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Brief Communication

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Phenotypic Characteristics and Clonal Relationships of *Stenotrophomonas maltophilia* Isolates in Hospitalized Adults from a Private Center in Lima, Peru

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ABSTRACT

Stenotrophomonas maltophilia is an opportunistic pathogen, often associated with nosocomial infections. Ten *S. maltophilia* were isolated from clinical samples during the period January 2021 and June 2022. Eight (80%) patients had cancer as a background disease and 2 patients had coronavirus disease 2019. A fatal outcome was recorded in 4 cases (40% of patients). All the isolates were susceptible to minocycline and levofloxacin. Trimethoprim/sulfamethoxazole and ceftazidime resistance rates were 20% and 40% respectively. Eight different patterns were observed by Pulsed-Field Gel Electrophoresis, only two isolates being clonally identical. The isolation of *S. maltophilia* in clinical settings requires the implementation of infection prevention measures.

Keywords: Drug Resistance; Pulsed-Field Gel Electrophoresis; *Stenotrophomonas maltophilia*

Stenotrophomonas maltophilia is a Gram-negative non-fermentative bacillus and opportunistic pathogen. *S. maltophilia*, mainly affects immunocompromised individuals and it is often associated with nosocomial infections [1]. Additionally, rates of mortality of 69% have been described in systemic infections related to this microorganism [2].

S. maltophilia is intrinsically resistant to different antibiotics such as aminoglycosides and carbapenems, which limits the therapeutic options [3]. Furthermore, recent studies have reported alarming increases in the number of isolates and resistance rates of *S. maltophilia* [4]. However, there are a limited number of studies in Peru and the characteristics of this emerging bacteria have not been reported in the area. This study aimed to analyze the antimicrobial susceptibility profile and clonal relationship of *S. maltophilia* isolates recovered from a Peruvian healthcare center.

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S. maltophilia were isolated from clinical samples including blood, bronchial secretion, and throat swabs submitted for diagnostic purposes in two centers of Lima (Peru), Oncosalud and Clinica Delgado, belonging to the network of Auna Clinics during the period January 2021 and June 2022. Oncosalud is a private healthcare center primarily dedicated to care of cancer patients, meanwhile Clinica Delgado is a generalist center attending a variety of pathologies.

The isolates were identified by the Vitek®2 system (bioMérieux, Marcy l'Etoile, France) and confirmed by mass spectrometry using a Matrix-Assisted Laser Desorption/Ionization-Time Of Flight (MALDI-TOF) (MALDI Biotyper®, Bruker Daltonics GmbH & Co. KG, Bremen, Alemania). The results were analyzed using the MBT Compass Library V11.0.0.0 (July 2021) database. Those isolates that had a low MALDI-TOF confidence score were confirmed as *S. maltophilia* by sequencing of 16S rRNA [5].

Antimicrobial susceptibility testing was performed by disc diffusion method. Tested antibiotics were levofloxacin (5 μg), minocycline (30 μg), and trimethoprim/sulfamethoxazole (TMP/SMX) (1.25/23.75 μg). Additionally, the minimum inhibitory concentration (MIC) of ceftazidime was determined with Vitek®2 system (bioMérieux). All the values were interpreted according to the recommendation of the Clinical Laboratory Standard Institute guidelines [6].

The clonal relationships of the strains were established by pulsed-field gel-electrophoresis (PFGE). Bacterial DNA embedded in agarose plugs were prepared [7] and digested by the *XbaI* restriction enzyme. The PFGE condition was one ramp at 6 V/cm, at 14ºC and with pulse time ranging from 5 s to 35 s during 20 h. DNA profiles were analyzed using the GelJ Software [8].

Ten *S. maltophilia* strains were isolated from blood (5 isolates, 50%), bronchial secretion (2 isolates, 20%), and one isolate each from throat swabs, abdominal drainage, and bile, respectively. Six (60%) patients were admitted to the intensive care unit (ICU). The mean age of the patients was 66 years, and 60% of them were male. Regarding comorbidities, 8 (80%) patients had cancer as a background disease and 2 patients had a diagnosis of coronavirus disease 2019. A fatal outcome was recorded in 4 patients (40% of patients); all of them with comorbidities: 4 patients had a tumor (40% of patients with this comorbidity), and one of them also had diabetes mellitus. Demographic data and patient characteristics are shown in **Table 1**.

Table 1. Demographic data and characteristics of patients with *Stenotrophomonas maltophilia* infection

Patient	Isolation Date	Age	Sex	Hospital stay (days)	Sample	Comorbidities	TMP/SXT	MIN	LVX	CAZ (MIC in μg/mL)	Outcome	Unit	Clinic
1	Feb/14/2021	74	Male	144	Bronchial secretion	Malignant tumor of colon, Diabetes mellitus type 2	R	S	S	R (32)	D	ICU	Clinica Delgado
2	Mar/02/2021	51	Male	17	Pharyngeal secretion	COVID-19	S	S	S	R (≥64)	L	Emergency	Oncosalud
3	Oct/10/2021	64	Male	19	Bronchial secretion	High blood pressure	S	S	S	S (0, 5)	L	ICU	Clinica Delgado
4	May/09/2022	60	Female	26	Blood culture	Large cell non-Hodgkin lymphoma	R	S	S	R (32)	L	ICU	Clinica Delgado
5	May/13/2022	89	Male	>150	Blood culture	Multiple myeloma	S	S	S	S (4)	L	ICU	Clinica Delgado
6	May/17/2022	69	Female	31	Abdominal drainage secretion	Malignant ovarian tumor	S	S	S	S (4)	L	ICU	Oncosalud
7	May/20/2022	73	Female	11	Biliary drain secretion	Intrahepatic bile ducts carcinoma	S	S	S	S (1)	D	General medicine	Oncosalud
8	Jun/06/2022	58	Male	24	Blood culture	Peripheral T-cell lymphoma	S	S	S	R (≥64)	D	General medicine	Clinica Delgado
9	Jun/16/2022	44	Female	11	Blood culture	Malignant tumor of the head of the pancreas	S	S	S	S (4)	D	Emergency	Oncosalud
10	Jun/28/2022	73	Male	>150	Blood culture	Malignant tumor of the prostate, COVID-19	S	S	S	S (4)	L	ICU	Clinica Delgado

TMP/SXT, trimethoprim/sulfamethoxazole; MIN, minocycline; LVX, levofloxacin; CAZ, ceftazidime; MIC, minimum inhibitory concentration (CAZ Resistance Breakpoint ≥32 μg/mL); R, resistant; S, sensitive; D, death; L, live; ICU, intensive unit care; COVID-19, coronavirus disease 2019.

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Recovering of *S. maltophilia* in samples from respiratory tract might be related to the ability of *S. maltophilia* for colonize epithelium of respiratory tract [9]. Nevertheless, isolates from patients 1, 2 and 3 came from non-sterile sites (bronchial and pharyngeal secretions), but *S. maltophilia* colonization might not be ruled out, because two of these patients attended to the ICU (patients 1 and 3), and the other one has a history of previous admissions, all three presenting different comorbidities which might compromise immune system. *S. maltophilia* is a common cause of respiratory tract infections in patients with these characteristics [10].

Overall, *S. maltophilia* isolates were susceptible to levofloxacin and minocycline. The rates of resistance to ceftazidime were 40% while those to TMP/SMX were 20%. All the strains could be recovered for molecular typification. The PFGE showed eight different patterns. Two blood-recovered *S. maltophilia* strains (isolates from patients 5 and 10) showed identical PFGE-pattern, and both patients were admitted to the same ICU, coinciding more than 100 days. Other two strains (isolates from patients 3 and 8) showed identity levels higher than 80% and thereby being clonally related (**Fig. 1**).

S. maltophilia, an opportunistic bacterium, has become an important nosocomial pathogen. A great number of studies around the world shows an alarming increased number of isolates in patients with comorbidities [11]. This microorganism is often associated with immunocompromising conditions, invasive procedures, prolonged length of stay in the hospital, ICU admission, and exposure to broad-spectrum antibiotics [11, 12]. In this work, accordingly to obtained results, 80% of inpatients had immunocompromising conditions, and most of them had ICU admission. Fatal outcomes were frequent in the present study (40% of patients), with this finding also in agreement with previous reports [13]. Thus, while often opaqued by the higher number of difficult to treat and fatal infections related to other pathogens such as the members of the *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter* spp. (ESKAPE) group [13], mortality rates related to *S. maltophilia* infections are of relevance, with studies showing mortality rates >60% with a special negative impact in patients with malignancies attending to ICU [14].

TMP/SMX was considered as election treatment for *S. maltophilia* infections [15]. Reports around 2012 showed that *S. maltophilia* clinical isolates presented 100% susceptibility to TMP/SMX [1]. However, TMP/SMX resistance has slowly increased in the last ten years and recent studies showed that treatment with other antibiotics such as minocycline or levofloxacin had the same or better outcome [16]. In the present study, all strains were susceptible to minocycline and levofloxacin, whereas 2 of 10 strains showed TMP/SMX resistance, alerting about the need to consider the presence of TMP/SMX-resistant *S. maltophilia* isolates in the area. High rates of resistance to ceftazidime have been reported since 2015 [3]. While no data about Peru situation was available, and according to our findings, resistance to ceftazidime was higher than 40%, suggesting worldwide resistance rates to cephalosporins.

PFGE typification showed eight different patterns among the 10 analyzed isolates, that represent a high clonal diversity degree. Thereby no obvious epidemic spread of *S. maltophilia* was found in this study. These results are consistent with several studies that indicate low cross-transmission of this bacteria, and high clonal heterogeneity in clinical settings [17-19].

The present study has several limitations. The number of isolates was small; hence, the findings may not be

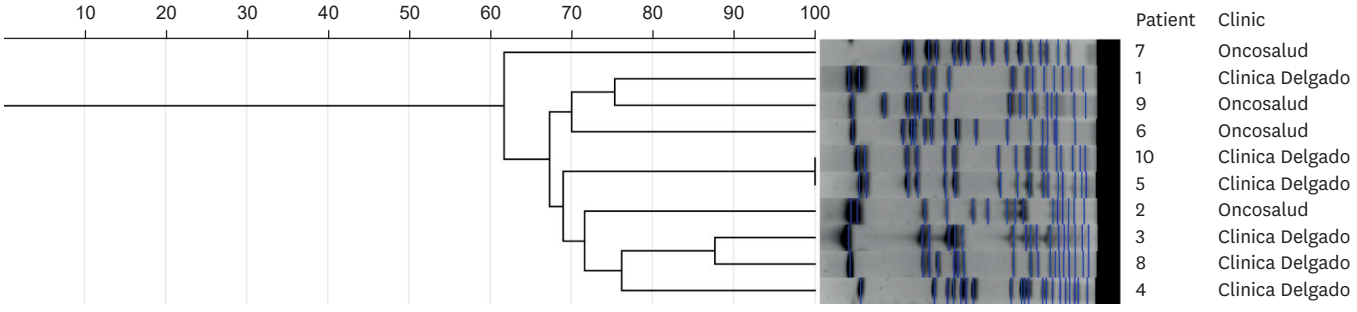

Figure 1. Dendrogram of the obtained *XbaI* PFGE profiles of clinical *Stenotrophomonas maltophilia* isolates.
PFGE, Pulsed-Field Gel Electrophoresis.

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generalizable. In addition, we could not investigate the history of the use of antibiotics which is important because it is a factor related to the selection of antibiotic resistance as well as relevant in the analysis of patient outcomes. Furthermore, the fatal outcomes might be attributable to the underlying pathology instead to *S. maltophilia*, but the presence of bacterial infections undoubtedly has a role in the aggravation of patient's status.

S. maltophilia is currently considered an opportunistic pathogen. Most of the isolates belonged to patients with risk factors such as ICU attendance and immunocompromising conditions. The association of *S. maltophilia* with nosocomial infections and the observed worrisome lethality rates require the implementation of effective measures for infection prevention, including continuous surveillance and monitoring of the resistance rates. This work represents the first study of clonal relatedness and an overview of antibiotic resistance of *S. maltophilia* clinical isolates in Peru.

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Ethics statement
This study was approved by the IRB of Universidad Científica del Sur (Approval: 074-2020-PRO99). No informed consent forms of any patient were required since this study used laboratory test registers and patient medical records in obtaining data.

Conflict of Interest
No conflict of interest.

Author Contributions
Conceptualization: TOG, JR. Data curation and Formal analysis: ACG. Investigation: PT,ML,CAA. Methodology: TOG, PT. Project administration: JL,YS. Resources: JL,YS. Software: PT,ML. Supervision: JL,YS. Writing - original draft: TOG, ACG, JR. Writing - review & editing: TOG, PT, ACG, ML, CAA, JR, JL, YS.

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