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# Detection and Clinical Implications of Biofilm Formation Among Clinical Isolates of *Sphingomonas paucimobilis* in Turkey

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## Abstract

**Background:** *Sphingomonas paucimobilis* is a non-fermentative bacillus and found widely in nature. It acquires great interest in biofouling by production of biofilm. However, *S. paucimobilis* as a biofilm producer, is not studied in medical aspect. In this study we aimed to assess the biofilm production as a virulence factor in clinical isolates of *S. paucimobilis* together with patient demographics, clinical aspects, risk factors, and outcomes.

**Methods:** During 5 year-period, total numbers of 43 *S. paucimobilis* isolates identified in a clinical microbiology laboratory of an university hospital in Turkey. Thirty-three of the isolates, which were isolated from patients with clinically determined infection, were enrolled in this study. Patients' data were collected retrospectively. VITEK II automated system (bioMérieux, Marcy L'Eoile, France) was used for identification and antimicrobial susceptibility testing. Christiansen tube method was used to determine biofilm formation.

**Results:** All the clinical isolates of *S. paucimobilis* produced biofilms. Primary bacteraemia (n = 16) was the most common clinical manifestation. Twenty-four of the patients were followed in the intensive care unit. Twenty-two patients had indwelling catheters. Malignancy (n = 11) and diabetes mellitus (n = 10) were the most common concomitant diseases. Tigecycline, carbapenems and aminoglycosides were the most susceptible antimicrobial agents. Degree of biofilm formation was correlated only with blood samples (P = 0.003) in the sample types group and a stay in the intensive care unit (P = 0.002) in the risk factors group.

**Conclusions:** *Sphingomonas paucimobilis* can cause serious infections, especially in immunocompromised patients with determined risk factors such as indwelling catheters and diabetes mellitus, due to the effects of multiple virulence factors, together with biofilm formation.

*Keywords:* *Sphingomonas paucimobilis*, Biofilm, Virulence Factors, Risk Factors

## 1. Background

*Sphingomonas paucimobilis* (formerly *Pseudomonas paucimobilis*) is an aerobic, non-fermentative, Gram-negative bacillus characterised by production of a yellow pigment known as nostoxanthin, slow motility with a single polar flagellum, and positive oxidase and catalase reactions (1). *Sphingomonas paucimobilis* is distributed widely in nature, especially in water and soil (2). It is an oligotrophic bacterium and can be isolated from low-nutrient environments, such as drinking water distribution systems, water treatment plants, tap water, and water demineralisation filters and biofilms collected from water system (3-6). This bacterium was even isolated from water supply and humidity condensate samples gathered from the international space station (7).

In hospital settings, *S. paucimobilis* is seen in sporadic cases of various infections, such as catheter-related sepsis, primary bacteraemia, pneumonia, meningitis, peritonitis, septic arthritis, and urinary tract infections, and small outbreaks caused by contaminated hospital devices and contaminated intravenous fluids (8-17). The presence of indwelling devices, an impaired immune system, and co-morbidities such as malignancy and diabetes mellitus are reported risk factors for *S. paucimobilis* infection (14, 15, 18, 19). Biofilm production is a well-known bacterial virulence factor and causes treatment failure, particularly in patients with indwelling devices (20). Biofilm production by *S. paucimobilis* has been investigated extensively in non-clinical, but not clinical, isolates (4, 6, 21, 22).

## 2. Objectives

This is the first study to assess biofilm production by *S. paucimobilis* clinical isolates, together with patient demographics, clinical aspects, risk factors, and outcomes.

## 3. Methods

### 3.1. Patients

The study was conducted at in a 750-bed Training and Research hospital in Sakarya/Turkey from January 2010 to December 2014 with the ethical approval number 71422473/050.01.04/54. Forty-three non-duplicate *S. paucimobilis* isolates were identified from clinical samples, but ten of the samples were excluded from the study because they were deemed either colonisation or contamination based on clinical signs and laboratory and radiographic findings. Consequently, 33 isolates from patients clinically determined to have *S. paucimobilis* infections were enrolled in the study. Clinical and demographic data for these patients were collected retrospectively from the hospital records.

### 3.2. Bacteriological Studies

Conventional cultivation methods were used to isolate *S. paucimobilis* from clinical specimens. Identification and antimicrobial susceptibility tests were performed using a VITEK II Automated System (bioMérieux, Marcy L'Eoile, France). The EUCAST 2014 criteria were used to assess antimicrobial resistance. The strains were stored at -80°C as stock cultures until biofilm production was evaluated.

### 3.3. Detection of Biofilm Formation With Tube Method

The tube method described by Christensen et al. in 1982 (23) and 1985 (24) was used to assess biofilm formation qualitatively, with some modifications as proposed by Stepanovic et al. (25). *Sphingomonas paucimobilis* isolates were recultivated from stock cultures and incubated for 24 hours at 37°C. A loopful of freshly grown colonies was inoculated into glass tubes (13 × 10 cm) containing 3-mL tryptic soy broth (Merck, Darmstadt, Germany) with 2.5% glucose (Merck, Darmstadt, Germany). The tubes were incubated overnight at 37°C under aerobic conditions. The content of each tube was removed carefully using an automatic pipette. Safranin solution (2 mL, 0.25%) from the Gram staining set was then added. After staining for 1 minute, the safranin was removed using a pipette. The tubes were placed upside down for 24 hours at room temperature. No wash steps were performed during the procedure. A non-inoculated tube containing tryptic soy broth was used as the negative control. The well-known biofilm producer *Escherichia coli* ATCC 25922 was used as the positive control (20). Biofilm formation was accepted as positive when adherent film material was attached to the inner wall and bottom of the tube. Colourful ring formation at the air-liquid interface was not considered. According to the intensity of the adherent dye, the tubes were scored as 0 (absent), +1 (low), +2 (moderate), and +3 (high). Experiments were repeated three times for each isolate.

### 3.4. Statistical Analyses

Groups were compared using the chi-square or Fisher's exact test for categorical variables and Student's t-test for continuous variables. A $P < 0.05$ was considered to indicate significance. Statistical analyses were performed using SPSS ver. 21.0 (SPSS, Chicago, IL, USA).

## 4. Results

*Sphingomonas paucimobilis* infection was identified in 33 patients (17 females, 16 males). The mean age of the patients was 61.2 years, ranging from a 1-year-old male to a 78-year-old female. The infections included 27 nosocomial and six community-acquired infections. *Sphingomonas paucimobilis* was isolated most commonly from blood samples (n = 16) as primary bacteraemia. In addition, seven cases of pneumonia, six cases of wound infection, and four cases of urinary tract infection were detected. Twenty-four of the patients were followed in the intensive care unit. Twenty-two patients had indwelling catheters. Malignancy (n = 11) and diabetes mellitus (n = 10) were the most common concomitant diseases. Biofilm formation by all isolates was determined and the degree of biofilm formation and other data are summarised in Table 1.

Table 2 shows the antimicrobial susceptibility test results. Tigecycline (84.85%) was the antimicrobial agent to which the isolates were most frequently susceptible, together with carbapenems and aminoglycosides, whereas fewer isolates were susceptible to ampicillin (21.21%), ampicillin/sulbactam (24.24%), cefuroxime (24.24%), and cefuroxime axetil (24.24%).

All isolates produced biofilms. Table 3 shows the correlations of biofilm formation intensity with demographic data and clinical variables. The intensity of biofilm formation was correlated only with blood samples ($P = 0.003$) in the sample types group and a stay in the intensive care unit ($P = 0.002$) in the risk factors group. No other variable was correlated with biofilm formation intensity ($P > 0.005$).

## 5. Discussion

*Sphingomonas paucimobilis* was first isolated from the leg ulcer of a Japanese seaman in 1979 (26). Since then, many case reports, case series, and outbreaks have been presented. Clinical infections related to *S. paucimobilis* include bacteraemia, peritonitis, wound infections, adenitis, diarrhoeal disease, sepsis arthritis, osteomyelitis, and meningitis (8, 13, 18). Outbreaks have also been attributed to contaminated water sources or contaminated intravenous fluids (10, 16, 17, 27). Bacteraemia is the most common clinical infection caused by *S. paucimobilis* (8, 15, 18).

**Table 1.** Demographic Data and Clinical Characteristics of the *S. paucimobilis* Infections

| | Age | Sex | Nosocomial | Sample | Biofilm Formation | ICU Stay | Indwelling Catheter | Surgery | Steroid Use | Concominant Disease |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 69 | F | - | Urine | +++ | - | + | - | - | - |
| **2** | 64 | M | + | Blood | +++ | + | + | - | - | MA |
| **3** | 53 | M | - | Wound | ++ | - | - | - | - | - |
| **4** | 86 | M | + | Blood | +++ | + | + | + | - | DM , ARF |
| **5** | 68 | F | + | Blood | ++ | + | + | - | + | MA |
| **6** | 64 | F | + | Tr. Asp. | +++ | + | + | - | - | CVD |
| **7** | 64 | M | + | Blood | + | - | + | - | - | - |
| **8** | 77 | M | - | Wound | + | - | - | + | - | - |
| **9** | 71 | F | + | Blood | ++ | + | - | - | - | HT,DM, CVD |
| **10** | 62 | F | + | Urine | + | + | + | - | - | HT ,DM |
| **11** | 72 | F | + | Tr. Asp. | +++ | + | + | - | - | CAD, DM |
| **12** | 47 | M | - | Wound | ++ | - | - | - | - | MA |
| **13** | 59 | M | - | Wound | + | + | - | - | - | MA, DM |
| **14** | 54 | F | - | Urine | ++ | - | + | - | - | CRI |
| **15** | 63 | F | + | Tr. Asp. | ++ | + | - | - | - | MA |
| **16** | 49 | M | + | Blood | +++ | + | + | - | - | MA |
| **17** | 78 | M | - | Wound | + | - | + | + | - | - |
| **18** | 49 | M | + | Blood | +++ | + | + | - | - | MA |
| **19** | 59 | M | + | Blood | ++ | - | + | - | - | MA , DM |
| **20** | 15 | F | + | Urine | +++ | - | - | - | - | - |
| **21** | 79 | F | + | Blood | +++ | + | + | - | + | MA |
| **22** | 77 | F | + | Blood | ++ | - | + | - | - | DM, HT |
| **23** | 78 | F | + | Tr. Asp. | +++ | + | - | - | - | - |
| **24** | 79 | M | + | Blood | +++ | + | + | + | - | - |
| **25** | 67 | M | + | Tr. Asp. | ++ | + | - | - | - | HT, DM, CAD |
| **26** | 69 | F | + | Wound | + | - | + | - | - | - |
| **27** | 49 | F | + | Tr. Asp. | ++ | + | - | - | - | - |
| **28** | 59 | M | + | Blood | +++ | + | + | - | + | MA |
| **29** | 59 | F | + | Tr. Asp. | ++ | + | + | - | - | - |
| **30** | 1 | M | + | Blood | +++ | + | + | - | - | - |
| **31** | 54 | F | + | Blood | ++ | + | + | - | - | DM |
| **32** | 52 | F | + | Blood | +++ | + | - | - | - | COLD, HT |
| **33** | 75 | M | + | Blood | +++ | + | + | + | - | MA, DM |

Abbreviations: F, female; M, male; Tr. Asp., trakeal aspiration; MA, malignancy; DM, diabetes mellitus; ARF, acute renal failure; CRI, chronic renal failure; HT, hypertension; COLD, chronic obstructive lung disease; CVD, cerebrovascular disease; CAD, coronary artery disease.

In our series, 48.48% of the cases were identified as bacteraemia, followed by pneumonia, wound infections, and urinary tract infections. Most of the cases (78.79%) were nosocomial in origin. According to the reviews of Lin et al., Huesh et al., and Cheong et al. (8, 15, 19), most *S. paucimobilis* infections are healthcare associated. However, Toh et al. investigated 55 cases of *S. paucimobilis* infection and Bayram et al. evaluated 24 paediatric patients; both reported that the incidence of community-acquired infections was higher than that of nosocomial cases (14, 28). Since these studies assessed relatively few cases, it is impossible to reach a reliable conclusion regarding the source of such infections.

In many case reports, indwelling catheters and an immunosuppressed host were identified as risk factors for *S. paucimobilis* infections (8, 9, 18, 19, 28-30). Community-acquired infection, diabetes mellitus, and alcoholism were determined as risk factors for primary bacteraemia in the multivariate logistic regression presented by Toh et al. (14). Comorbidities such as malignancy and diabetes mellitus were also reported to be risk factors (18, 19). In our study, the most common concomitant diseases were malignancy (33.33%) and diabetes mellitus (30.30%). The presence of an indwelling catheter (72.73%) and hospitalisation in the intensive care unit (66.67%) were the most common risk factors in our study.

The antimicrobial susceptibility patterns of *S. paucimobilis* differ among studies. Tigecycline (84.85%) was the agent to which *S. paucimobilis* was most frequently susceptible in this study, but there are no data in the

**Table 2.** Antimicrobial Susceptibilities of the *S. paucimobilis* Isolates

| Antimicrobial Agent | *S. paucimobilis* ,n = 33 | | | | | |
|---|---|---|---|---|---|---|
| | Resistant | | Intermadiate | | Sensitive | |
| Amikacin | 8 | 24.24 | 2 | 6.06 | 23 | 69.70 |
| Amoxicillin-clavulanate | 23 | 69.70 | 0 | 0.00 | 10 | 30.30 |
| Ampicillin | 25 | 75.76 | 1 | 3.03 | 7 | 21.21 |
| Ampicillin-sulbactam | 23 | 69.70 | 1 | 3.03 | 9 | 27.27 |
| Cefazolin | 23 | 69,70 | 2 | 6.06 | 8 | 24,24 |
| Cefepime | 19 | 57.58 | 0 | 0.00 | 14 | 42.42 |
| Cefoperazone-sulbactam | 21 | 63.64 | 2 | 6.06 | 10 | 30.30 |
| Ceftazidime | 22 | 66.67 | 0 | 0.00 | 11 | 33.33 |
| Cefuroxime | 25 | 75.76 | 0 | 0.00 | 8 | 24.24 |
| Cefuroxime-axetil | 25 | 75.76 | 0 | 0.00 | 8 | 24.24 |
| Ciprofloxacin | 22 | 66.67 | 0 | 0.00 | 11 | 33.33 |
| Ertapenem | 10 | 30.30 | 0 | 0.00 | 23 | 69.70 |
| Gentamicin | 10 | 30.30 | 2 | 6.06 | 21 | 63.64 |
| Imipenem | 8 | 24.24 | 0 | 0.00 | 25 | 75.76 |
| Levofloxacin | 18 | 54.55 | 0 | 0.00 | 15 | 45.45 |
| Meropenem | 8 | 24.24 | 0 | 0.00 | 25 | 75.76 |
| Netilmicin | 6 | 18.18 | 1 | 3.03 | 26 | 78.79 |
| Piperacillin | 24 | 72.73 | 0 | 0.00 | 9 | 27.27 |
| Piperacillin-tazobactam | 18 | 54.55 | 3 | 9.09 | 12 | 36.36 |
| Tigecycline | 5 | 15.15 | 0 | 0.00 | 28 | 84.85 |
| Trimethoprim-sulfamethoxazole | 20 | 60.61 | 0 | 0.00 | 13 | 39.39 |

literature for comparison. *Sphingomonas paucimobilis* was also found to be sensitive to imipenem (75.76%) and meropenem (75.76%), netilmicin (78.79%), and amikacin (69.70%). Toh et al. and Bayram et al. (14, 28) reported that fluoroquinolones, carbapenems, and trimethoprim/sulfamethoxazole were the most effective antibiotics. Lin et al. stated that *S. paucimobilis* was frequently sensitive to fluoroquinolones, carbapenems, and beta-lactam/beta-lactamase combinations (19). Conversely, in our study, cephalosporins and beta-lactam/beta-lactamase were found to be less effective. In our study, the antimicrobials most commonly used for *S. paucimobilis* infections were carbapenems and third-generation cephalosporin/aminoglycoside combinations. With the exception of two patients who died of clinical syndromes other than infections, the remaining 31 patients were treated successfully. Some researchers suggest third-generation cephalosporin/aminoglycoside combinations for the treatment of this type of infection (8, 18, 19). However, standardised therapies cannot be established at present, because of the different antimicrobial susceptibility patterns among studies. Relying on antimicrobial susceptibility testing results is the most logical and appropriate approach, as always.

Demographic data showed no correlation with the degree of biofilm formation. However, biofilm formation intensity was significantly higher in primary bacteraemia ($P < 0.005$). Intensive care unit stay was also positively correlated with a high degree of biofilm production. Higher biofilm production is expected to correlate with the presence of an indwelling catheter, but that was not the case in our study ($P = 0.346$). This situation might be due to the relatively small number of isolates. There was no correlation between the degree of biofilm formation and presence of concomitant diseases. Studies including more patients and isolates are needed to explain the correlation of biofilm production with such variables.

Previously, this bacterium was regarded as being of low virulence (18, 19, 28, 31). In a recent study, however, the *S. paucimobilis* virulence factors were reported to re-

**Table 3.** Correlation of Intensity of Biofilm Formation With Patient Characteristics[a]

| Patient Characteristics | *S. paucimobilis* Infection | Biofilm Formation | | | *P Value* |
|---|---|---|---|---|---|
| | | +1 | +2 | +3 | |
| **Age, y** | | | | | |
| 1 - 50 | 6 (18.18) | 0 | 3 (50.0) | 3 (50.0) | 0.098 |
| 50 - 70 | 17 (51.52) | 4 (23.53) | 9 (52.94) | 4 (23.53) | |
| over 70 | 10 (30.30) | 2 (20.00) | 1 (10.00) | 7 (70.00) | |
| **Sex** | | | | | |
| Female | 17 (51.52) | 2 (11.76) | 9 (52.94) | 6 (35.29) | 0.241 |
| Male | 16 (48.48) | 4 (25.00) | 4 (25.00) | 8 (50.00) | |
| **Source of infection** | | | | | |
| Nosocomial | 26 (78.79) | 3 (11.54) | 9 (34.62) | 14 (53.85) | 0.024 |
| Community | 7 (21.21) | 3 (42.86) | 4 (57.14) | 0 | |
| **Sample** | | | | | |
| Blood | 16 (48.48) | 1 (6.25) | 4 (25.00) | 11 (68.75) | 0.003 |
| Tracheal aspiration | 7 (21.21) | 0 | 4 (57.14) | 3 (42.86) | |
| Wound | 6 (18.18) | 4 (66.67) | 2 (33.33) | 0 | |
| Urine | 4 (12.12) | 1 (25.00) | 3 (75.00) | 0 | |
| **Risk factors** | | | | | |
| Indwelling catheter | 24 (72.73) | 4 (16.67) | 8 (33.33) | 12 | 0.346 |
| ICU stay | 22 (66.67) | 2 (9.09) | 6 (27.27) | 14 | 0.002 |
| Surgery | 5 (15.15) | 2 (40.00) | 0 | 3 | 0.262 |
| Steroid use | 3 (9.09) | 0 | 1 (33.33) | 2 | 0.792 |
| **Concominant disease** | | | | | |
| Malignancy | 11 (33.33) | 6 (54.55) | 4 (36.36) | 1 (9.09) | 0.507 |
| Diabetes mellitus | 10 (30.30) | 2 (20.00) | 4 (40.00) | 4 (40.00) | 0.977 |
| Hypertension | 5 (15.15) | 1 (20.00) | 2 (40.00) | 2 (40.00) | 0.990 |
| Chronic renal insufficiency | 3 (9.09) | 1 (33.33) | 1 (33.33) | 1 (33.33) | 0.774 |
| Coronary artery disease | 2 (6.06) | 0 | 1 (50.00) | 1 (50.00) | 0.778 |
| Cerebrovascular disease | 2 (6.06) | 0 | 0 | 2 (100.00) | 0.236 |
| Chronic obstructive lung disease | 1 (3.03) | 0 | 0 | 1 (100.00) | 0.497 |

[a] Values are expressed as No. (%).

semble those of *Pseudomonas* spp. These factors included proteases (alkaline protease, LasA, LasB), adherence factors (lipopolysaccharide, type IV pili), iron uptake (pyoverdin, pyochelin), a biosurfactant (rhamnolipid), and antiphagocytosis factors (alginate) (32). Type IV pili and alginate production are also involved in biofilm formation. We determined biofilm production in all clinical isolates of *S. paucimobilis* included in this study. Therefore, biofilm production by *S. paucimobilis* can be accepted as an important virulence factor, especially in patients in intensive care units and those with suspected primary bacteraemia.

### 5.1. Conclusion

Our study is the first research article to demonstrate biofilm production by clinical *S. paucimobilis* isolates. *Sphingomonas paucimobilis* infections are not uncommon as has been thought, and can cause serious infections, especially in immunocompromised patients with determined risk factors, due to the effects of multiple virulence factors, together with biofilm formation.

## Footnote

**Authors' Contribution:** Study concept and design: Tayfur Demiray; acquisition of data: Tayfur Demiray and Mehmet Koroglu; analysis and interpretation of data: Tayfur Demiray, Mehmet Koroglu and Ahmet Ozbek; drafting of the manuscript: Tayfur Demiray, Mehmet Koroglu, Ahmet Ozbek and Mustafa Altindis; critical revision of the manuscript for important intellectual content: Tayfur Demiray, Mehmet Koroglu and Ahmet Ozbek; statistical analysis: Mehmet Koroglu and Ahmet Ozbek; administrative, technical, and material support: Mehmet Koroglu, Ahmet Ozbek and Mustafa Altindis; study supervision: Ahmet Ozbek and Mustafa Altindis.

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