Five Years Surveillance of Nosocomial *Stenotrophomonas maltophilia* Infections in Gazi University Hospital

Gazi Üniversitesi Tıp Fakültesi Hastanesinde Beş Yıllık Nozokomiyal *Stenotrophomonas maltophilia* Enfeksiyonu Sürveyansı

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ABSTRACT Objective: The aim of this study was to evaluate the epidemiology of Stenotrophomonas maltophilia infections in the Gazi University Hospital. **Material and Methods:** The incidence, clinical characteristics, antimicrobial susceptibility patterns and outcomes of nosocomial S. maltophilia infections during a five years period (2003-2007) were retrospectively analyzed. **Results:** Eighty-nine cases with nosocomial *S. maltophilia* infection were enrolled in the study. S. maltophilia was identified from 1.6% of the nosocomial isolates. S. maltophilia infections were seen mostly in intensive care units (ICU) and the hematology department. Nosocomial S. maltophilia infection incidence was 0.6 per 1000 admissions. Pneumonias were the most common nosocomial infections, followed by bloodstream infections. The crude mortality rate was 50.6%. Stay in ICU, increased age, prolonged hospitalization, using invasive procedures, and the presence of pneumonia were significantly higher in fatal cases. The most active antimicrobial agents against *S. maltophilia* were trimethoprim-sulfamethoxazole, ciprofloxacin, and cefoperazone-sulbactam. **Conclusions:** The incidence of S. maltophilia infections did not significantly change during the study period. The mortality rate was higher in ICUs. Pneumonias were the most common nosocomial infections with a high mortality rate. The high resistance rates for many currently available broad-spectrum antibiotics and its known association with prior antibiotic use indicates the importance of rational antibiotic use and regular infection surveillance in the hospital, especially in ICU settings.

Key Words: Infections, nosocomial; *Stenotrophomonas maltophilia*; epidemiology

ÖZET Amaç: Bu çalışmada Gazi Üniversitesi Tıp Fakültesi Hastanesinde gelişen Stenotrophomonas maltophilia enfeksiyonlarının epidemiyolojik özellikleri incelenmiştir. **Gereç ve Yöntemler:** 2003-2007 yılları arasındaki beş yıllık süre içinde gelişen nozokomiyal S. maltophilia enfeksiyonlarının insidansı, klinik özellikleri, antimikrobiyal duyarlılıkları ve sonuçları retrospektif olarak analiz edilmiştir. **Bulgular:** Çalışmada toplam 89 nozokomiyal S. maltophilia olgusu yer almıştır. S. maltophilia, nozokomiyal izolatların %1.6'sından izole edilmiştir. S. maltophilia enfeksiyonları en sık yoğun bakım üniteleri ve hematoloji bölümünde gözlenmiştir. Nozokomiyal S. maltophilia insidansı her 1000 yeni yatan hasta için 0.6 olarak saptanmıştır. Pnömoniler en sık saptanan nozokomiyal enfeksiyon olmuştur; bunu kan dolaşımı enfeksiyonları takip etmiştir. Kaba mortalite oranı %50.6 olarak belirlenmiştir. Yoğun bakım ünitesinde yatış, ileri yaş, hastanede uzun süre yatma, invaziv girişimlerin uygulanması ve pnömoni varlığı fatal olgularda anlamlı derecede yüksek saptanmıştır. Trimetoprim-sülfametoksazol, siprofloksasin ve sefoperazon-sulbaktamın S. maltophilia'ya karşı en etkili antimikrobiyal ilaçlar olduğu bulunmuştur. **Sonuçlar:** Çalışma süresi boyunca nozokomiyal S. maltophilia enfeksiyonlarının insidansı istatistiksel olarak değişiklik göstermemiştir. Yoğun bakım ünitelerinde mortalite yüksek saptanmıştır. Pnömoniler en sık gözlenen ve mortalitesi yüksek enfeksiyonlar olmuştur. Bilinen antibiyotiklere direnç oranlarının yüksek olması ve bu durumun önceden antibiyotik kullanımı ile ilişkisinin olması antibiyotiklerin akılcı kullanımının ve düzenli sürveyansın önemini ortaya koymaktadır.

Anahtar Kelimeler: Nozokomiyal enfeksiyon; *Stenotrophomonas maltophilia*; sürveyans

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Recently, *Stenotrophomonas maltophilia* has become one of the most important nosocomial pathogens in a hospital setting and it has been increasingly isolated from immunosupressed as well as immunocompetent patients.[1,2] Prolonged hospitalization and admission to an intensive care unit (ICU), invasive procedures such as central venous catheter (CVC) and mechanical ventilation (MV), prior exposure to antimicrobial agents, underlying malignancy and neutropenia are major risk factors for *S. maltophilia* infections.[1] This microorganism is associated with a wide variety of infections, including bloodstream, respiratory, urinary tract, skin and soft tissue, intraabdominal, and central nervous system infections.[3] The high mortality due to *S. maltophilia* infections and the high levels of intrinsic or acquired resistance to different antimicrobial agents among this species may challenge the clinicians in the timely appropriate management of these infections.[4,5]

In this retrospective study, we analyzed the incidence, clinical characteristics, antimicrobial susceptibility and outcomes of nosocomial *S. maltophilia* infections during the period 2003 to 2007 in our institution.

MATERIAL AND METHODS

Gazi University Hospital is a 1000 bed tertiary care teaching hospital in Ankara, Turkey. From January 2003 to December 2007, all patients with nosocomial infection (NI) due to *S. maltophilia* were included in the study. The data were obtained from infection control committee records. Nosocomial infection surveillance was performed actively based on both laboratory and patient records during the period. The diagnosis of NI was made according to the criteria of the Centers for Diseases Control and Prevention (CDC).[6] The following data were collected and analyzed: age, sex, wards, duration of hospitalization, prior antibiotic use within 30 days, neutropenia (less than 500 neutrophils per mm^3), immunosupressive therapy including corticosteroids, invasive procedures like mechanical ventilation, presence of central venous catheter, urinary catheter and drainage catheter more than 48 hours, tracheostomy, endoscopy, hemodialysis, and underlying diseases of the patients (malignancy, chronic liver disease, solid organ transplantation, diabetes mellitus, trauma), the type of NI, microbiological data and outcome.

Microorganisms were identified by the BBL Crystal Enteric/Nonfermenter ID Kit (Becton Dickinson, USA). The in vitro activities of antimicrobial agents were tested against the clinical isolates of *S. maltophilia* using the disk diffusion method according to the Clinical Laboratory Standards Institute (CLSI) criteria.[7]

The statistical analysis of the data was performed using the SPSS version 11.5 software package. Categorical variables were analyzed using chi-square or Fisher's exact tests where appropriate. Student's t-test was used for comparison of continuous variables. Statistical significance was set at a p value of < 0.05.

RESULTS

During the study period, *S. maltophilia* was isolated from 89 patients as a causative agent of NI. *S. maltophilia* was the etiological agent in 1.6% of NI isolates, and in 2.3% of gram-negative microorganisms. *S. maltophilia* infections developed mostly in ICUs and hematology-oncology departments. NI incidence was 30.5 per 1000 admissions and nosocomial *S. maltophilia* infection incidence was 0.6 per 1000 admissions. There was no significant change in the incidence of *S. maltophilia* infection between the years (p=0.789). The incidence of *S. maltophilia* infections, its percentage among nosocomial pathogens, wards, and type of NIs by years were shown in Table 1.

Male/female ratio was 1.38; mean age was 46.2 ± 26.5 years (median 54 years). Mean duration of hospitalization was 31.5 ± 26.3 days (median 24 days). There was an accompanying pathogen in 17.9% of *S. maltophilia* (n= 16) infections: 5 *Acinetobacter baumannii*, 4 *Staphylococcus aureus*, 4 *Escherichia coli*, 2 *Klebsiella* spp. and 1 *Enterobacter* spp. The crude mortality rate was not significantly different between the patients with and without polymicrobial infection (p=0.166).

The crude mortality rate was 24.3% for all NIs, and 50.6% for *S. maltophilia* infections (p=0.001).

TABLE 1: Incidence of *Stenotrophomonas maltophilia* infections, isolation percentages, wards, and infection types by years.

	2003	2004	2005	2006	2007	Total
No. of *S. maltophilia* isolates	12	19	15	22	21	89
Incidence (per 1000 admission)*	0.47	0.68	0.53	0.70	0.60	0.60
% of *S. maltophilia* among NI isolates	1.4	1.9	1.1	1.4	1.4	1.6
% of *S. maltophilia* among gram-negative isolates	2.4	2.8	1.8	2.2	2.3	2.3
Wards, n (%)						
Medical wards	6 (6.8)	9 (10.1)	12 (13.5)	8 (9)	8 (9)	43 (48.2)
Surgical wards	1 (1.1)	2 (2.2)	0	2 (2.2)	1 (1.1)	6 (6.8)
Intensive care units	5 (5.6)	8 (9)	3 (3.4)	12 (13.5)	12 (13.5)	40 (45)
Type of NI, n (%)						
Pneumonia	3 (3.4)	8 (9)	9 (10.1)	6 (6.8)	12 (13.5)	38 (42.6)
Bloodstream infection	6 (6.8)	6 (6.8)	2 (2.2)	11 (12.4)	3 (3.4)	28 (31.5)
Urinary tract infection	-	1 (1.1)	3 (3.4)	1 (1.1)	4 (4.5)	9 (10.1)
Surgical site infection	2 (2.2)	3 (3.4)	-	2 (2.2)	1 (1.1)	8 (9)
Skin-soft tissue infection	1 (1.1)	1 (1.1)	1 (1.1)	2 (2.2)	1 (1.1)	6 (6.8)
TOTAL, n (%)	**12 (13.5)**	**19 (21.3)**	**15 (16.9)**	**22 (24.7)**	**21 (23.6)**	**89 (100)**

* p= 0.789.

NI, nosocomial infection

Stay in ICU, increased age, prolonged hospitalization, using invasive procedures such as mechanical ventilation, endoscopy, tracheostomy, central venous catheterization and existence of pneumonia were significantly higher in fatal cases. We did not attempt to analyze the independent risk factors related with mortality in this study, as it was not a case-control study and because of its retrospective design. Only, we analyzed to find out any difference for the clinical and demographic features among the patients survived and died. The demographic and clinical characteristics of patients according to the mortality status were shown in Table 2. The most commonly used prior antibiotics were carbapenems, quinolones, penicillins, third generation cephalosporins, and aminoglycosides in the patients. A statistical analysis regarding the antibiotic classes was not performed because most of the patients had been treated with at least two classes of antibiotics. Carbapenems were used in 21 of 29 (72.4%) patients who received prior antibiotic treatment.

The antimicrobial susceptibility of *S. maltophilia* isolates was summarized in Table 3. The most active antimicrobial agents were trimethoprim-sulfamethoxazole (TMP-SMZ), ciprofloxacin, and cefoperazone-sulbactam. Resistance to carbapenems and aminoglycosides were over 70% in the study. Seventy-three percent of the isolates were resistant to at least three different antibiotic groups.

DISCUSSION

S. maltophilia has emerged as an important nosocomial pathogen in many institutions over the past 15 years. Increased numbers of immunocompromised and critically ill patients, as well as increased use of carbapenems, were found to be associated with emerging rates of nosocomial *S. maltophilia* infections.[8,9] Epidemic occurrence of *S. maltophilia* infections also appears to be increasing in many centers. Most of the studies were run after perceived increase in the incidence. In the SENTRY Antimicrobial Surveillance Programme, epidemic clusters of *S. maltophilia* isolated from pneumonias and bloodstream infections were detected in some medical centers.[10] In a study by Del Toro et al, however, the incidence was lower, ranging from 3.4 to 12.1 cases per 10.000 discharges, with no apparent clusters of cases.[11] Meyer et al found a significant decrease in the incidence density of *S. maltophilia* infections in ICUs during a 4-year pe-

TABLE 2: The demographic and clinical characteristics of 89 patients according to mortality status.

Characteristic	No. (%) of patients			p
	Survived (n= 44)	Mortality (= 45)	Total (n= 89)	
Sex, male/female	28/16	23/22	51/38	0.232
Age, mean + SD (year)	40.5 ± 25.6	51.8 ± 24.5	46.2 ± 26.5	0.010
Setting, ICU/non-ICU	10 (22.7)	33 (73.3)	43 (48.3)	0.001
Duration of hospitalization (days)	25.8 ± 24.5	37.5 ± 27.1	31.5 ± 26.3	0.244
Underlying diseases/risk factors				
Neutropenia	9 (20.4)	6 (13.3)	15 (16.8)	0.370
Malignancy	21 (47.7)	11 (24.4)	32 (35.9)	0.022
Immunosupressive therapy	9 (20.4)	3 (6.6)	12 (13.4)	0.069
Prior antibiotic use	13 (29.5)	16 (35.5)	29 (32.5)	0.545
Tracheostomy	3 (6.8)	16 (35.5)	19 (21.3)	0.001
Endoscopy	5 (11.3)	21 (46.6)	26 (29.2)	0.001
Hemodialysis	1 (2.2)	5 (11.1)	6 (6.7)	0.203
Mechanical ventilation	10 (22.7)	35 (77.7)	45 (50.5)	0.001
Central venous catheter	31 (70.4)	44 (97.7)	75 (84.2)	0.001
Urinary catheter	15 (34)	36 (80)	51 (57.3)	0.001
Drainage catheter	8 (18.1)	6 (13.3)	14 (15.7)	0.530
Chronic liver disease	0	4 (8.8)	4 (4.4)	0.117
Solid organ transplant	2 (4.5)	2 (4.4)	4 (4.4)	1.000
Diabetes mellitus	6 (13.6)	7 (15.5)	13 (4.6)	0.798
Trauma	0	3 (6.6)	3 (3.3)	0.242
Type of infection				
Pneumonia	11 (25)	27 (60)	38 (42.6)	0.001
Bloodstream infection	14 (31.8)	14 (31.1)	28 (31.4)	0.943
Urinary tract infection	8 (18.1)	1 (2.2)	9 (10.1)	0.031
Surgical site infection	7 (15.9)	1 (2.2)	8 (8.9)	0.059
Skin-soft tissue infection	4 (9)	2 (4.4)	6 (6.7)	0.651

ICU, intensive care unit

riod, even though total antibiotic use and carbapenem use increased slightly.[12] Studies reporting increasing *S. maltophilia* incidence seem to be very individual in centers. In our study, *S. maltophilia* incidence was 1.6 per 1000 admissions and there was no significant increase by years. *S. maltophilia* was responsible for 1.6% of nosocomial isolates and 2.3% of gram-negative microorganisms.

Pneumonia and bloodstream infections are the most common manifestations of *S. maltophilia* infections.[3,4] In the SENTRY Programme, the number of respiratory *S. maltophilia* isolates was fourfold higher than bloodstream isolates, and an increasing trend in the incidence of respiratory tract infections was observed in Europe.[10] In our hospital, similarly, 38% and 28% of *S. maltophilia* isolates were recovered from pneumonias and bloodstream infections, respectively. Pneumonias were more prevalent in ICUs related to mechanical

TABLE 3: Antimicrobial resistance rates of *S. maltophilia* isolates (n= 89).

Antibiotics	Resistance (%)
Amikacin	73
Amoxycilline-clavulanic acid	73
Imipenem	79.8
Meropenem	73
Gentamycin	76
Piperacillin-tazobactam	43.7
Ceftazidime	45.1
Ceftriaxone	76.5
Ciprofloxacin	22.5
Cefoperazone-sulbactam	26.7
Trimethoprim-sulfamethoxazole	21.9
Cefepime	55.7

ventilation, and bloodstream infections were most common in patients with hematological malignancy and immunosupression in medical wards.

Pneumonia and bacteremia are the most common clinical conditions associated with high mortality. The mortality of pneumonias is reported to be 40-50% in cancer patients and 23% in critically ill trauma patients. Crude and attributable mortalities of *S. maltophilia* bacteremia ranged from 14 to 69% and 12.5 to 41%, respectively.[1] In our study, crude mortality was 71% in pneumonias, and 50% in bloodstream infections. Since many patients have significant underlying diseases, the proportion of deaths directly attributable to *S. maltophilia* infections remains unclear. Most of the patients were ICU patients or patients with underlying hematological malignancies, which were considered the most significant confounding factor in high mortality. In a study performed on critically ill trauma patients, the mortality rate of *S. maltophilia* ventilator-associated pneumonia (VAP) was not different from the rate of VAP caused by other gram-negative bacteria and the clinical presentation of pneumonia was similar in both groups.[13]

The crude mortality of *S. maltophilia* infections was 50.6% in our study. The mortality rate was higher among the patients in ICUs ($p<0.001$). This may be attributed to the severity of underlying diseases of patients, excessive use of invasive procedures as well as broad-spectrum antibiotics in ICUs. In fact, the use of invasive procedures such as mechanical ventilation, central venous catheters, tracheostomy and endoscopy were significantly higher in fatal cases in our study. Our results were similar to those in the study by Nicholson et al, in which they found higher mortality rates among ICU patients compared to non-ICU patients (44% vs 4.8%).[14] In another study by Caylan et al, crude mortality in patients with *S. maltophilia* was reported to be 25%.[15]

Antimicrobial test results revealed that the most active antimicrobial agent was TMP-SMZ with a 21.9% resistance rate. The rate of resistance to TMP-SMZ ranges from 0–6% in Canada and Latin America to 3–19% in Europe.[10] Nevertheless, the resistance rate is higher in certain centers as reported to be approximately 30%.[15,16] *S. maltophilia* is intrinsically resistant to carbapenems and in vitro activity of cephalosporins against *S. maltophilia* is limited due to beta-lactamase production and low beta-lactam activity. Thus, these agents cannot be recommended in the empirical treatment of *S. maltophilia* infections.[5] Resistance to imipenem, meropenem, ceftazidime, cefepime, and ceftriaxone was 79.8%, 73%, 45.1%, 55.7%, and 76.5%, respectively. Resistance to combinations with beta-lactamase inhibitors, piperacillin-tazobactam and cefoperazone-sulbactam, were lower than for other beta-lactam antibiotics in the study. Ciprofloxacin has shown variable activity against *S. maltophilia* isolates ranging from 13.1 to 92%.[16,17] Newer fluoroquinolones such as moxifloxacin and levofloxacin seem to be more effective on clinical strains of *S. maltophilia*.[5,16] Resistance to ciprofloxacin, which was the second most active agent against *S. maltophilia* in our study, was 22.5%.

In conclusion, although the incidence of *S. maltophilia* infections are reported to be increasing in some institutions, our study revealed that the incidence was stable during the five-year period in our hospital. *S. maltophilia* is considered an important nosocomial pathogen, not less important than the other gram-negative organisms, with high crude mortality rates, especially in the ICU setting and in patients with pneumonia. However, *S. maltophilia*, unlike other gram-negative microorganisms, is resistant to widely used antimicrobial agents to treat serious infections including carbapenems and excessive use of these antibiotics is well known to increase the risk of *S. maltophilia* infection. Resistance rates to antimicrobial agents were high except for TMP-SMZ and ciprofloxacin in our study as well. Therefore, both the rational use of broad-spectrum antibiotics including carbapenems and regular surveillance of *S. maltophilia* infections might be the most important considerations in hospital settings.

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