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Original Article

Antibiotic sensitivity of *Stenotrophomonas maltophilia* in a 5-year period and investigation of clonal outbreak with PFGE

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Abstract

Introduction: *Stenotrophomonas maltophilia,* which is able to form a biofilm, has mostly been related to catheters when it is the agent in hospital infections; these infections generally present as bacteremia and pneumonia, which may progress with complications and result in death.

Methodology: The study included 153 *S. maltophilia* strains isolated from clinical samples sent to our hospital laboratory between 1 January 2014 and 30 June 2018. The bacteria were identified and their antibiotic sensitivity was determined using the VITEK-2 automated system. PFGE (Pulsed Field Gel Electrophoresis): The strains isolated from 34 patient clinical samples and from 1 patient bedcover were taken for PFGE examination.

Results: The TMP/SXT and levofloxacin sensitivity of 153 *S. maltophilia* strains was examined. TMP/SXT resistance was determined to be 39% and levofloxacin resistance at 5%. Among 35 *S. maltophilia* strains, seven genotypes were identified using the PFGE method. While three strains showed a specific genotype profile, the other 32 were determined to consist of four clusters. The cluster rate was therefore 91.4% (32/35).

Conclusions: There was a clonal relationship between the vast majority of the 35 *S. maltophilia* isolates, which suggests that there was a cross-contamination problem in the hospital. One strain (#4) was identified by dendrogram analysis showed a high rate of similarity to the other strains and was determined to be the common source of the cross-contamination.

Key words: Pulsed Field Gel Electrophoresis; clonal outbreak; antibiotic sensitivity.

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Introduction

Stenotrophomonas maltophilia was first isolated from pleural fluid in 1943 and has recently acquired increasing importance in relation to hospital infections and opportunistic infections [1]. A high incidence of *Stenotrophomonas maltophilia* infections is seen in those who have risk factors such as prolonged stay in hospital, admission to intensive care unit, chronic respiratory tract disease, broad spectrum antibiotic use, malignancy, immune suppression, impaired mucocutaneous barrier (such as mechanical ventilation, catheter intervention, tracheotomy, peritoneal dialysis), or prematurity [2]. As *Stenotrophomonas maltophilia* is able to form a biofilm, when it is the agent in hospital infections, it has mostly been found in relation to catheters in hospital infections. These infections generally present as bacteremia and pneumonia, which progress with complications and can result in death. *S. maltophilia* is intrinsically resistant to many antibiotics because it has pulse pump encoding genes and the enzyme that can inactivate beta lactamase, aminoglycoside, acetyl transferase and erythromycin. As it has shown resistance to many broad-spectrum antibiotics, including carbapenems, the treatment options for *S. maltophilia* infections are limited [3]. These bacteria develop resistance to other anti-bacterials through mutations or transfer of genetic material between species in addition to their existing mechanisms [4].

In the past, determination of epidemiological relationships among nosocomial pathogens isolated from different sources was based on comparisons of phenotypic characteristics such as biotype, serotype, types of bacteriophage or bacteriocin, and antimicrobial sensitivity profiles. With developments in new DNA-based technologies and molecular analysis applications,

this approach has change during the last 20 years. DNA-based molecular typing is done using *Pulsed Field Gel Electrophoresis* (PFGE) and other restriction-based methods, plasmid analysis, and polymerase chain reaction (PCR) typing methods [5-7].

The aims of this study were to determine the resistance rates of *S. maltophilia* strains isolated in our hospital throughout a 5-year period, to evaluate its importance as an agent of infection, and to determine the clonal relationships among strains using the PFGE method.

Methodology

The local ethics committee approved the study in issue number 33, dated November 07, 2018.

Bacterial identification and antibiotic sensitivity testing

The study included 152 *S. maltophilia* strains isolated from clinical samples sent to the Microbiology Laboratory of Kahramanmaraş Necip Fazil City Hospital between 1 January 2014 and 30 June 2018. These strains were evaluated as the infection agents. One more isolate of *S. maltophilia* strain was recovered from the bedcovers of a patient in Anesthesia Reanimation Intensive Care Unit (AICU) in the same time period, after examination of 20 environmental samples taken from different surfaces. The blood cultures were incubated for 7 days in the BacT/ALERT (bioMerieux, Marcy l'Etoile, France) automated blood culture system. Urine samples were implanted in 5% sheep blood and eosin methylene blue media, and other samples in 5% sheep blood, eosin methylene blue, and chocolate media. The resulting bacteria were identified and their antibiotic sensitivity determined using the VITEK-2 automated system (bioMerieux, Marcy l'Etoile, France).

Trimethoprim/sulfamethoxazole (SXT) was selected as report group A and levofloxacin as group B in the Clinical and Laboratory Standards Institute M100-S23 test of *S. maltophilia* sensitivity [8].

PFGE (Pulsed Field Gel Electrophoresis

For the identification of the bacteria and determination of antibiotic sensitivity, the 152 patient samples and the *S. maltophilia* strain recovered from the environment sample were stored in beaded storage medium (Microbank, Ontario, Canada) at -20˚C until assayed.

All the strains kept in the storage media, which were thought to have caused outbreaks in 2015-2016 were implanted in tryptic soy broth and incubated in an aerobic environment at 37˚C for 24-48 hours. The strains produced from 34 patient clinical samples and from 1 patient bedcover were taken for PFGE examination. Bacteria which did not proliferate after being in storage were excluded from the PFGE study.

Strains were subcultured in nutrient agar and incubated for 18 hours at 37°C. The cells were collected and then resuspended in 3 mL of SE buffer (75 mM NaCl, pH 8.0; 25 mM EDTA pH 8.0). The absorbance of the suspended bacteria was adjusted to 1.1 absorbance at 595 nm. Then, 1.5 % SeaKem® Gold agarose dissolved in TE buffer (10 mM Tris, 0.1 mM EDTA, pH 8.0) was inserted into plug moulds (10×5×1.5 mm). Each plug was placed into a 5-ml tube containing 1 mL of lysis buffer (50 mM Tris-HCl [pH 8.0], 50 mM EDTA [pH 8.0], 1% lauroyl sarcosine) and the tubes were incubated overnight at 55°C in a water

Table 1. Distribution of *Stenotrophomonas maltophilia* strains among clinical wards.

Wards/material	Blood culture n (%)	Tracheal aspirate n (%)	Wound culture n (%)	Urine culture n (%)	Other cultures n (%)	Environment culture	Total strains (%)
Anaesthesia ICU	70	17	1	1	-	1	90 (59)
Internal ICU	6	3	-	-	-	-	9 (6)
Coronary ICU	3	-	-	-	-	-	3 (2)
CVD ICU	7	2	-	-	-	-	9 (6)
General surgery ICU	2	-	-	-	-	-	2 (1.3)
Burns ICU	1	-	6	-	-	-	7 (4.6)
Neurology ICU	4	2	-	1	-	-	7 (4.6)
General surgery ward	-	2	3	-	-	-	5 (3)
Internal ward	1	-	-	-	-	-	1
Fever ward	1	-	2	1	-	-	4 (2.6)
Palliative care unit	-	1	1	2	-	-	4 (2.6)
Wound care unit	-	-	3	-	-	-	3 (2)
Other wards	-	1	4	-	4	-	9 (6)
Total	**95 (62)**	**28 (18)**	**20 (13)**	**5 (3.2)**	**4 (2.6)**	**1**	**153 (100)**

ICU: intensive care unit, n: number.

bath. Each plug was then placed in 1 mL of TE buffer, and washed for 20 min four times. After digestion with endonuclease *Xba*I (30 U), restriction fragments were resolved by 1% PFGE agarose gels using the CHEF-DRII system (BioRad Laboratories, Nazareth, Belgium). The electrophoresis conditions were as follows: pulse times were increased from 5 to 15 s over 10 hours at 6 V/c with a second increase from 15 to 60 s over 11 hours at 6 V/cm at 14°C. In the evaluation of the clonal relationships, the criteria recommended by Tenover *et al*. were used [9-10].

Results

The distribution of 152 *S. maltophilia* strains isolated from various clinical samples sent to the Microbiology Laboratory of Kahramanmaraş Necip

Figure 1. The distribution of *Stenotrophomonas maltophilia* strain according to the years.

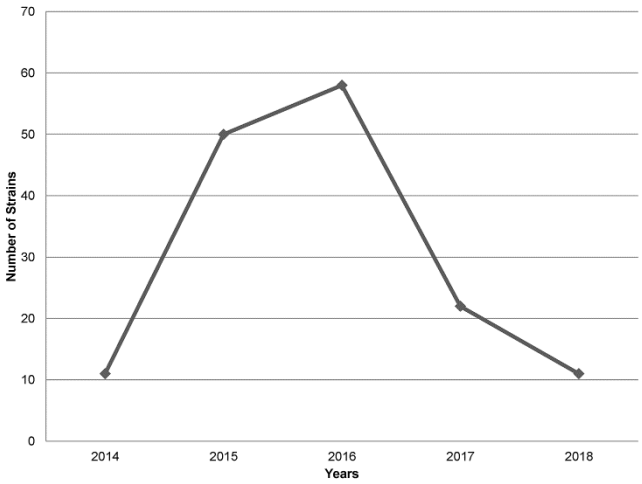


Table 2. The PFGE types and epidemiological data of the *Stenotrophomonas maltophilia* isolates.

ID strain	PFGE type	Source	Ward	TMP/SXT	levofloxacin	isolation date
1	A	Pus culture	Infectious diseases service	S	S	04.08.2016
2	B	Pus culture	Surgery service	S	S	04.11.2016
3	C	Endotracheal-aspiration culture	Medical care unit	R	S	08.02.2016
4	C	Environment culture	Anesthesia intensive care unit	R	S	12.02.2016
5	D	Blood culture	Anesthesia intensive care unit	R	S	16.02.2016
6	D	Blood culture	Anesthesia intensive care unit	S	S	17.02.2016
7	D	Blood culture	Anesthesia intensive care unit	R	S	31.05.2016
8	D	Blood culture	Infectious diseases service	R	S	08.07.2016
9	D	Endotracheal-aspiration culture	Anesthesia intensive care unit	R	S	03.08.2016
10	D	Blood culture	Anesthesia intensive care unit	R	S	17.08.2016
11	D	Blood culture	Anesthesia intensive care unit	R	S	29.08.2016
12	D	Blood culture	Anesthesia intensive care unit	R	S	30.08.2016
13	D	Blood culture	Anesthesia intensive care unit	R	S	23.05.2016
14	D	Blood culture	Anesthesia intensive care unit	R	S	29.09.2016
15	D	Blood culture	Fever ward	R	S	23.02.2017
16	D	Blood culture	Anesthesia intensive care unit	S	S	10.03.2016
17	D	Blood culture	Anesthesia intensive care unit	S	S	25.03.2016
18	E	Endotracheal-aspiration culture	Anesthesia intensive care unit	S	S	29.06.2016
19	E	Blood culture	Anesthesia intensive care unit	S	S	15.09.2016
20	E	Urine culture	Anesthesia intensive care unit	S	S	16.09.2016
21	E	Blood culture	Anesthesia intensive care unit	S	S	26.09.2016
22	E	Urine culture	Infectious diseases service	S	S	12.10.2016
23	E	Blood culture	Anesthesia intensive care unit	S	S	15.11.2016
24	E	Endotracheal-aspiration culture	Anesthesia intensive care unit	S	S	15.11.2016
25	F	Blood culture	Coronary care unit	S	S	11.01.2017
26	F	Pus culture	Surgery	S	S	14.01.2017
27	F	Endotracheal-aspiration culture	Anesthesia intensive care unit	S	S	20.01.2017
28	F	Pus culture	Infectious diseases service	S	S	20.01.2017
29	F	Blood culture	Anesthesia intensive care unit	R	S	29.10.2015
30	F	Blood culture	Anesthesia intensive care unit	S	S	08.02.2016
31	F	Blood culture	Anesthesia intensive care unit	S	S	15.03.2016
32	F	Blood culture	Anesthesia intensive care unit	R	S	28.05.2016
33	F	Blood culture	Anesthesia intensive care unit	R	S	30.05.2016
34	F	Blood culture	medical care unit	R	S	06.06.2016
35	G	Blood culture	Anesthesia intensive care unit	S	S	24.04.2017

R: Resistance, S: Sensitivity, TMP/SXT: Trimethoprim/Sulfamethoxazole.

Fazil City Hospital between 1 January 2014 and 30 June 2018 and evaluated as infection agents are shown in the graph below according to the years.

The samples from which the 153 strains of *S. Maltophilia* were isolated included 95 (62%) blood cultures, 28 (18%) tracheal cultures, (13%) wound cultures, (3.2%) urine cultures, (2.6%) other cultures and (1.2%) enviromental cultures. The departmental distribution of clinical samples containing *S. maltophilia* strains were: anaesthesia ICU (59%), internal ICU (6%), CVD ICU (6%), burn ICU (4,6%), and neurology ICU (4,6%). The results are shown in Table 1.

The range of samples produced and distribution in the wards and clinics of *S. maltophilia* strain produced on the bedcover of a patient in AICU and the patient isolates in the same period are shown in Table 1.

Among the 153 strains of *S. Maltophilia* isolated, resistance was found to TMP/SXT (39%) and to levofloxacin (5%).

The distribution over the whole period of sample collection of samples positive for S. *maltophilia* was 11 patients in 2014, 50 in 2015, 58 in 2016, 22 in 2017 and in 11 patients in the first 6 months of 2018 (Figure 1).

A total of 34 patient samples and 1 environmental sample were examined using PFGE, which identified 7 genotypes among the total 35 *S. maltophilia* strains tested. While three strains showed a specific genotype profile, the remaining 32 strains were determined to form four clusters. The cluster rate was determined to be 91.4% (32/35). The results are shown in Figure 2.

The PFGE types and epidemiological data of these *Stenotrophomonas maltophilia* isolates are shown in Table 2.

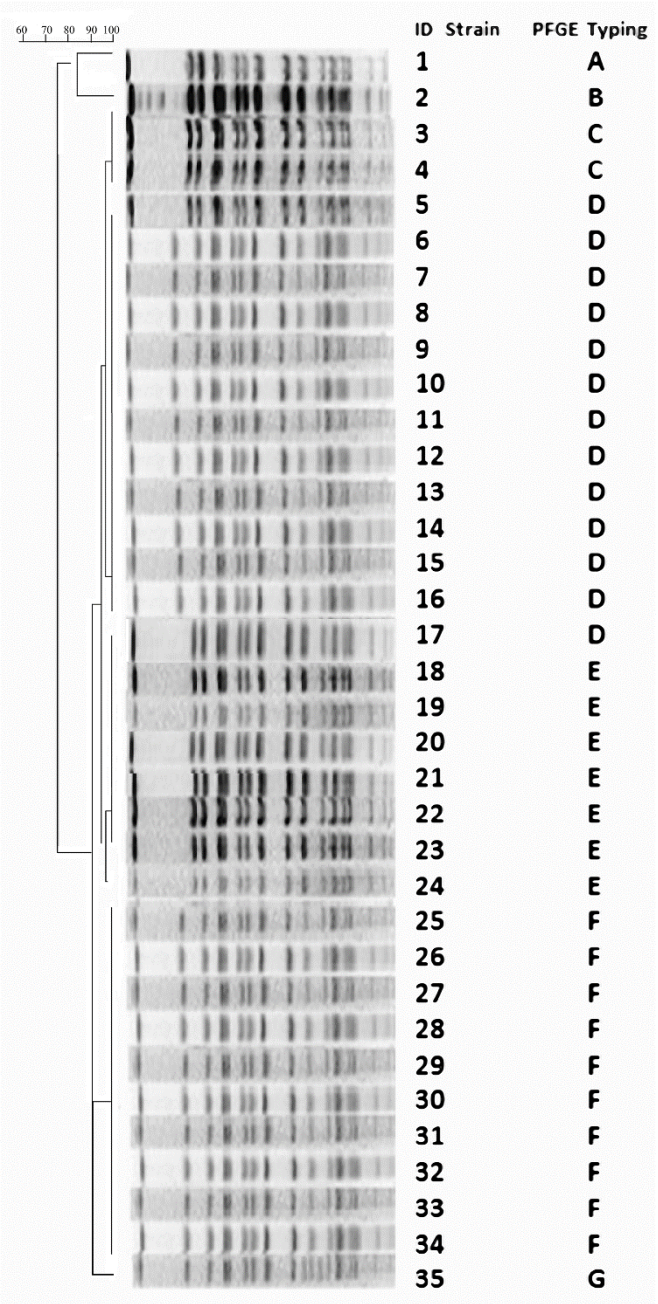
Discussion

The main aim of this study was to determine the antibiotic resistance of all *Stenotrophomonas maltophilia* isolates derived from clinical samples in our hospital between January 2014 and June 2018 and accepted as infection agents, and to determine the clonal relationship between isolates thought to be the cause of infection outbreaks in 2015-2016. This information would facilitate reducing outbreaks to the lowest acceptable levels by preventing spread among the wards and patients.

Approximately 83% of the strains isolated in the study were isolated from patients in the ICUs, which is consistent with several previous studies of *S. maltophilia* in Turkey, in which the majority of isolates were shown to have been isolated from ICUs [11,12]. In the current study, the highest rate, 59%, was determined among isolates from AICU patients.

Malignancy and central venous catheters have been reported as the major sources of episodes related to hospital-origin *S. maltophilia* bacteremia [13]. Of the varied culture samples sent to the laboratory in the current study, the greatest proliferation was in blood cultures (62%). However, differences have been seen between this and previous studies in Turkey. Kandemir *et al*. and Caylan *et al*. had results compatible with those

Figure 2. The clusters of the *Stenotrophomonas maltophilia* isolates.



of the current study, in that *S. maltophilia* was isolated most from blood samples [14,15]. In contrast, Özkaya *et al*. reported respiratory tract samples as the leading source of *S. maltophilia*, at the rate of 58% [16]. As nosocomial *S. maltophilia* has intrinsic resistance to several antimicrobial agents, the use of common standard empirical antibiotics is severely limited. *S. maltophilia* is resistant to β-lactams, β-lactamase inhibitors and aminoglycosides [17,18]. In the SENTRY (www.jmilabs.com) Antimicrobial Surveillance Program, levofloxacin (6.5% resistance) was seen to be the most effective of the new fluoroquinolones [19].

Due to low resistance (5%), trimethoprim/sulfamethoxazole (TMP/SXT) continues to be the preferred treatment choice around the world. Recently, lower resistance levels of 3.8% have been seen in Europe, Latin America and North America; this level seems to be higher in Latin America than in North America [20,21]. Although there have been few surveillance studies, resistance to TMP/SXT has emerged, which has led to combinations in recent *in vitro* modeling studies. The combination of TMP/SXT + ciprofloxacin has been shown to be more effective than TMP/SXT alone [22,23].

In this study, the *S. maltophilia* isolates of 152 patients were examined and 39% were seen to be resistant to TMP/SXT. In previous studies in Turkey of SXT resistance, the rate of resistance has been reported to be 43% by Kandemir *et al*. [14], 43% by Tekin *et al*. [24], 7% by Usta *et al.* [25], 6% by Caylan *et al*. [26], as 9.4% by Ozkaya *et al*. [16], and as 10% by Turk Dagı *et al*. [11] Thus the rate of SXT resistance determined in the current study was extremely high compared to previous studies in Turkey. In other countries, relatively high rates of resistance were also reported: Song *et a*l. in Korea 16% [27] and Hu *et al*. in China 68% [28].

Earlier studies in Turkey reported levofloxacin resistance at the rate of 22.7% by Kandemir *et al*. [14], 20% by Turk Dağı *et al*. [11], 5% by Usta *et al*. [25], and 25% by Tekin *et al*. [24] A study conducted in Taiwan found 20.4% resistance [29]. In the current study, levofloxacin resistance was determined as 5%, which is extremely low compared to both previous studies in Turkey and those from other countries.

When the dates were examined of the proliferation of the *S. maltophilia* strains from samples sent to the laboratory from patients in our hospital, the numbers fluctuated through the years, with a low of 11 patients in 2014, and a high of 58 patients in 2016. The proliferation of *S. maltophilia* was seen to peak in 2015 and 2016 (Figure 1), which is suggestive of an outbreak. During that same period, environmental samples were taken from 20 different points in AICU and *S. maltophilia* proliferation was detected in blood culture and on the bedcover of one patient.

In the total 35 *S. maltophilia* strains, 7 genotypes were determined with the PFGE method. While 3 strains showed a specific genotype profile, the other 32 formed 4 clusters. giving a cluster rate of 91.4% (32/35).

The first cluster comprised two strains. The second cluster was the largest, including13 strains, 12 of which originated in the AICU and 1 from the Fever Ward. Another noticeable feature was that 12 of the isolates with positive cultures were from blood cultures. The first was found on 12/02/2016 and the last on 29/08/2016, suggesting that isolates in this cluster constituted an outbreak lasting approximately six months.

The third cluster was formed of 7 strains, 6 of which were isolated from the AICU and 1 from the Internal Ward; of these, 6 were derived from blood cultures and 1 from urine culture.

The fourth cluster included 10 strains, of which 6 were isolated from AICU, 1 from Coronary ICU, 1 from Adult ICU, 1 from the General Surgery Ward and 1 from the Fever Ward.

Of the 32 isolates in the 4 clusters, 23 were from AICU, and 22 of the isolates with proliferation of *S. maltophilia* in these clusters were from blood cultures, suggesting an outbreak in AICU. This outbreak seems to have started in AICU in October 2015 and lasted for a period of 16 months until February 2017.

Conclusion

The results of this study show that there was a clonal relationship among the vast majority of the 35 *S. maltophilia* isolates. This similarity is evidence of a cross-contamination problem in the hospital. The sample obtained as a result of the dendrogram analysis (#4 strain) showed a high rate of similarity to the other strains, and was determined to be the common source of the cross-contamination. These strains could be stable for a long time, although the disinfection procedures applied in hospitals could result in a slight chance that the same clone might cause another epidemic. In this context, to prevent persistent bacteria from causing hospital infections like *Stenotrophomonas maltophilia*, it is imperative that prevention and follow-up procedures are conducted on a continuous basis. There is also a need for more comprehensive molecular follow-up studies.

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