disease, PBSCH: peripheral blood stem cell harvest, CBT: cord blood transplantation, BMT: bone marrow transplantation, ICU: intensive care unit, SOFA: sequential organ failure aseessment, CRBSI: catheter-related bloodstream infection, UTI: urinary tract infection

Table 2. Characteristics of the *Stenotrophomonas maltophilia* (SM) Hemorrhagic Pneumonia Group.

case number	age	sex	underlying disease	Charlson's score	SOFA score	WBC (/μL)	Neu (/μL)	Plt ($\times10^4$/μL)	ST pre-administration	quinolone pre-administration	SM isolated from lower airway specimen	susceptibility of LVFX	death	time to death (days)	cause of death
1	61	M	ALL	3	4	<100	<100	3	-	+	+	R	+	3	pneumonia
2	60	M	AML	4	7	1,200	350	2	+	-	-	S	+	5	pneumonia
3	50	M	AML	3	5	<100	<100	2	-	+	+	S	+	9	pneumonia
4	59	F	AML	2	3	<100	<100	3	+	+	+	S	+	43	MOF

SOFA: sequential organ failure assessment, WBC: white blood cell, Neu: neutrophil, Plt: platelet, ST: sulfamethoxazole/trimethoprim, LVFX: levofloxacin, M: male, F: female, ALL: acute lymphoid leukemia, AML: acute myelogenous leukemia, R: resistant, S: susceptible, MOF: multiple organ failure

group included 19 men and 12 women, with a median age of 59.5 years. All patients with SM hemorrhagic pneumonia had hematologic malignancies, diarrhea, and thrombocytopenia. Furthermore, all such patients had positive blood cultures from central venous catheters. Three patients (75%) had a history of using quinolone within 30 days. The characteristics of the SM bacteremia with hemorrhagic pneumonia group are summarized in Table 2. The following factors were significantly more frequent in the SM bacteremia with hemorrhagic pneumonia group than in the SM bacteremia without hemorrhagic pneumonia group: hematologic malignancy, 100% vs. 38.7%, p=0.03; thrombocytopenia, 100% vs. 38.7%, p=0.04; history of using quinolones, 75% vs. 19.4%, p=0.04. The man-to-woman ratio, using the antitumor agent ratio, and the history of stem cell transplantation ratio did not differ markedly between the two groups. There were also no significant differences between the two groups in terms of the age, Charlson Comorbidity index, and SOFA score. In cases of bacteremia with hemorrhagic pneumonia, the onset of hemorrhagic pneumonia and bacteremia is almost simultaneous; it was therefore difficult to judge whether bacteremia had developed from pneumonia or vice versa. The infection focus of the SM bacteremia without hemorrhagic pneumonia group was as follows: nine patients had catheter-related bloodstream infections, and one had pneumonia. The focus of 14 infections could not be identified (Table 1).

Treatment and mortality

In the SM bacteremia with hemorrhagic pneumonia group, although 3 patients (75%) received appropriate empiric antibacterial treatment for SM, all (100%) of the patients died within the hospitalization period. The time interval to death and the causes are listed in Table 2. In contrast, in the SM bacteremia without hemorrhagic pneumonia group, 6 patients (19.4%) received appropriate empiric antibacterial treatment for SM, and 10 patients (32.3%) died within the hospitalization period. While the rate of receiving appropriate empiric antibacterial treatment was significantly higher in the SM bacteremia with hemorrhagic pneumonia group, the mortality was also significantly higher in that group.

Discussion

Our study produced two main results. First, hematologic malignancy, thrombocytopenia, and the pre-administration of quinolones within 30 days might be risk factors for SM bacteremia with hemorrhagic pneumonia. Second, the mortality rate of SM bacteremia with hemorrhagic pneumonia was high. At present, no reports have performed a statistical analysis regarding the risk factors of hemorrhagic pneumonia caused by SM. However, a systematic review was performed on a total of 30 cases of hemorrhagic pneumonia induced by SM (8). In that report, the author observed that severe neutropenia was the most important risk factor for hemorrhagic pneumonia caused by SM, as 25 of 26 patients with hemorrhagic pneumonia caused by SM were also severely neutropenic. In our study as well, 3 of the 4 (75%) SM bacteremia patients with hemorrhagic pneumonia were severely neutropenic (<100 μL), but there were no significant differences between the SM bacteremia with hemorrhagic pneumonia group and the SM bacteremia without hemorrhagic pneumonia group. This maybe be why SM

bacteremia is likely to occur in patients whose immune state is already compromised. Based on similar reasoning, the neutrophil counts were also very low in the SM bacteremia without hemorrhagic pneumonia group. However, our study also suggested that hematologic malignancy may be a risk factor for hemorrhagic pneumonia caused by SM. While previous studies have reported that a majority of patients with SM infections have hematologic malignancy or solid malignancy (13-15), we observed a particularly large proportion of patients with hematologic malignancy, especially in the SM bacteremia with hemorrhagic pneumonia group. The immune conditions due to cancer may be related to the susceptibility to SM infection and aggravation.

It was previously suggested that thrombocytopenia might be related to hemorrhagic pneumonia caused by SM (16). However, the report did not describe the mechanism underlying such a relationship. In our study, thrombocytopenia was also a risk factor for hemorrhagic pneumonia caused by SM. Indeed, all four cases with hemorrhagic pneumonia were accompanied by severe thrombocytopenia (Table 2). This may be simply because patients with severe thrombocytopenia tend to bleed easily.

Why hemorrhagic pneumonia caused by SM is likely to develop in patients who have received quinolone within the last month may be due to the side effects of quinolones. It was reported that the protease produced by SM and coded by the StmPr1 gene degrades the collagen and fibrinogen in the plasma and causes the destruction of fibroblasts *in vitro*. This process might be related to the destruction of the alveolar micro vessels, thereby causing hemorrhagic pneumonia (8, 17). However, it was previously reported that the use of fluoroquinolone carries a risk of tendon rupture and aortic aneurysm (18-20). This is because fluoroquinolones appear to upregulate multiple matrix metalloproteinases, resulting in a reduction in the amount of type I collagen fibrils. As Type I and III collagen are the dominant forms in the aortic wall, quinolones contribute to the destruction of the aortic wall and lead to aortic aneurysms and dissections (18, 21). Quinolone might weaken the wall of alveolar micro vessels too, with the protease produced by SM leading to the destruction of alveolar micro vessels. Furthermore, in hematology patients undergoing chemotherapy or stem cell transplantation, thrombocytopenia may occur at a high rate, and quinolones are also used in these patients as a preventive drug for bacterial infection, sometimes for a long time. If these processes happen at the same time, the probability of hemorrhagic pneumonia occurring might increase. However, this is only a hypothesis, and all of these factors are basically related to hematologic malignancy. We need to verify this hypothesis *in vivo*, such as in an SM-infected mouse model, in the future. Ultimately, the most important risk factor for SM hemorrhagic pneumonia may be hematologic disease.

The mortality in the SM bacteremia with hemorrhagic pneumonia group was significantly higher than in the SM bacteremia without hemorrhagic pneumonia group. We defined "mortality" as death from any cause during hospitalization. Nevertheless, the rate of receiving the correct empiric antibacterial treatment was significantly higher in the SM bacteremia with hemorrhagic pneumonia group than in the SM bacteremia without hemorrhagic pneumonia group in our study. This indicates that hemorrhagic pneumonia caused by SM was a very severe condition. Indeed, the mortality rate of hemorrhagic pneumonia caused by SM has been reported to be 100% (2). It is very difficult to save a patient once hemorrhagic pneumonia develops. Therefore, the early diagnosis and treatment of SM bacteremia is important for preventing the progression to hemorrhagic pneumonia.

Two limitations associated with the present study warrant mention. First, the number of patients was small. As the developmental rate of SM bacteremia with hemorrhagic pneumonia was very low, it was difficult to collect adequate cases. For this reason, we were unable to perform a multivariate analysis. A multi-institutional joint study is needed to obtain enough cases of hemorrhagic pneumonia caused by SM to perform a multivariate analysis. Second, the definition of hemorrhagic pneumonia caused by SM is not consistent. In their studies, Araoka et al. and Mori et al. defined hemorrhagic pneumonia caused by SM as pneumonia with bloody sputum or hemoptysis, and the culture of the sputum or the fluid from the bronchoalveolar lavage should be positive (2, 8). We did not follow this definition, as these criteria cannot eliminate SM colonization of a lower respiratory airway. Using our definition, it is highly likely that identified SM cases are truly pathogenic. As it was reported that the isolation of SM from a blood culture should prompt a careful evaluation of the patient, to differentiate between contamination, colonization, and true blood-stream infection (1), we also need to carefully differentiate a true infection from a false one. In case 2 of SM bacteremia with hemorrhagic pneumonia (Table 2), only the blood culture was positive for SM. In this case, we determined that it was a true infection because the blood culture was positive multiple times, and the sputum culture was not submitted due to the presence of a large amount of sputum blood; no tracheal intubation was performed. To accumulate more cases, the definitions of hemorrhagic pneumonia caused by SM should be integrated.

In conclusion, our study suggested that hematological malignancy, thrombocytopenia, and pre-administration of quinolones within 30 days might be risk factors for hemorrhagic pneumonia in SM bacteremia patients. In addition, the mortality of SM bacteremia with hemorrhagic pneumonia was high in our study. As *S. maltophila* bacteremia in patients with hematologic malignancy, thrombocytopenia, and the pre-administration of quinolones can have a serious outcome, we must treat these patients carefully.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

I appreciate having received the Award of the 61st Annual Conference of The Japanese Association for Infectious Diseases, Central Regional Conference for this research.

References

1. Looney WJ, Narita M, Mühlemann K. *Stenotrophomonas maltophilia*: an emerging opportunist human pathogen. Lancet Infect Dis **9**: 312-323, 2009.

2. Araoka H, Fujii T, Izutsu K, et al. Rapidly progressive fatal hemorrhagic pneumonia caused by *Stenotrophomonas maltophilia* in hematologic malignancy. Transpl Infect Dis **14**: 355-363, 2012.

3. Ortín X, Jaen-Martinez J, Rodríguez-Luaces M, Alvaro T, Font L. Fatal pulmonary hemorrhage in a patient with myelodysplastic syndrome and fulminant pneumonia caused by *Stenotrophomonas maltophilia*. Infection **35**: 201-202, 2007.

4. Pathmanathan A, Waterer GW. Significance of positive *Stenotrophomonas maltophilia* culture in acute respiratory tract infection. Eur Respir J **25**: 911-914, 2005.

5. Fujita J, Yamadori I, Xu G, et al. Clinical features of *Stenotrophomonas maltophilia* pneumonia in immunocompromised patients. Respir Med **90**: 35-38, 1996.

6. Elsner HA, Dührsen U, Hollwitz B, Kaulfers PM, Hossfeld DK. Fatal pulmonary hemorrhage in patients with acute leukemia and fulminant pneumonia caused by *Stenotrophomonas maltophilia*. Ann Hematol **74**: 155-161, 1997.

7. Takahashi N, Yoshioka T, Kameoka Y, et al. Fatal hemorrhagic pneumonia caused by *Stenotrophomanas maltophilia* in a patient with non-Hodgkin lymphoma. J Infect Chemother **17**: 858-862, 2011.

8. Mori M, Tsunemine H, Imada K, Ito K, Kodaka T, Takahashi T. Life-threatening hemorrhagic pneumonia caused by *Stenotrophomonas maltophilia* in the treatment of hematologic diseases. Ann Hematol **93**: 901-911, 2014.

9. Gutierrez C, Pravinkumar E, Balachandran D, Schneider V. Fatal hemorrhagic pneumonia: Don't forget *Stenotrophomonas maltophilia*. Respir Med Case Rep **19**: 12-14, 2016.

10. Harada K, Sekiya N, Konishi T, et al. Predictive implications of albumin and C-reactive protein for progression to pneumonia and poor prognosis in *Stenotrophomonas maltophilia* bacteremia following allogeneic hematopoietic stem cell transplantation. BMC Infect Dis **17**: 638, 2017.

11. Williamson DR, Albert M, Heels-Ansdell D, et al; PROTECT collaborators, the Canadian Critical Care Trials Group, and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Thrombocytopenia in critically ill patients receiving thromboprophylaxis: frequency, risk factors, and outcomes. Chest **144**: 1207-1215, 2013.

12. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; 27th informational supplement. M100-S28. Clinical and Laboratory Standards Institute, Wayne, PA, 2018.

13. Hotta G, Matsumura Y, Kato K, et al. Risk factors and outcomes of *Stenotrophomonas maltophilia* bacteraemia: a comparison with bacteraemia caused by Psudomonas aeruginosa and Acinetobacter species. PLoS One **9**: e112208, 2014.

14. Senol E, DesJardin J, Stark PC, Barefoot L, Snydman DR. Attributable mortality of *Stenotrophomonas maltophilia* bacteremia. Clin Infect Dis **34**: 1653-1656, 2002.

15. Metan G, Hayran M, Hascelik G, Uzun O. Which patient is a candidate for empirical therapy against *Stenotrophomonas maltophilia* bacteraemia? An analysis of associated risk factors in a tertiary care hospital. Scand J Infect Dis **38**: 527-531, 2006.

16. Mori M, Kitagawa T, Sasaki Y, et al. Letal pulmonary hemotthage caused by *Stenotrophomonas maltophilia* pneumonia in a patient with acute myeloid leukemia. Kansenshogaku Zasshi **86**: 300-305, 2012 (in Japanese, Abstract in English).

17. Windhorst S, Frank E, Georgieva DN, et al. The major extracellular protease of the nosocomial pathogen *Stenotrophomonas maltophilia*: characterization of the protein and molecular cloning of the gene. J Biol Chem **277**: 11042-11049, 2002.

18. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ Open **5**: e010077, 2015.

19. Nyyssönen T, Lantto I, Lüthje P, Selander T, Kröger H. Drug treatments associated with Achilles tendon rupture. A case-control study involving 1118 Achilles tendon ruptures. Scand J Med Sci Sports **28**: 2625-2629, 2018.

20. Pasternak B, Inghammar M, Svanström H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. BMJ **360**: k678, 2018.

21. Tsai WC, Hsu CC, Chen CP, et al. Ciprofloxacin up-regulates tendon cells to express matrix metalloproteinase-2 with degradation of type I collagen. J Orthop Res **29**: 67-73, 2011.