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Molecular Epidemiology of *Stenotrophomonas maltophilia* Strains Isolated from Bacteremia in Hospitalized Children

Hadis Divakan[1], Mohammad Yousef Alikhani[2] and Leili Shokoohizadeh[2]*

[1]Department of Microbiology, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran
[2]Infectious Disease Research Center, Hamadan University of Medical Sciences, Hamadan, Iran

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ABSTRACT

Objectives: The aim of this study was to determine the phenotypic and genotypic characteristics of *Stenotrophomonas maltophilia* isolates obtained from blood culture samples of pediatric patients hospitalized in Borujerd and Hamadan hospitals in western Iran. ***Methods***: Oxidase-negative isolates were collected from the blood cultures of pediatric patients. *S. maltophilia* isolates were identified and confirmed by routine microbiological and molecular testing. Antibiotic susceptibility of the isolates was determined. The phenotypic and genotypic biofilm-forming ability of the isolates were investigated. Molecular typing of all isolates was performed by repetitive element sequence-based polymerase chain reaction. ***Results:*** Out of 450 oxidase-negative bacilli, 72 (16.0%) were identified as *S. maltophilia* isolates. Biofilm assay results showed strong biofilm formation in 19 (26.4%) isolates, moderate in 38 (52.8%), weak in 10 (13.9%), and no biofilm formation in five (6.9%) isolates. Biofilm-associated genes *rmlA*, *rpf*F, and *spg*M were detected respectively in 59 (81.9%), 54 (75.0%), and 72 (100%) of isolates. Antimicrobial susceptibility testing showed that 67 (93.1%) isolates were sensitive to trimethoprim-sulfamethoxazole. All isolates were sensitive to levofloxacin and resistant to ceftazidime. The *S. maltophilia* isolates were grouped into 14 different types of repetitive sequence by repetitive element sequence-based polymerase chain reaction analysis. ***Conclusions:*** The results of this study indicate that *S. maltophilia* should be considered an important opportunistic pathogen in pediatric units. Different genotypes of *S. maltophilia* with the ability to form a biofilm (an important virulence factor) were circulating in the hospitals investigated. Levofloxacin and trimethoprim-sulfamethoxazole are recommended to treat *S. maltophilia* infections.

Stenotrophomonas maltophilia is a gram-negative, non-fermentative, catalase-positive, and oxidase-negative bacterium.[1] It is an opportunistic nosocomial pathogen and infections associated with it are difficult to control, being multiple drug resistant.[2] This bacterium is widely distributed in nature and has been isolated from humans, animals, and hospital environment.[3,4] *S. maltophilia* is a common cause of infections in patients with cystic fibrosis, cancer, neutropenia, intravenous catheterization, and patients with a history of multiple antibiotic use.[5]

S. maltophilia has also been recognized as a cause of nosocomial bacteremia in intensive care units (ICUs) and in immunocompromised patients. This bacterium can cause 20–75% of deaths in the case of pneumonia and 20–60% of cases of bacteremia.[6–8] Children and infants are often susceptible to *S. maltophilia* infection. Many factors can contribute to infections, especially bloodstream infections (BSI) in hospitalized children. There are few epidemiological studies on *S. maltophilia* infections in Iranian children.

Treatment options for *S. maltophilia* infection are limited due to the pathogen's innate resistance to most antibiotics. Trimethoprim-sulfamethoxazole combination is the current therapy of choice.[9,10] Biofilm formation is known to be a preferred survival strategy for *S. maltophilia*, in addition to tolerance to high doses of antibiotics. Through biofilm production, *S. maltophilia* strains can readily adhere to the surfaces in hospitals, facilitating transmission.[11]

Nowadays, molecular typing is widely used to study the transmission routes of bacterial infections, especially nosocomial infections. Polymerase chain reaction (PCR)-based molecular typing method

*Corresponding author: ✉leilishokoohizadeh@gmail.com

has advantages such as high speed, simplicity, and low cost. Among the PCR-based molecular typing methods, repetitive extragenic palindromic (rep)-PCR is often preferred due to its low cost and rapidity.[12]

Given that *S. maltophilia* bacteremia is an emerging infection of concern associated with high mortality in immunocompromised hospitalized pediatric patients, this study aimed to evaluate the frequency, antibiotic resistance patterns, biofilm-formation ability, and prevalence of biofilm-related genes, as well as the genetic relationships of *S. maltophilia* strains isolated from blood cultures of hospitalized children in Iran.

METHODS

In this cross-sectional study, 450 oxidase-negative bacilli were isolated from the blood cultures of pediatric inpatients hospitalized in two western Iranian cities of Hamadan and Borujerd from June 2020 to June 2021. Identification of *S. maltophilia* was made using standard microbiological tests and a biochemical identification kit (Microgen GN-B kit). *S. maltophilia* isolates were also confirmed by PCR using 16S rRNA primer.[13] This study was approved by the ethics committee of Hamadan University of Medical Sciences (Ref. IR.UMSHA.REC. 1399.092).

Antibiotic susceptibility of *S. maltophilia* strains was determined by the Kirby–Bauer disk diffusion method and Etest. The antibiotic panel included trimethoprim/sulfamethoxazole (TMP/SMX: 1.25/23.75 µg), levofloxacin (LEV: 5 µg), and ceftazidime (CAZ: 30 µg). Quality control was maintained using *Escherichia coli* ATCC 25922. Results were interpreted as stipulated by the Clinical and Laboratory Standards Institute (CLSI 2021).[14]

The biofilm formation of *S. maltophilia* isolates was investigated by microtiter plate (96-well plate) using the dye crystal violet dye. *S. maltophilia* biofilm quantitation was performed by a spectrophotometric method as previously described.[15] All experiments were performed in triplicate.

The genomic DNA of *S. maltophilia* was extracted by boiling method. DNA was extracted after treating cells (colonies) with alkali (NaOH).[16] The presence of *S. maltophilia* biofilm-related genes *(rpfF, spgM,* and *rmlA)* was detected by PCR with specific primers previously described.[17]

The genetic relationships of the isolates of *S. maltophilia* were investigated by rep-PCR typing. The rep-PCR analysis was performed with a single primer BOX-A1R (5'-CTA CGG CAA GGC GAC GCT GAC G-3'). The PCR reaction mixture consisted of a total volume of 25 µL. Thermal cycling was performed according to the following procedure: initial denaturation (94 °C for 10 min), followed by 25 cycles of denaturation (at 94 °C for 45 sec), annealing (at 50 °C for 1.5 min), extension (at 65 °C for 8 min) and a final cycle of extension at 65 °C for 16 min.[18] The rep-PCR products were loaded on a 2% agarose gel at 70 V for one hour, and the repetitive sequence band patterns (REP profiles) were visualized in a gel documentation system.[17] The REP patterns were analyzed by an online data analyzer accessed from insilico.ehu.eus/dice_upgma. The REP profiles were compared using the Dice method and clustered according to the unweighted paired group method with arithmetic mean (UPGMA).[18]

RESULTS

In total, out of 450 oxidase-negative bacilli, 72 (16.0%) strains of *S. maltophilia* were identified; 30 strains (41.7%) were from hospitals in Hamadan and 42 strains (58.3%) were from hospitals in Borujerd. The ages of the patients ranged from < 1 year to 12 years. More than 80% of patients were under 10 years of age. There was a significant difference between the ages of patients from Hamadan and Borujerd hospitals (p = 0.010). The majority were male (43; 59.7%). There was no statistically significant relationship between the patients' sex and isolates of *S. maltophilia* (p = 0.808).

According to the phenotypic biofilm formation assay, among the 72 strains of *S. maltophilia*, 19 (26.4%), 38 (52.8%), and 10 (13.9%) isolates produced strong, moderate, and weak biofilm, respectively. Five isolates (6.9%) did not produce biofilm. The frequencies of biofilm-related genes by PCR were given as follows: *rmlA* (59; 81.9%), *rpfF* (54; 75.0%), and *spgM* (72; 100%) [Box 1].

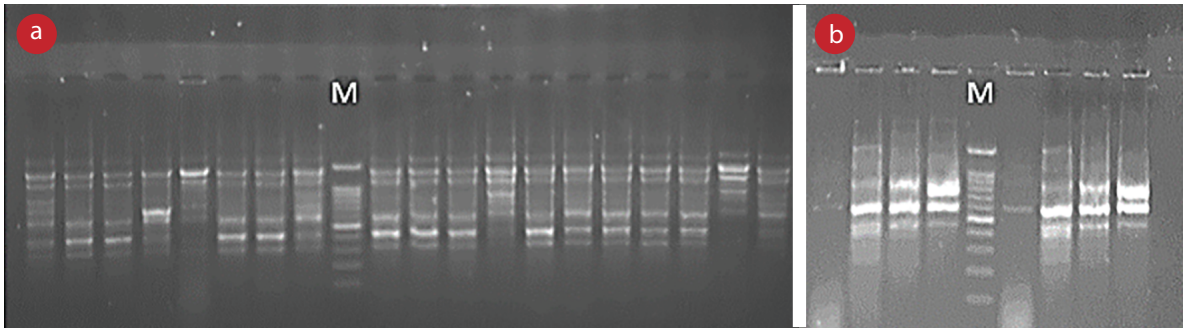
Antimicrobial susceptibility analysis showed that 93.1% of the *S. maltophilia* strains were sensitive to TPM/SMX (6.9% were intermediate). All isolates were sensitive to LEV and resistant to CAZ [Box 1].

According to the results of the rep-PCR analysis, the size of the amplicons varied from 300

Biofilm associated genes	*spgM*	*rmlA*	*rpfF*
	100	81.9	75.0
Biofilm-formation ability	Weak	Moderate	Strong
	13.9	52.8	26.4
Antibiotic sensitivity	LEV	TMP/SMX	CAZ
	100	93.1	0

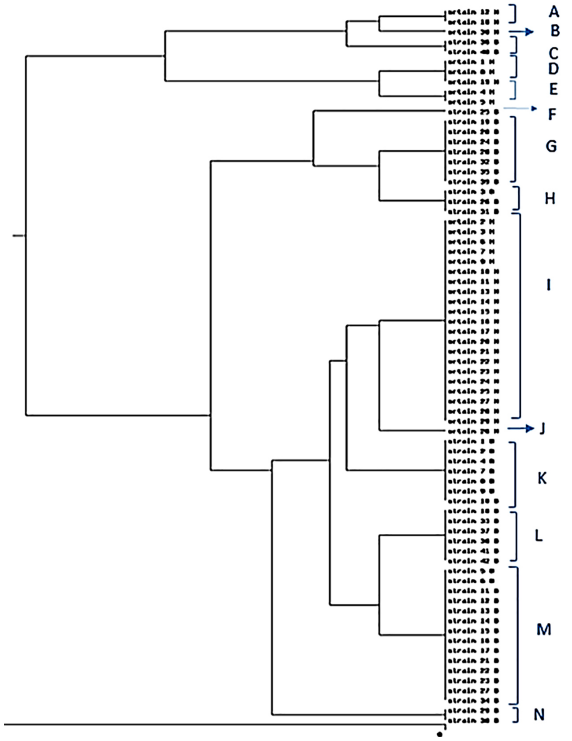
LEV: levofloxacin; TMP/SMX: trimethoprim-sulfamethoxazole; CAZ: ceftazidime.

Box 1: Frequency of biofilm-related genes, biofilm-forming ability, and antibiotic susceptibility of isolates of *S. maltophilia.*



M: Marker 100 bp; REP: repetitive sequence.

Figure 1: Band patterns resulting from amplification of REP regions in *S. maltophilia* isolates. **(a)** Band patterns of Hamadan city isolates and **(b)** band patterns of Borujerd city isolates.



UPGMA: unweighted pair group method with arithmetic mean; rep-PCR: repetitive element sequence-based polymerase chain reaction.

Figure 2: Dendrogram of rep-PCR fingerprinting of *S. maltophilia* isolates, comparison by Dice method and clustering by UPGMA method.

bp to > 1 kb. Through analysis of the results, the genetic diversity among *S. maltophilia* strains was observed [Figure 1]. The rep-PCR analysis revealed 14 different REP types, which were divided into 11 common types (CTs) and three single types. CTs included 2–21 isolates [Figure 2]. Hamadan city isolates are represented by H and Borujerd city isolates are represented by B in Figure 2. The REP profiles of Hamadan and Borujerd isolates are completely different. The largest CT belonged to Hamadan containing 21 isolates [Figures 1 and 2]. Different types of REP show the same antibiotic resistance pattern. The difference between isolates is mainly related to the differences in biofilm formation strength.

DISCUSSION

In this study, the prevalence of *S. maltophilia* isolated from blood cultures of pediatric patients was 16.0%. Although this may be low compared with other hospital-acquired bacteria, it is significant due to this pathogen's intrinsic resistance to common antimicrobial agents, presence of virulence genes, and biofilm-formation ability. There are various reports on the prevalence of *S. maltophilia* in Iran.

In a previous study from Hamadan, 12 (4.8%) *S. maltophilia* were isolated from blood cultures.[19] The isolates were verified by standard biochemical methods. Based on the results of that study and ours, the incidence of *S. maltophilia* in Hamadan hospitals has increased over time. In another study performed by Bostanghadiri et al,[17] from Iran, 164 clinical isolates of *S. maltophilia* were identified and confirmed using standard biochemical tests and PCR. Most (83.5%) samples positive for *S. maltophilia* were blood cultures. As per our results, the prevalence of *S. maltophilia* was higher in males than in females in the ratio of 1.15 to 1.[17] In another new study in Iran, 117 strains of *S. maltophilia* were isolated from different clinical sources. *S. maltophilia* isolates were identified by routine microbiological and biochemical tests. The highest *S. maltophilia* prevalence was observed in the blood (92.3%) and the lowest in wounds (0.85%).[20] In a study by Duan et al,[21] from Shanghai, China, a total of 104 strains of *S. maltophilia* were collected from different pediatric wards. Contrary to our results, most strains of *S. maltophilia* were isolated from sputum sources.[21] In a retrospective cohort study of hospitalized pediatric patients in Saudi Arabia, most (88.2%) bacteremia cases were catheter-related BSI.[6]

In our study, over 80% of children with *S. maltophilia* were < 9 years old. According to several studies, hospitalized infants and children of any age can be susceptible to *S. maltophilia* infection.[6,17,21] Various factors can contribute to infection in hospitalized children, especially BSI. Risk factors for *S. maltophilia* BSI may be length of ICU stay, use of mechanical ventilators, indwelling catheters, and length of hospital stay.[22]

TMP/SMX is considered the most effective antibiotic to treat *S. maltophilia* infections. However, a number of recent reports of resistance from *S. maltophilia*-induced infections have raised concerns over its continued efficacy. Alternative antibiotics, such as LEV and minocycline, have been reported effective against invasive *S. maltophilia* infections, especially in severe infections.[17,23] In this study, LEV and TMP/SMX were found to be effective for *S. maltophilia* and CAZ as unsuitable. However, the efficacy of minocycline was not studied, because it is unavailable in Iranian hospitals and is generally not prescribed here.

Different results of antimicrobial susceptibility from ours were reported from Iran and elsewhere. In a previous study in Hamadan hospitals, all strains of *S. maltophilia* were found susceptible to ofloxacin (a fluoroquinolone antibiotic) and TMP/SMX; however, another study that used data from hospitals in various regions in Iran found that 91.0%, 99.3%, and 63.5% of *S. maltophilia* isolates were susceptible to TMP/SMX, LEV, and CAZ, respectively.[17,19] In a cross-sectional study in Southwest Iran, all of the 44 *S. maltophilia* isolates from different clinical specimens were susceptible to TMP/SMX.[24] Inconsistent with our results, a study in Tehran hospitals, a total of 150 *S. maltophilia* isolates were collected from various clinical specimens including respiratory specimens, secretions from ventilator-associated pneumonia, as well as from surgical instruments and catheters. Eighty percent of the isolates were resistant to TMP/SMX while 20% were resistant to a fluoroquinolone such as ofloxacin. One of the main reasons for this difference in the results compared to ours might be the differences in type of samples examined and the location of their study. Studies outside Iran also show variations resistance to TMP/SMX across geographical areas.[24] However, *S. maltophilia* resistance to TMP/SMX has not been reported > 10% except in respiratory infections and in patients with cystic fibrosis.[17,25–28]

The rate of resistance to CAZ in our patients was higher than the rates previously reported from different parts of Iran and from other countries.[6,17,19,27,29] This antibiotic should be considered inappropriate against *S. maltophilia* in children in the studied hospitals.

Another factor investigated in this study was the biofilm-forming ability of *S. maltophilia* strains. Biofilm formation on hospital surfaces and in human tissues is an important survival feature of *S. maltophilia*. In this study, most *S. maltophilia* isolates were biofilm producers. All isolates of *S. maltophilia* carried the *spgM* gene. However, other related-biofilm genes, *rmlA* and *rpfF* were found in 81.9% and 75.0% of the isolates, respectively. Our results are in agreement with the results of Bostanghadiri et al,[17] where most of the isolates were biofilm producers, and 88.4%, 83.5%, and 100% of the isolates were positive for *rmlA*, *rpfF,* and *spgM* genes. In a study by Flores-Treviño et al,[30] the rate of biofilm formation and isolation of potent biofilm procedure was higher than both in our study and that by Bostanghadiri et al.[17] Studies have shown

that the *spgM* gene plays an important role in the formation of strong biofilm.[17,29–31]

In this study, the genetic diversity of the isolates of *S. maltophilia* was determined inexpensively and quickly using the rep-PCR technique using a single primer,[12] showing clonal diversity among *S. maltophilia* isolates. Our 72 isolates of *S. maltophilia* were classifiable into 14 different REP types. Genetic diversity in *S. maltophilia* isolates has been confirmed by many studies.[17,20,32,33] In a study by Bostanghadiri et al,[17] high clonal diversity (16 CTs and 114 single types) was detected by rep-PCR assay in *S. maltophilia* isolates. The reasons for their findings have a greater genetic diversity than us due to their larger sample size and the fact that their samples were sourced from different regions of Iran. Duan et al,[21] identified 104 highly diverse isolates of *S. maltophilia* from a children's hospital in China. They used two different molecular typing methods, pulsed-field gel electrophoresis and Multilocus sequence typing of *S. maltophilia* isolates, which were found divided into 93 clusters and 59 sequence types.[21]

There are limitations to our study. It was conducted during the COVID-19 pandemic. Therefore, we encountered challenges in taking samples. Clinical information of the patients, some antibiotics offered at CLSI, and full funding were not available. Another limitation was the lack of testing for environmental samples, as *S. maltophilia* could be present in the hospital environment and on the equipment. By analyzing environmental samples and using molecular typing techniques, we were able to identify the source of the contamination. These limitations were overcome by the hospital administrators who engaged with laboratories and research centers.

CONCLUSION

The results of this study indicate that *S. maltophilia* may cause diseases such as bacteremia in hospitalized pediatric patients. Given the immunodeficiency in some hospitalized children, it is important to isolate *S. maltophilia* from samples taken from vulnerable pediatric population. Biofilm formation by *S. maltophilia* should be considered a major challenge in eliminating drug-resistant pathogens from hospitals. As of now, LEV and TMP/SMX can be considered effective antibiotics against *S. maltophilia*.

Disclosure

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