# Molecular Epidemiology of *Stenotrophomonas Maltophilia* Isolates Collected from Bacteremia in Hospital Pediatric Units

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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 the western of Iran.

***Methods***: In this study, 450 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 isolates was determined. The phenotypic and genotypic biofilm-forming ability of the isolates was investigated. Molecular typing of all isolates was performed by rep-PCR.

***Results***: A total of 72(16%) *S. maltophilia* isolates were identified from 450 oxidase-negative bacilli. Biofilm assay results showed strong, moderate, weak, and no biofilm formation in 26.3%, 52.7%, 13.8%, and 6.9% of the isolates, respectively. Biofilm- associated genes *rmlA*, *rpf*F, and *spg*M were detected in 82%, 75%, and 100% of isolates, respectively. Antimicrobial susceptibility testing showed that 93.1% of the isolates were sensitive to trimethoprim-sulfamethoxazole. All isolates were sensitive to levofloxacin, whereas all were resistant to ceftazidime. Isolates were grouped into 14 different Rep types by rep-PCR analysis.

***Conclusions***: The results of this study indicated that *S. maltophilia* should be considered an important opportunistic pathogen in pediatric units. Different genotypes of *S. maltophilia*, which has the ability to form biofilm, are circulating in hospitals investigated. Biofilm formation can be considered an important virulence factor for *S. maltophilia.* Prescription of Levofloxacin and trimethoprim-sulfamethoxazole can be continued for *S. maltophilia*.

**Keywords**: *Stenoterphomonas maltophilia*; Pediatric; Bacteremia; Antibiotic-Resistance; Biofilm; rep-PCR.

## Introduction

*Stenotrophomonas maltophilia* is a Gram-negative, non-fermentative, catalase-positive, and oxidase-negative bacterium[1]. *S. maltophilia* is an opportunistic nosocomial pathogen and associated infections are difficult to control because of its ability multiple drugs resistance.[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 bacteremia, especially in the intensive care units (ICUs) and in immunocompromised patients. Like other nosocomial disorders, bacteremia is one of the complications of *S. maltophilia*. This bacterium can cause 20 to 75% of deaths in the case of pneumonia and 20 to 60% of cases of bacteremia[6-8]. Bacteremia is a life-threatening infection, but it usually occurs in relatively rare cases[6]. Children

and infants are often susceptible to *S. maltophilia* infection. Many different factors can contribute to infections, especially bloodstream infections (BSI) in hospitalized children. There are few epidemiological studies on *S. maltophilia* infection in Iranian children.

Resistance to a various antibiotics in immunocompromised patients significantly increases the mortality rate.[9] Treatment options for *S. maltophilia* infection are very limited due to the pathogen's innate resistance to certain antibiotics. Although trimethoprim-sulfamethoxazole combination therapy is used as the drug of choice against this bacterium.[9, 10] Biofilm formation is known as a preferred survival strategy for *S. maltophilia*, and increased tolerance to high doses of antibiotics. Through the biofilm production, *S. maltophilia* strains can readily adhere to the surfaces in hospitals and facilitate its transmission. [11]

Nowadays molecular typing is widely used to study of transmission routes of bacterial infections, especially nosocomial infections. The PCR-based molecular typing method has advantages such as high speed, simplicity and low cost. Among PCR-based molecular typing methods, repetitive extragenic palindromic (rep)-PCR is a conventional method due to its low cost and rapidity.[12] Given that *S. maltophilia* bacteremia is a worrisome emerging infection associated with high mortality in pediatric immunocompromised hospitalized patients, the objective of this study was to evaluate the frequency, antibiotic resistance patterns, biofilm formation ability, prevalence of biofilm-related genes, and the genetic relationships of *S. maltophilia* strains isolated from blood cultures of pediatric patients hospitalized in hospitals in two central cities in the western of Iran.

## Methods

In a cross-sectional study, 450 oxidase-negative bacilli were isolated from the blood cultures of pediatric patients at hospitals in the cities of Hamadan and Borujerd in western of Iran from June 2020 to June 2021. Identification of *S. maltophilia* was performed according to standard microbiological tests and a biochemical identification kit (Microgen GN-B kit). *S. maltophilia* isolates were also confirmed by PCR using 16SrRNA primer [13]. This study was approved by the Ethics Committee of Hamadan University of Medical Sciences (IR.UMSHA. REC. 1399.092).

Antibiotic susceptibility of *S. maltophilia* strains was determined by the Kirby–Bauer disk diffusion method and E test. The antibiotic panel included trimethoprim-sulfamethoxazole (SXT: 1.25/23.75µg), levofloxacin (LEV: 5µg), and ceftazidime (CAZ: 30µg). Quality control was performed using *E. coli* ATCC 25922. Results were interpreted according to 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 of cells (colonies) with alkaline (NaOH) [16]. The presence of *S. maltophilia* biofilm-related genes *(rpfF, spgM,* and *rmlA)* was detected by PCR with specific primers have been described, previously [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 BOXA1R (5′-CTA CGG CAA GGC GAC GCT GAC G-3′). The PCR reaction mixture consisted of a total volume of 25µl. Thermal cycling was performed according to the following procedure: initial denaturation (94°C for 10 min), followed by 25 cycles of denaturation (94 °C for 45 s), annealing (50° C for 1.5 min), extension (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 1 h, and the REP band patterns (REP profiles) were visualized in a gel documentation system [17]. The REP patterns were analyzed by an online data analyzer (inslico.ehu.es). The REP profiles were compared using the Dice method and clustered according to the UPGMA (Unweighted Paired group Method with Arithmetic Mean) [18].

## Results

In total, out of 450 oxidase-negative bacilli, 72 (16%) strains of *S. maltophilia* were identified; 30 strains (41.7%) and 42 strains (58.3%) were from Hamadan and Borujerd hospitals, respectively. According to the age of the patients, the age range was from less than one year old to 12 years old. 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-value = 0.010). Based on the gender of the patients, 29 (40.3%) were female and 43 (59.7%) were male. There was no statistically significant relationship between sex and isolates of S. *maltophilia* (P-value = 0.808).

According to the phenotypic biofilm formation assay, among 72 strains of *S. maltophilia*, 19 (26.3%), 38 (52.7%), and 10 (13.8%) isolates produced strong, moderate, and weak biofilm, respectively. While 5 isolates (6.9%) did not produce biofilm. The frequencies of biofilm-related genes by PCR were given as follows: *rml*A (n=59; 82%), *rpf*F (n=54; 75%), and *spg*M (n=72; 100%), the results showed in Table 1.

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

| **Biofilm associated genes (%)** | ***spg*M** | ***rml*A** | ***rpf*F** |
|---|---|---|---|
| | 100% | 82% | 75% |
| **Biofilm-formation ability (%)** | **Weak** | **Moderate** | **Strong** |
| | 13.8% | 52.7% | 26.3% |
| **Antibiotic sensitivity (%)** | **LEV** | **SXT** | **CAZ** |
| | 100% | 93.7% | 0% |

LEV; levofloxacin, SXT; trimethoprim-sulfamethoxazole, CAZ; ceftazidime

The antimicrobial susceptibility analysis showed that 93.1% of the *S. maltophilia* strains were sensitive to trimethoprim-sulfamethoxazole (6.9% were intermediate). All isolates were sensitive to levofloxacin, whereas all were resistant to ceftazidime (Table 1).

According to the results of the rep-PCR analysis, the size of the amplicons varied from 300 bp to more than 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 (CT) and 3 single types. Common types include of 2 to 21 isolates (Figure 2). Hamadan isolates are represented by H and Borujerd 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, 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.

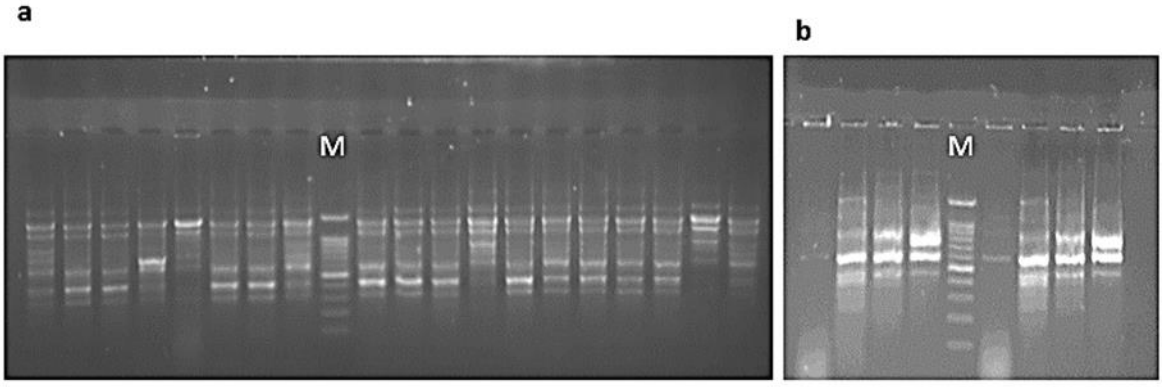


**Figure 1**: Band patterns resulting from amplification of REP regions in *S. maltophilia* isolates, M: Marker 100 bp, **a**: Band patterns of Hamedan isolates, **b**: Band patterns of Boroujerd isolates

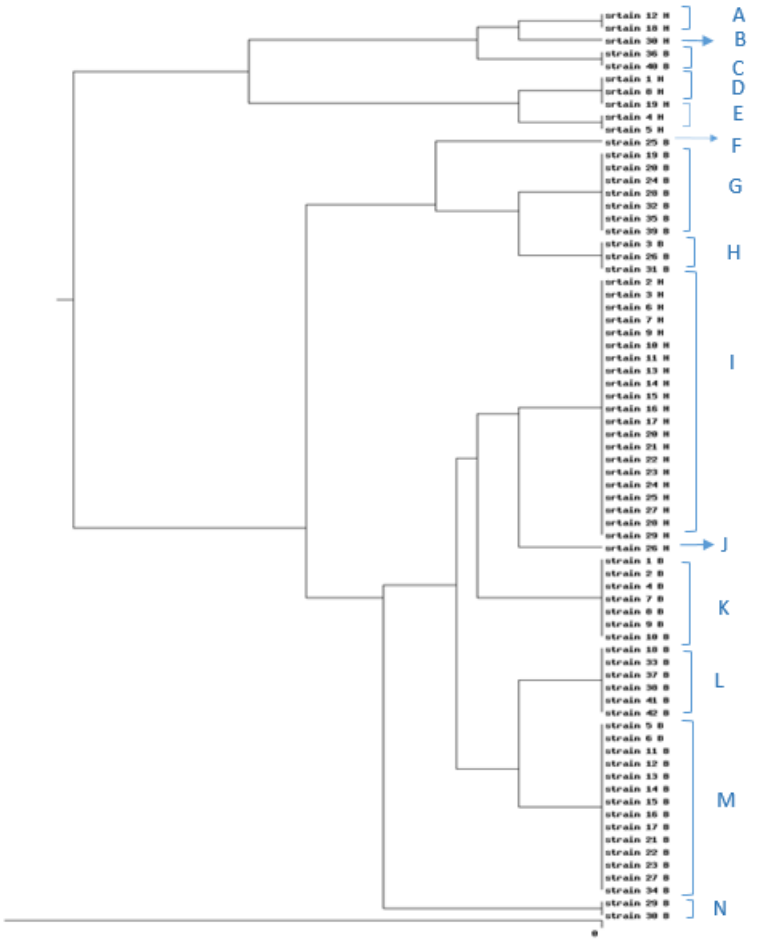


**Figure 2**: Dandogram of rep-PCR fingerprinting of *S. Maltophilia* isolates, comparison by Dice method and clustering by UPGMA method

## Discussion

In this study, the prevalence of *S. maltophilia* isolated from blood cultures of pediatric patients was 16%. Although this number may be relatively low compared with other hospital-acquired bacteria, it is significant due to intrinsic resistance to some antimicrobial agents, virulence genes, and biofilm formation ability of *S. maltophilia*. 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 the mentioned study and our study, the incidence of *S. maltophilia* in Hamadan hospitals has increased. In another study performed by Bostanghadiri *et al*. 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 the results of our study, the rate of *S. maltophilia* in males was higher than in females (ratio 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* was observed in the blood (92.3%) and the least in wounds (0.85%) [20]. In a study by Duan *et al*. from China at a pediatric university hospital in Shanghai, a total of 104 strains of *S. maltophilia* were collected from different pediatric wards. Contrary to our study results, most strains of *S. maltophilia* were isolated from sputum sources[21]. In a retrospective cohort study of hospitalized pediatric patients in a hospital in Saudi Arabia most (88.2%) bacteremia cases were catheter-related BSI [6].

In our study, over 80% of children with *S.maltophila* were under 9 years old. According to the results of the mentioned studies, hospitalized children from the youngest age (a few days) to the oldest age can be exposed to *S. maltophilia* infections [21, 6, 17]. Various factors can contribute to infection, especially BSI in hospitalized children.

Risk factors for *S. maltophilia* BSI may be length of ICU stay, use of mechanical ventilators, indoor catheters, and length of hospital stay [22].

The inherent resistance of *S. maltophilia* to many antibiotics makes it a therapeutic challenge. Trimethoprim/sulfamethoxazole (TMP/SMX) is considered the most effective antibiotic to treat of *S. maltophilia* and was recommended as a first choice for *S. maltophilia* infections. However, reports of resistance to this antibiotic have raised concern in a number of studies on the treatment of *S. maltophilia*-induced infections. Other alternative antibiotics, such as levofloxacin and minocycline, have been reported as effective agents against invasive *S. maltophilia* infections, especially in severe infections [17, 23]. In this study levofloxacin and TMP/SMX were found to be effective and ceftazidime as an unsuitable antibiotic for *S. maltophilia*. In this study, the susceptibility to minocycline has not been studied because it is unavailable in Iranian hospitals and is generally not prescribed here. Different antimicrobial susceptibility results have been reported in Iran as well as outside of Iran. In a previous study in Hamadan hospitals, all *S.maltophilia* were susceptible to ofloxacin (a fluoroquinolone antibiotic) and TMP-SMX; however in another study from hospitals in various regions in Iran, 91.04%, 99.3% and 63.5.5% of *S. maltophilia* isolates were susceptible to TMP-SMX, levofloxacin and ceftazidime, respectively [17, 19]. In a cross-sectional study in Southwest Iran, forty-four S. *maltophilia* isolates were recovered from different clinical specimens, all of the *S. maltophilia* isolates were susceptible to TMP/SMX [24]. Inconsistent with our results, in a study in Tehran hospitals, total of 150 *S. maltophilia* isolates were collected from various clinical specimens, including respiratory specimens, secretions from ventilator-associated pneumonia, as well as surgical instruments and catheters. Eighty percent of the isolates were resistant to TMP-SMX and 20% of the isolates were resistant to a fluoroquinolone such as ofloxacin. One of the main reasons for this difference in the results of this study compared to our study can be due to the type of samples examined and the location of their study. The results of studies outside Iran also show the different levels of resistance to TMP-SMX results in various geographical areas [24]. Although resistance to TMP-SMX was not reported at more than 10% with the exception of cases such as respiratory infections and in patients with cystic fibrosis [17, 25-28].

The rate of resistance to ceftazidime is higher than other reported rates in different parts of Iran and outside of Iran [6, 17, 19, 27, 29]. This antibiotic should be considered an inappropriate antibiotic against *S. maltophilia* in pediatric 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 feature of *S. maltophilia*. In this study, most *S. Maltophilia* isolates were biofilm producers. All isolates of *S. maltophilia* carried the *spg*M gene. However, 82% and 75% of the isolates contained other related biofilm genes; *rml*A and *rpf*F, respectively. Our results are in agreement with the results of Bostanghadiri et al, where most of the isolates were biofilm producers as well as 88.41%, 83.53% and 100% of the isolates were positive for *rml*A, *rpf*F and *spg*M genes. [17]. In a study by Flores-Trevino et al. the biofilm formation rate and isolation of potent biofilm procedure was higher than our study and Bostanghadiri et al. research. [30]. The results of some studies have shown that the *spg*M gene plays an important role in the formation of strong biofilm [17, 29-31]. As in our study, the frequency of this gene was high in isolates of *S. maltophilia*

In this study, the genetic diversity of the isolates of *S. maltophilia* was determined by the rep-PCR technique using a single primer in a short time and under inexpensive conditions [12.] In this study, the rep-PCR analysis showed clonal diversity among *S. maltophilia* isolates. Totally *S. maltophilia* isolated were divided into 14 different REP types. Genetic diversity in *S. maltophilia* isolates has been confirmed in many studies.[17, 20, 33, 34] In a study conducted by Bostanghadiri *et al*. a high clonal diversity among *S. maltophilia* isolates was detected by rep-PCR assay. The isolates were divided into 16 common types and 114 single types. One of the reasons for the high genetic diversity in their study is their larger sample size and their samples were taken from different regions of Iran. According to a study by Duan *et al*. from a children hospital in China, 104 isolates of *S. maltophilia* were highly diverse. According to two different molecular typing methods; Pulsed-field gel electrophoresis (PFGE) and Multilocus sequence typing (MLST) of *S. maltophilia* isolates were divided into 93 clusters and 59 sequence types, respectively [21].

There are limitations to our study. It was conducted during the COVID-19 pandemic. Therefore, we encountered many problems and limitations when taking samples at the hospital. Clinical information of the patients, some antibiotics offered at CLSI and full funding were not available. One of the main limitations of this study was the lack of testing for environmental samples, as *S. maltophilia* could be present in the hospital environments and on the equipment. By analyzing environmental samples and using molecular typing techniques,

we were able to identify the source of the contamination. These restrictions are resolved by hospital administrators working with laboratories and research centers.

## Conclusion

The results of this study indicate that *S. maltophilia* may cause diseases such as bacteremia in pediatric patients. Given the children's immunodeficiency, it is important to isolate her *S. maltophilia* from the children. Biofilm formation by *S maltophilia* in hospitals should be considered a major problem in hospitals. Levofloxacin and trimethoprim-sulfamethoxazole can be considered effective antibiotics against *S. maltophilia*. Molecular typing by rep-PCR revealed the clonal diversity *of S. maltophilia* isolates. Appropriate strategies should therefore be applied to control resistant and biofilm-forming *S. maltophilia* strains in hospital pediatrics.

## Disclosure

The authors declare that they have no competing interests.

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