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ORIGINAL ARTICLE

Risk factors influencing mortality related to *Stenotrophomonas maltophilia* infection in hematology–oncology patients

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Abstract *Stenotrophomonas maltophilia* infection is of concern in patients with cancer. Antibiotics active against *S. maltophilia* are rarely used in the treatment of febrile neutropenia, making it important to identify the factors influencing mortality in cancer patients with *S. maltophilia* infection. The objective of this study was to analyze the clinical characteristics and outcomes of cancer and hemopathic patients with *S. maltophilia* infection and assess the factors influencing the mortality. The microbiology laboratory records of Erciyes University, Faculty of Medicine Hospital were reviewed to retrospectively identify patients with *S. maltophilia* infection between January 2007 and June 2011. A total of 38 patients (25 male, 13 female) were eligible for the study. The median age of the patients was 53 years. The underlying disease was hematological malignancy and disorders in 76.3 % (29 cases), solid tumors in 15.8 % (six cases), aplastic anemia in 7.9 % (three cases), while 18.4 % (seven cases) were hematopoietic stem cell transplantation (HSCT) recipients. An indwelling central venous catheter was used in 32 cases (84.2 %). Twenty-seven patients (71.1 %) were neutropenic at the onset of infection. Nine patients (23.7 %) were receiving corticosteroid therapy. The overall 14-day mortality rate was 50 %. Three of the patients received empirical antibacterial treatment, and three HSCT recipients received trimethoprim–sulfamethoxazole prophylaxis, which is active against *S. maltophilia*. Severe sepsis (OR 13.24, 95 % confidence interval (CI) 1.62–108.57) and the duration of the treatment (OR 0.73, 95 % CI 0.60–0.90) were related to death based on logistic regression analysis findings. In immunocompromised hematology–oncology patients with severe sepsis, *S. maltophilia* should be considered as a possible cause of infection, and should be given effective empirical antibiotic treatment immediately; the antimicrobial spectrum may be narrowed according to results of antibiotic susceptibility test.

Keywords *Stenotrophomonas maltophilia* · Hematologic malignancy · Solid tumor · Cancer · Severe sepsis · Neutropenia · Mortality

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Introduction

Stenotrophomonas maltophilia is motile, glucose-nonfermentative gram-negative bacilli [1]. It may be obtained from various environmental sources, such as tap water, or contaminated solutions [2]. It is an important nosocomial pathogen, particularly in cancer patients who previously hospitalized and received broad-spectrum antibiotics [1]. It can form biofilm and once growing in biofilm, it is more resistant to phagocytes and antibiotics [3]. The presence of central venous catheter is associated with an increased risk

for *S. maltophilia* infection [4]. *S. maltophilia* is also naturally resistant to imipenem because it produces different types of carbapenemases [5]. The increasing rate of carbapenem usage, particularly in neutropenic patients, leads to the coming out of this bacterium in hospitalized patients. Thus, there is an increase in proportion of *S. maltophilia* among the gram-negative organisms during 1998 to 2004 period [6].

Stenotrophomonas maltophilia is related to bacteremia in cancer patients. Therefore, in cancer patients, usage of broad spectrum antimicrobials, long duration of profound neutropenia and presence of mucositis may increase the risk of bacteremia [7]. In patients with *S. maltophilia* bacteremia, inappropriate initial antibiotic treatment is associated with higher mortality rate, however, attributable mortality rate for bacteremia has found similar to other nosocomial bacteremia [3, 8, 9]. Risk factors for *S. maltophilia* infection include underlying malignancy, the presence of indwelling devices, chronic respiratory disease, immunocompromised host, prior use of antibiotics, and long-term hospitalization or intensive care unit (ICU) stay [10–12].

In the past few years, we have noticed an increasing number of *S. maltophilia* infections in patients with cancer and hematological disorders. Patients with *S. maltophilia* infection were not initially suspected because they did not have conventional risk factors for *S. maltophilia.* Herein, the aim of this study is to determine the factors influencing mortality in cancer or hemopathic patients with *S. maltophilia* infection.

Patients and method

This study was conducted by Erciyes University, Faculty of Medicine Hospitals (1300-beds, tertiary teaching hospital, Kayseri, Turkey). After the approval of local ethics committee, the records of the microbiology laboratory between January 2007 and June 2011 were reviewed to identify the patients with *S. maltophilia* infection, retrospectively.

Definitions

In patients (>16 years) admitted to Hematology and Oncology departments, growing *S. maltophilia* in clinical samples including blood, sputum, bronchoalveolar lavage fluid, urine, and other sterile body fluids were recruited. Only one episode from each patient was included.

Nosocomial infections and sources of infection were defined according to the criteria advised by Centers for Disease Control and Prevention (CDC) [13, 14]. Sepsis, severe sepsis and septic shock were defined by Levy et al. [15, 16].

Prior antibiotic treatment was defined as any antibiotic treatment during the 1 month preceding hospital admission. Neutropenia was defined as peripheral blood neutrophils below 500/mm^3. Therapy was considered empirical if it was initiated no later than 24 h after the specimen from whom the *S. maltophilia* strain was isolated and definitive if it was initiated or continued after the result of the blood culture, and the relevant susceptibility testing was available to the clinicians [14, 17]. Antimicrobial therapy was considered to be appropriate when at least one antibiotic active in vitro against the organism was administered to treat the infection [18]. Proven and possible invasive fungal diseases were defined according to guideline [19]. Cytomegalovirus infection was considered to be detection of viral proteins or nucleic acid in any body fluid or tissue specimen [20]. Aplastic anemia was defined and classified according to guideline [21].

Infection-associated mortality was defined as death of a patient during hospitalization when *S. maltophilia* infection was judged to be the cause of death within 2 weeks of the first positive *S. maltophilia* culture in the absence of other causes of death, such as intracranial hemorrhage, myocardial infarction or pulmonary embolism. Severity of illness was calculated by the Charlson's weighted index of morbidity [22].

Microbiology

The bacteria isolated from samples were identified and antimicrobial susceptibility tests were performed in Erciyes University, Central Laboratory by automated systems according to Clinical and Laboratory Standards Institute (CLSI) guidelines [23].

Statistical analysis

The patients were divided into two groups according to survival status in 14 days after the first positive culture was obtained. All data were analyzed in terms of factors influencing mortality depending on *S. maltophilia*. On base of statistical analysis, Chi-square test or Fisher's exact test were used to analyze categorical data. We employed Mann–Whitney test or Student's *t* test as appropriate to analyze numerical data. Mortality-related factors were detected by binary logistic regression analysis. Odds ratios (ORs) and their 95 % CIs were calculated [24].

A two-sided p value of <0.05 was considered indicative of statistical significance. All analyses were conducted with SPSS software for Windows (version 15.0; SPSS Inc., Chicago, IL, USA).

Results

Stenotrophomonas maltophilia was isolated in 455 of the various clinical samples, 78 of them belonged to 52

patients with cancer between January 2007 and June 2011. Fourteen patients without any clinical symptoms related to *S. maltophilia* were considered as colonization and excluded from the study evaluation, and remaining 38 patients were assessed.

There were 25 males and 13 females, with a median age of 53 years (range 19–79 years). The most common underlying disease with 76.3 % of cases was hematological malignancy. Eighteen (47.4 %) cases were acute myeloid leukemia (AML), others were lymphoma 15.8 % (6 cases), acute lymphoblastic leukemia (ALL) 7.9 % (3 cases), chronic myeloid leukemia (one case), chronic lymphocytic leukemia (one case), severe aplastic anemia 7.9 % (three cases), and solid cancer 15.8 % (six cases). Moreover, seven cases (18.4 %) were hematopoietic stem cell transplantation (HSCT) recipients. Three of them were autologous HSCT patients; four were allogeneic HSCT, and one of them had aplastic anemia, two had AML, and one had MDS. Three HSCT recipients were received trimethoprim–sulfamethoxazole (TMP–SXT) prophylaxis Thirty-two cases (84.2 %) had a central venous catheter and nine patients (23.7 %) were receiving corticosteroid therapy at the beginning of infection. Twenty-seven patients (71.1 %) were neutropenic at the onset of the infection, and 24 (88.9 %) of them had neutrophil which was less than 100 cell/mm^3. Eleven patients (28.9 %) had been admitted to ICU. A concurrent infection was noted for 21 (55.3 %) patients who had probable/proven IFI (12 cases), other gram-negative bacteria infection (six cases), cytomegalovirus infection (three cases). All patients who had a concurrent infection were receiving effective therapy against their concomitant infection diseases. According to the results of CMV PCR and CMV pp65 antigenemia, if patients have adequate number of peripheral blood leukocytes, antiviral therapy was given against CMV. Only three out of 12 patients had proven IFI, and one of three patients died. Demographic characteristics of the patients are shown in Table 1.

The subjects were divided into two groups based on 14-day survival status. Nineteen of them survived and nineteen (50 %) died. Mean survival time were 6.1 days in dead patients versus 244 days survived patients after the detected time of bacteria. Bacteremia was detected in 17 cases (44.7 %) and nine of them (52.9 %) died. Also, ten (58.8 %) of the cases with bacteremia were primary bacteremia, two (11.8 %) patients were associated with pneumonia and five (29.4 %) were associated with central catheter infection. There were no significant differences between the two groups about age, gender, the mean length of hospital stay, receiving chemotherapy, HSCT, receipt of carbapenem antibiotics, and corticosteroid usage, presence of mucositis, central venous catheter and neutropenia (Table 1). The 30-day mortality was 23/38 (60.5 %) as well.

Seventeen patients had no additional infections. There were no significant differences in terms of concurrent infection between survival and death groups. The sources of *S. maltophilia* infection were pneumonia in 14 (36.8 %) cases, urine in 6 (15.8 %), central catheter in 5 (13.2 %), abscess in 3 (7.9 %), and primary bacteremia in 10 (26.3 %). There were no differences in terms of focuses of infection between groups. The crude 14-day mortality rates were 42.9 % (6/14) in pneumonia cases, 60 % (3/5) in catheter infections, and 40 % in primary bacteremia cases.

Nineteen patients (50 %) had severe sepsis, and fifteen (78.9 %) of them died. Severe sepsis was significantly more common in died patients ($p = 0.001$). Logistic regression analysis showed that the relative risk for death increased by 13 (95 % CI 1.61–108.57) times for those patients having severe sepsis.

Twenty-seven (71.1 %) patients received appropriate definitive antibiotic treatment. Eighteen of (66.6 %) them were in survival group and 94.7 % of survived patients received at least an effective antibiotic. The rate of patients received effective antibiotic treatment against *S. maltophilia* was significantly less in died patients than survived ones. Because 11 patients (57.8 %) died by the time the bacteria were identified (before fourth day), eight of them had not received effective antimicrobial treatment against *S. maltophilia.* Ten of 11 patients were neutropenic, all patients had CVC, four patients were in ICU and all patients except one had severe sepsis. Four patients suffered from pneumonia, three had catheter-related blood stream infection (CRBSI), three patients had urinary tract infection and one of them had primary bacteremia. Although only three of 11 received effective empirical treatment to *S. maltophilia*, all patients were received carbapenem antibiotics. The median duration of antimicrobial therapy among 27 patients was significantly shorter in died patients (7 days) than in survived patients (13.5 days).

Three patients who had undergone HSCT were receiving TMP–SXT prophylaxis because of in 100 days after transplantation. The definitive therapy consisted of TMP–SXT in 59.2 % (16 patients), ciprofloxacin in 33.3 % (9 patients), ceftazidime in one and colistin in one patient. Colistin was administered to one patient because it was resistant to TMP–SXT, quinolon, ceftazidime In addition, ten (62.5 %) of survived patients and 6 (37.5 %) of died patients were receiving the TMP–SXT. There were no significant differences in associated with mortality between two groups ($p = 0.071$). Susceptibility rates of *S. maltophilia* against TMP–SXT, quinolone, and ceftazidime were 97.4 % (37/38), 81.6 % (31/38), and 28.6 % (10/35), respectively. However, the colistin susceptibility test has not been performed for *S. maltophilia* isolates routinely.

Table 1 Overall characteristics of patients with *Stenotrophomonas maltophilia* infection

Characteristics	Total, $n = 38$ (%)	Survived, $n = 19$ (%)	Death, $n = 19$ (%)	p
Age (years), mean ± SD	49.6 ± 16.7	48.5 ± 19.2	50.4 ± 15.4	0.740
Gender				
Male	25 (65.8)	13 (68.4)	12 (63.2)	0.732
Female	13 (34.2)	6 (31.6)	7 (36.8)	
Underlying disease				
Leukemia	23 (60.5)	9 (39.1)	14 (60.9)	
AML	18 (47.4)	8 (44.4)	10 (55.6)	
Lymphoma	6 (15.8)	4 (66.7)	2 (33.3)	
Solid tumors	6 (15.8)	4 (66.7)	2 (33.3)	0.431
Aplastic anemia	3 (7.9)	2 (66.7)	1 (33.3)	
HSCT	7 (18.4)	3 (42.9)	4 (57.1)	0.676
Source of infections				
Primary bacteremia	10 (26.3)	6 (60.0)	4 (40.0)	0.422
Pneumonia	14 (36.8)	8 (57.1)	6 (42.9)	
Urinary infection	6 (15.8)	1 (16.7)	5 (83.3)	
Catheter infection	5 (13.2)	2 (40.0)	3 (60.0)	
Abscess	3 (7.9)	2 (66.7)	1 (33.3)	
Charlson' co-morbidity index (mean ± SD)	3.55 ± 2.50	3.89 ± 2.92	3.21 ± 2.01	0.406
Present of neutropenia	27 (71.1)	12 (63.2)	15 (78.9)	0.283
Mean day of neutropenia (mean ± SD)	19.7 ± 15.0	24.7 ± 17.2	15.6 ± 12.1	0.118
Presence of central venous catheter	32 (84.2)	14 (73.7)	18 (94.7)	0.075
Mucositis	12 (31.6)	5 (26.3)	7 (36.8)	0.485
Mean length of hospitalization (days)	26 ± 29	23 ± 16	29 ± 38	0.537
Prior carbapenem usage	34 (89.5)	17 (89.5)	17 (89.5)	1.000
Bacteraemia	17 (44.7)	8 (47.1)	9 (52.9)	0.744
Admission to ICU	11 (28.9)	5 (26.3)	6 (31.6)	0.721
Concurrent infections	21 (55.3)	11 (52.9)	10 (47.1)	0.744
IFI	12 (31.6)	6 (50.0)	6 (50.0)	
CMV	3 (7.9)	2 (33.3)	1 (66.7)	0.942
Gram-negative bacteria	6 (15.8)	3 (50.0)	3 (50.0)	
Presence of severe sepsis	19 (50.0)	4 (21.1)	15 (78.9)	**0.001**
Appropriate definitive antibacterial therapy	27 (71.1)	18 (94.7)	9 (47.4)	**0.001**
Mean duration of therapy (days)	10.7 ± 4.4	12.5 ± 3.3	7.3 ± 4.4	**0.002**

Bold values are statistically significant ($p < 0.05$)

AML acute myeloid leukemia, *HSCT* hematopoietic stem cell transplantation, *ICU* intensive care unit, *SD* standard deviation

Risk factors for mortality

In the univariate analysis, the presence of severe sepsis ($p = 0.001$), appropriate definitive antimicrobial therapy ($p = 0.001$) and duration of antimicrobial therapy ($p = 0.002$) were significantly related to mortality. Binary logistic regression analysis showed that the mortality risk increased by 13 (95 % CI 1.61–108.57, $p = 0.001$) times for those patients having severe sepsis. In the multivariate logistic regression model, presence of severe sepsis and duration of antibiotic therapy were variables that were independently associated with mortality (OR 13.2, 95 % CI 1.61–108.57, $p = 0.001$ and OR 0.7, 95 % CI 0.6–0.9, $p = 0.002$, respectively) (Table 2). Each additional day on antimicrobial therapy duration against *S. maltophilia* decreased the mortality risk by 1.36. However, appropriate definitive antimicrobial therapy was not related with mortality in multivariate logistic regression analysis.

Discussion

Even though *S. maltophilia* is not a highly virulent pathogen, it has emerged as an important nosocomial pathogen

Table 2 Logistic regression analysis of factors associated with mortality from *S. maltophilia*

Variables	*B*	Exp (*B*)	95 % CI
Presence of severe sepsis	2.583	13.237	1.614–108.566
The course of antibiotics therapy	−0.310	0.734	0.598–0.900

CI confidence interval, *SE* standard error

associated with crude mortality rates ranging from 14 to 69 % in immunocompromised hematological patients with bacteremia [25, 26]. In our study, we found that the overall 14-day mortality rate was 50 %, and it was not related to infection sources including pneumonia, catheter infection, urinary tract infection, and primary bacteremia. The crude mortality rates were 42.9 % in pneumonia cases, 60 % in catheter infections, and 40 % in primary bacteremia cases. The important data indicate that 57.8 % of "death" group patients died before bacteria were identified. Only three patients were receiving an antimicrobial therapy against *S. maltophilia* and all patients except one not only neutropenic but also had severe sepsis. It shows considering of *S. maltophilia* infection in patients who have severe sepsis is crucial.

The most common clinical manifestation of *S. maltophilia* infection is pneumonia, followed by blood stream infection and, less frequently, wound and urinary tract infection [3, 27]. The proportion of pneumonia in cancer patients caused by *S. maltophilia* has changed between 5.3 and 34 %, and the mortality rates vary between 25 and 88 % [3, 13, 28, 29]. Pneumonia patients accompanying bacteremia, refractory neutropenia, sepsis syndrome, and delayed appropriate antimicrobial treatment have a high probability of death [9, 25]. Patients who have respiratory tract colonization with *S. maltophilia* were excluded from our study. Concurrent bacteremia was less than 50 % of cases. The rate of pneumonia was found in 36 % of patients, and mortality rate was 42.9 % (6/14) in pneumonia cases, but there were no statistical differences between "death" and "survival" groups.

Usage of CVC is common in cancer patients because they received many chemotherapeutic drugs in short periods. Therefore, a CVC is indwelled in more than 80 % of the cases with *S. maltophilia* infection. In addition, CVC is not only a risk factor for *S. maltophilia* bacteremia but also an important source of infection. Although approximately 84 % of our patients had a CVC, the source of infection was central catheter in 5 (13.2 %) of patients and primary bacteremia in 10 (26.3 %). Bouktour et al. [30] reported that 73 % of bacteremic cancer patients were associated with catheter-related bacteremia, but only one-third of these patients were definite diagnosed. Also, *S. maltophilia* is independently factor associated with CRBSI in cancer patients [31]. Nosocomial bacteremia, prior antibiotic therapy, immunosuppressive therapy and neutropenia are also clinical characteristics associated with CVC-related *S. maltophilia* bacteremia [25]. The rates of death attributed to *S. maltophilia* bacteremia are 11 % in patients who have definite CR-BSI and 57 % in patients who have secondary BSI [30]. The mortality rates were 60 % in our patients who had catheter infection, 40 % in primary bacteremia cases. HSCT recipients are at a high risk for infection as a result of prolonged neutropenia and break of the muco-cutaneous barrier. In these patients, when catheter-related infection is diagnosed, removal of the CVC and appropriate antibiotic therapy is crucial for infection control [11, 29, 31]. In our patients, there were no significant differences in terms of presence of mucositis and neutropenia between groups.

Many studies have been reported that risk factors for *S. maltophilia* infection include underlying malignancy, the presence of CVC, chronic respiratory disease, immunocompromised host, prior use of antibiotics, and long-term hospitalization or ICU stay. In cancer patients, the frequency of *S. maltophilia* infections is related to prolonged neutropenia, admission to ICU, increased to need for vasopressor, CVC presence and mucositis [10–13, 28, 32].

In our data, it was seen that although the rate of neutropenic patients was 71.1 %, there was no significant difference between "death" and "survival" groups in terms of frequency of neutropenia. Risk factors for *S. maltophilia* infection-associated mortality include malignancy, severe septic shock, and organ failure [25, 33]. In our study, risk factors for mortality were found severe sepsis and duration of appropriate antibiotic therapy. The relative risk of death has increased by 13.2 times in those patients having severe sepsis. Each additional day on antimicrobial therapy's duration against *S. maltophilia* decreased the mortality risk by 1.36.

Broad spectrum antibiotics including carbapenems were started to patients with neutropenic fever according to guidelines [34]. Many of the antimicrobial agents are not effective against *S. maltophilia*. It is important that the proportion of *S. maltophilia* among gram-negative bacteria in cancer patients has increased during last decade [27]. A meta-analysis is reported that the mortality rate of *S. maltophilia* infection is high; moreover, patient type and initial clinical condition of patient are risk factors [33]. Some studies noticed that independent predictors for fatal outcome is inadequate empiric antibiotic therapy, septic shock [9, 13, 35] but the meta-analysis has shown that data are insufficient to confirm that appropriate antimicrobial treatment reduces mortality rates [33]. Our data have shown that there was a statistical difference between "death" and "survival" groups in terms of receiving

appropriate antimicrobial therapy, but it was not related to mortality in logistic regression analysis.

TMP–SMX which is a bacteriostatic compound is used in the treatment of *S. maltophilia* infections [36]. Results from the SENTRY Antimicrobial Surveillance Program in 2004 were reported a level of resistance to TMP–SMX of 3.8 % for *S. maltophilia* [25, 37]. The resistance to *S. maltophilia* is rising and treatment is challenging. TMP–SXT remains the most active agent in many clinical settings; ticarcillin–clavulanic acid, ceftazidime, moxifloxacin, tigecycline, and colistin are alternatives. The safety and efficacy of an inhaled aminoglycoside and colistin plus systemic antibiotic therapy are under investigation [25, 38]. In our study, TMP–SMX was given to 14 of 27 (59.2 %) patients as first line therapy against *S. maltophilia*. There were no significant differences in terms of TMP–SMX usage between "death" and "survival" patients. Susceptibility rate of *S. maltophilia* against TMP–SMX was 97.4 % (37/38).

Our study has some limitations. It includes a small number of patients, and retrospective study. It was not evaluated in terms of many viral etiologies of the patients with pneumonia, except CMV. It is difficult to know true diagnosis of immunocompromised patients, because antimicrobial therapies must be started immediately, mixed bacterial–fungal infections may also occur, and to make some diagnostic procedures may threat life of patients due to thrombocytopenia, moving challenges in hospital, risk of infections.

In some health care centers, where *S. maltophilia* infection has infrequently been, prediction of *S. maltophilia* infection is very difficult. In cancer patients with severe sepsis, *S. maltophilia* should be considered as a cause of infection, and should be given effective empirical antibiotic therapy immediately; then, antimicrobial spectrum may be narrowed according to results of antibiotic susceptibility test.

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