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Clinical and microbiological characteristics of patients colonized or infected by *Stenotrophomonas maltophilia*: is resistance to sulfamethoxazole/trimethoprim a problem?

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ABSTRACT

Stenotrophomonas maltophilia has emerged as an important opportunistic pathogen in the last decade. Increased resistance to sulfamethoxazole/trimethoprim (SMX/TMP) has been reported in *S. maltophilia* strains in the past few years, leading to few therapeutic options. We conducted a prospective multicenter study at two Brazilian teaching hospitals that identified *S. maltophilia* isolates and evaluated their antimicrobial susceptibility profile, SMX/TMP resistance genes and their clonality profile. A total of 106 non-repeated clinical samples of *S. maltophilia* were evaluated. Resistance to SMX/TMP was identified in 21.6% of the samples, and previous use of SMX/TMP occurred in 19 (82.6%). PCR detected the *sul1* gene in 14 of 106 strains (13.2%). Of these isolates, nine displayed resistance to SMX/TMP. The resistant strains presented a polyclonal profile. This opportunistic pathogen has emerged in immunocompromised hosts, with few therapeutic options, which is aggravated by the description of emerging resistance mechanisms, although with a polyclonal distribution profile.

KEYWORDS: *Stenotrophomonas maltophilia*. Immunocompromised patients. Sulfamethoxazole/trimethoprim resistance. Gram-negative infection.

INTRODUCTION

The management of *Stenotrophomonas maltophilia* infection is usually challenging as a result of its intrinsic resistance profile to the various classes of antimicrobials[1]. *S. maltophilia* produces chromosomal β-lactamases (L1 and L2), which presents an impermeable membrane that expresses efflux pumps and acquires additional resistance genes in class 1 integrons[2]. To date, the treatment of choice for infections caused by *S. maltophilia* has been sulfamethoxazole/trimethoprim (SMX/TMP)[3]. However, resistance to this drug has increased in recent years, mainly due to the spread of *sul*-1, *sul*-2, and *dfr*A genes[4].

The aim of this study was to describe the clinical and microbiological characteristics of *S. maltophilia* isolates and to study its antimicrobial susceptibility, presence of resistance genes and clonality profile.

MATERIALS AND METHODS

Study design

A prospective multicenter study was conducted over a 2-year period

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(January 2009 to December 2010) in two Brazilian teaching hospitals: Hospital das Clinicas, Faculty of Medicine, Sao Paulo University (2,000 beds) and an oncology center at Hospital A.C. Camargo (450 beds). We collected clinical samples and evaluated demographic and clinical data of patients colonized or infected by *S. maltophilia.* Patients were classified as colonized by *S. maltophilia* if the isolates were identified from the tip of a central venous catheter (CVC) and/or CVC blood samples and infected based on the Centers for Diseases Control and Prevention (CDC) criteria[5]. The following variables were evaluated: sex, age, hospital unit (nursery, intensive care unit, transplantation unit etc.), underlying diseases, presence of CVC, site of colonization or infection, previous use of SMX/TMP and drug used to treat the *S. maltophilia* infection. A database was created using Epi Info software version 3.5.1 (Centers for Disease Control and Prevention, Atlanta, USA). Variables were evaluated as frequencies, means and medians.

Microbiology

Isolates were identified by API 20 NE (bioMérieux, Craponne, France). The microdilution method was used to evaluate susceptibility to SMX/TMP, ciprofloxacin, levofloxacin, minocycline, ceftazidime, chloramphenicol and ticarcillin/clavulanate according to the Clinical & Laboratory Standards Institute[6]. The minimum inhibitory concentration (MIC) of tigecycline was determined following the US Food and Drug Administration recommendation for Enterobacteriaceae. Endonuclease-digested genomic DNAs were separated by pulsed-field gel electrophoresis using a CHEF-DR III system (Bio-Rad, Hercules, CA, USA). Genomic DNA was digested with 10 U of SpeI (Fermentas, Waltham, MA, USA). Running conditions were 21 h at 14 °C, with an initial switching time of 1 s and final time of 30 s at 6 V/cm.

A polymerase chain reaction (PCR) was performed to evaluate resistance to SMX/TMP of the 106 samples and to detect the genes *sul1*, *sul2*, and *dfrA1*. The presence of mobile genetic elements with the *int1* and *iscr2* genes was also investigated. The presence of *sul1*, *sul2*, *dfrA*, *int1*, *iscr2* genes in each strain was assessed using the primers described below (Table 1).

After amplification of the genes by PCR, one of the products of each reaction was used to perform a new PCR with the oligonucleotides chosen for gene sequencing. The amplified gene was purified using a GFXTM PCR DNA and Gel Band Purification kit (GE Healthcare, Chicago, IL, USA) according to the manufacturer's instructions. The DNA quantification was estimated by using the Low DNA Mass Ladder (Invitrogen, Carlsbad, CA, USA).in 2% agarose gel electrophoresis.

Table 1 - Sequence of primers to amplify int1, sul1, sul2, dfrA and Iscr2 genes and the corresponding molecular weight of the targets.

Primer	Sequence 5´-3´	Target
Int1	CGAATTCTTGCGGTTTCTTTCAGC TTCGAATGTCTAACCGC	457
Sul1	ATGGTGACGGTGTTCGGATTCTGA CTAGGCATGATCTAACCCTCGGTCT	840
Sul2	CTAGGCATGATCTTAACCCTCGGTCT GAATAAATCGCTCATCATTTTCGG	810
dfrA	CTTTGGACCGCAGTTGACTC AGCTCTTCACCTTTGGC	425
Iscr2	CGAGGCATAGACTGTAC CACTGGCTGGCAATGTCTAG	425

Sequencing of three different strains were performed t at the human USP genome Institute, using an ABI 3730 DNA Analyzer DNA analysis system (Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, USA) and the BigDye Terminator v3.1 Cycle Sequencing Kit (NimaGem, Nijmegen, The Netherlands). The BioEdit software version 7.0.9 (Nucleics Pty Ltd., Woollahra, Australia) was used to perform the analyses. The genetic sequence was compared with BLAST[7]. This study was approved by the Ethics Committee of the two hospitals.

RESULTS

We evaluated data from 106 patients with *S. maltophilia* during the study period. The mean age was 57 years and 58% were male. There were 24 cases (22.6%) of colonization and 82 cases (77.6%) of infection.

Clinical samples

A total of 106 non-repeated clinical samples of *S. maltophilia* were evaluated, as described in Table 2. Forty-nine were isolated from blood cultures (46.2%). Table 2 also shows the distribution of *S. maltophilia* isolates according to the site of infection; bloodstream infection was the main site (44.2%) followed by the respiratory tract (34.9%). The patients' comorbidities suggest some degree of immunosuppression (25.3%) or chronic respiratory disease (37.7%) (Table 2).

The antimicrobial susceptibility profile of the strains is shown in Table 3. The strains displayed remarkable resistance to SMX/TMP 23 (21.6%), and 13.3% were resistant to levofloxacin. The MIC50 and MIC90 of the 106 isolates were determined by the broth microdilution

Table 2 - Clinical, epidemiological and microbiological description of 106 *S. maltophilia* isolates in two hospitals in Sao Paulo over a 2-year period.

Characteristics	Total 106, n (%)	SMX/TMT resistance, n (%)
Clinical isolates		
Blood	46 (44.3)	6 (26)
Catheter tip	4 (3.8)	4 (17.4)
Tracheal aspirate/bronchoalveolar lavage	31 (29.2)	10 (43.5)
Pleural fluid	1 (0.9)	0
Urine	11 (10.3)	1 (4.3)
Bone	2 (1.8)	1 (4.3)
Others	9 (8.5)	1 (4.3)
Site of infection		
Primary bloodstream infection	15 (14.1)	6 (20)
Central venous catheter infection	32 (30.1)	4 (12.5)
Respiratory tract infection	37 (34.1)	10 (27.7)
Urinary tract infection	11 (10.3)	1 (9)
Osteomyelitis	2 (1.8)	1 (50)
Others	9 (8.5)	1 (12.5)
Resistance genes		
sul1	14 (13.2)	8 (34.8)
sul2	1 (0.94)	1 (4.3)
dfrA1	1 (0.94)	0
Mobile genetic elements		
Integron	21 (19.8)	9 (39.1)
Iscr2	1 (0.94)	1 (4.3)
Underlying disease		
Chronic respiratory disease	40 (37.7)	
Hematologic malignancy	15 (14.1)	
Solid tumor	11 (10.3)	
Chronic renal insufficiency	10 (9.4)	
Cardiovascular disease	7 (6.6)	
Trauma	6 (5.6)	
AIDS	1 (0.9)	
Others	16 (15.6)	

method (Table 2). The characteristics of the 23 SMX/TMP-resistant samples are shown in Table 4. Most were isolated at Hospital das Clinicas (91.3%). Nine (39.2%) samples were from tracheal aspirates and 10 were from blood cultures (43.5%). Previous use of SMX/TMP was reported in 19 (82.6%) of the 23 patients, and the main comorbidity was cancer (39.1%). Fourteen (60.8%) patients were admitted to the intensive care unit. The *sul-1* gene was found in only 9 of 23 strains (39.1%). The antimicrobial susceptibility of the 23 SMX/TMP-resistant strains are shown in Table 4. All of them showed resistance to other antimicrobials, and 12 (52%) also displayed resistance to levofloxacin. PCR detected the *sul1* gene in 14 of 106 strains (13.2%) (Table 2). Of these isolates, nine displayed resistance to SMX/TMP, with MICs ranging from 8 to 128 µg/mL.

Twenty-one strains (19.8%) carried the integrase1 (*int1*) gene, of which nine displayed resistance to SMX/TMP. The *sul1* gene was detected in seven cases (MIC50, 8 µg/mL; MIC90, 128 µg/mL). On the other hand, 14 samples harboring *int1* and negative for the *sul1* gene presented lower SMX/TMP MICs (MIC50, 2 µg/mL; MIC90, 16 µg/mL). The *sul2* gene was detected in only one SMX/TMP-resistant

Table 3 - Minimal inhibitory concentrations (MIC50 and MIC90) by the microdilution method and antimicrobial susceptibility profile of 106 *S. maltophilia* isolates.

Antibiotics	MIC_{50} mg/µL	MIC_{90} mg/µL	Antimicrobial susceptibility profile (%)
Sulfamethoxazole/ trimethoprim	1	32	83 (78.3%)
Levofloxacin	1	4	87 (82%)
Ceftazidime	64	≥ 128	22 (20.7%)
Minocycline	≤ 0.25	2	105 (99%)
Ciprofloxacin	4	32	15(14.2%)
Chloramphenicol	16	64	33 (31.1%)
Ticarcillin-Acid. Clavulanate	32	128	29 (27.4%)
Tigecycline	1	2	97 (91.6%)

Table 4 - Description of the 23 *S. maltophilia* strains resistant to SMX/ TMP.

Hospital	Sample	Previous use of SMX/TMP	Integron	*sul1*	*sul2*	MIC SMX/TMP (µg/µL)	Other antimicrobial resistance					
							LVX	CAZ	CIP	CLO	TGC	TIM
HC	BAL	+	–	–	–	8	R	R	R	R	S	R
ACC	CVC	+	+	+	–	8	S	R	R	R	S	R
ACC	CVC	+	+	+	–	>128	S	R	R	R	S	R
HC	Blood	+	–	–	–	8	R	R	R	R	R	S
HC	Bone	–	+	–	–	16	S	R	R	R	S	R
HC	Blood	+	+	–	–	8	S	R	R	R	S	R
HC	Blood	–	–	–	+	16	S	R	R	R	S	R
HC	TA	+	+	–	–	32	S	R	R	S	S	R
HC	TA	+	+	–	–	8	R	R	R	R	S	R
HC	TA	+	–	–	–	8	S	R	R	R	S	R
HC	Blood	+	–	–	–	4	R	R	R	S	S	R
HC	CVC	+	+		–	32	R	R	R	S	S	S
HC	CVC	+	–	–	–	32	S	R	R	R	S	R
HC	Bile	–	–	–	–	16	R	R	R	R	S	R
HC	TA	+	+	–	–	16	R	R	R	S	S	R
HC	TA	+	–	–	–	4	S	R	R	S	S	R
HC	TA	+	–	–	–	16	R	R	R	R	R	R
HC	Blood	+	–	+	–	32	R	R	R	R	S	R
HC	Urine	–	–	+	–	8	R	R	R	S	S	R
HC	TA	+	–	+	–	4	R	R	R	R	S	R
HC	Blood	+	–	+	–	128	R	R	R	R	S	R
HC	TA	+	+	+	–	8	S	R	R	R	S	S
HC	TA	+	–	+	–	128	S	R	R	S	S	R

SMX/TMP = Sulfamethoxazole/trimethoprim; HC = Hospital das Clinicas da FMUSP; CVC = central venous catheter; BAL = bronchoalveolar lavage; TA = Tracheal aspirate; LVX = levofloxacin; CAZ = ceftazidime; CIP = ciprofloxacin; CLO = chloramphenicol; TGC = tigecycline; TIM = ticarcillin/clavulanate.

strain (MIC, 16 µg/mL), which was *sul1* negative. No SMX/TMP susceptible strain was positive for *sul2* (Table 4). Of all 106 strains tested, only one that was susceptible to SMX/TMP was positive for the *dfrA1* gene (MIC, 0.25 µg/mL) (Table 2). *ISCR2* was evaluated in the SMX/TMP-resistant strains and was identified only in the strain harboring the *sul2* gene.

Figure 1 shows a graphical representation of the genes from a *S. maltophilia* strain (number 24) carrying *sul2* and *iscr2* genes. It shows a sequence of 1,713 bp corresponding

to the *iscr2* gene, followed by a region of 184 bp representing the phosphoglucosamine (glmM) mutase pseudogene and the adjacent 730 bp *sul2* gene. The integron-1 sequence of the sample (number 15) with MIC >128 µg/mL showed an approximate size of 4,000 bp containing the *aac4* and *aadA1* cassette genes and the *qac*/*sul1* region (Figure 2). A schematic representation of integron class 1 in SMX/TMP-resistant *S. maltophilia* sample (number 13) with MIC of 8 µg/mL is shown in Figure 3. The strain presented in Figure 4 was sequenced (2,000 bp) and contains the aadA1 cassette gene and the qac/sul1 terminal region (SMX/TMP MIC, 8 µg/mL). Isolates were assigned the same pulse type if the Dice coefficient value of similarity was 80%[8].

DISCUSSION

This study described the epidemiological profile, antimicrobial susceptibility, and mechanisms of resistance of 106 strains of *S. maltophilia* in two teaching, tertiary hospitals in Brazil. This opportunistic pathogen has emerged in debilitated hosts, who are often hospitalized for prolonged periods, using invasive devices, and are on broad-spectrum antibiotic therapy[3]. This profile was confirmed in our series; 63.2% of the infected patients were immunocompromised or had a chronic respiratory disease and 60.8% were admitted to the intensive care unit.

Although *S. maltophilia* is not a highly virulent pathogen[9,10], it has a unique ability to colonize the respiratory tract and invasive devices. The main sites of infection in this study were CVC-related infection and lower respiratory tract infection as seen in many other studies[9-11].

SMX/TMP is the treatment of choice for this infection, presenting near 90% susceptibility in most centers[12,13]. However, SMX/TMP resistance has increased in the last decade[2,12,14]. In our case series, 78.3% of the *S. maltophilia* isolates showed susceptibility to SMX/TMP. Another concern is that, in our study, all strains resistant to SMX/TMP also displayed resistance to other antimicrobials, such as ceftazidime (100%), ticarcicline/clavulanate (87%)

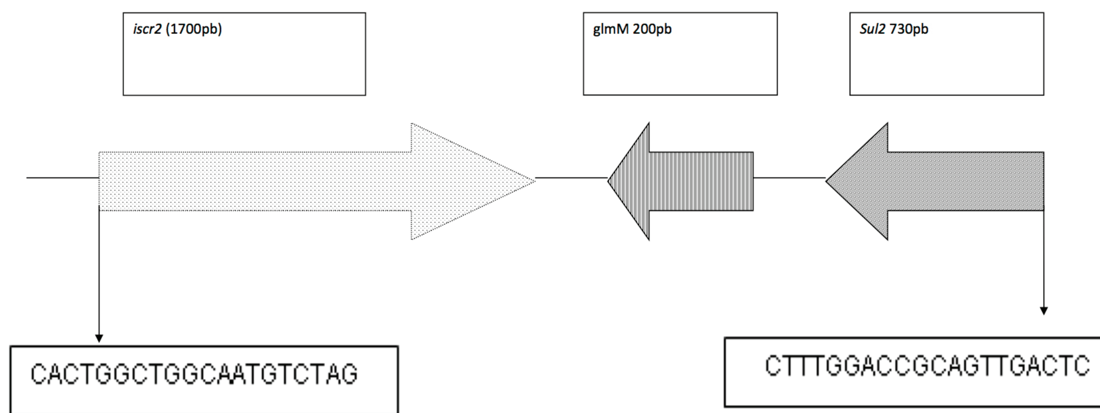


Figure 1 - Schematic representation of the *iscr2* sequence and adjacent genes from a positive sample for the *S. maltophilia sul2* gene.

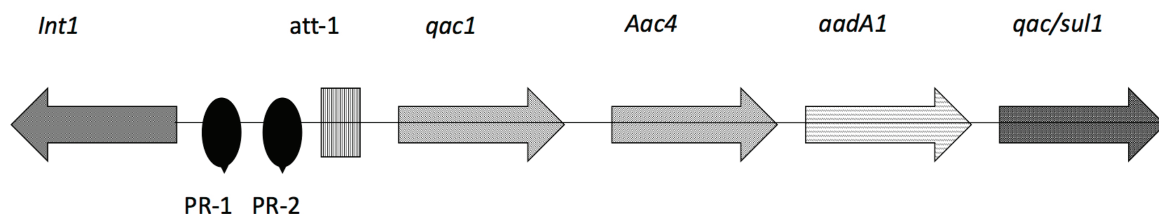


Figure 2 - Schematic representation of integron class 1 in an SMX/TMP-resistant *S. maltophilia* sample with MIC >125 µg/mL.

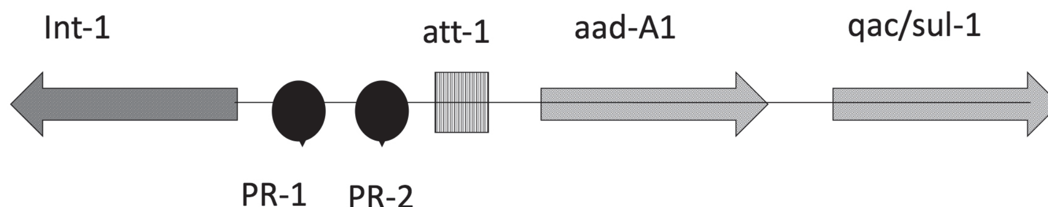
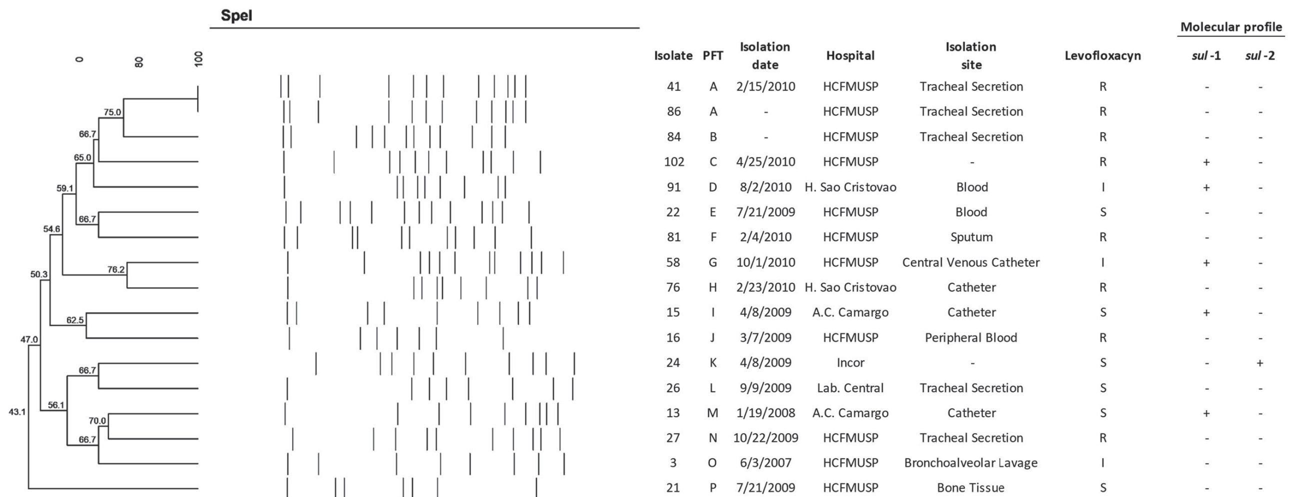


Figure 3 - Schematic representation of integron class 1 in an SMX/TMP-resistant *S. maltophilia* sample with MIC of 8 µg/mL.



Isolate	PFT	Isolation date	Hospital	Isolation site	Levofloxacyn	Molecular profile *sul*-1	*sul*-2
41	A	2/15/2010	HCFMUSP	Tracheal Secretion	R	-	-
86	A	-	HCFMUSP	Tracheal Secretion	R	-	-
84	B	-	HCFMUSP	Tracheal Secretion	R	-	-
102	C	4/25/2010	HCFMUSP	-	R	+	-
91	D	8/2/2010	H. Sao Cristovao	Blood	I	+	-
22	E	7/21/2009	HCFMUSP	Blood	S	-	-
81	F	2/4/2010	HCFMUSP	Sputum	R	-	-
58	G	10/1/2010	HCFMUSP	Central Venous Catheter	I	+	-
76	H	2/23/2010	H. Sao Cristovao	Catheter	R	-	-
15	I	4/8/2009	A.C. Camargo	Catheter	S	+	-
16	J	3/7/2009	HCFMUSP	Peripheral Blood	R	-	-
24	K	4/8/2009	Incor	-	S	-	+
26	L	9/9/2009	Lab. Central	Tracheal Secretion	S	-	-
13	M	1/19/2008	A.C. Camargo	Catheter	S	+	-
27	N	10/22/2009	HCFMUSP	Tracheal Secretion	R	-	-
3	O	6/3/2007	HCFMUSP	Bronchoalveolar Lavage	I	-	-
21	P	7/21/2009	HCFMUSP	Bone Tissue	S	-	-

Figure 4 - Representation of the clonality profile obtained by the pulsed-field gel electrophoresis method with the SpeI enzyme, of 17 positive strains for the *S. maltophilia sul1* gene with resistance to SMX/TMP.

and levofloxacin (52%). On the other hand, minocycline and tigecycline exhibited good activity *in vitro* in our study. However, there is a lack of evidence evaluating the clinical efficacy of these antimicrobials to treat severe infections caused by *S. maltophilia*. Shohaib *et al.*[15] described broad-spectrum antimicrobial use and previous intensive care unit admission as risk factors for multidrug-resistant *S. maltophilia* infections. We observed that, among the patients with SMX/TMP-resistant strains, 82.7% had already used this antibiotic previously.

The *sul1* gene is the main mechanism of resistance to SMX in *S. maltophilia* described to date. This gene is in the conserved 3' region of class 1 integrons, which are located in plasmids ranging in size from 2.1 to 54.2 kB[2]. Another study described 55 genetically unrelated strains of which 25 were resistant to SMX/TMP, and 17 had the *sul1* gene located in the 3' region of the class-1 integron. The authors asserted that susceptible strains did not contain the *sul1* gene[16]. In our series, the *sul1* gene was found in 39.1% of SMX/TMP-resistant strains and in only 6% of the 83 susceptible ones, suggesting an association of this gene with resistance to SMX/TMP. A recent study conducted in a Brazilian hospital reported the presence of both *sul1* and *sul2* in SMX/TMP-resistant *S. maltophilia*[16]. In our study, five positive samples for the *sul-1* gene were susceptible to SMX / TMP. Hu *et al.*[2] also found that 66% sensitivity to SMX/ TMP in positive *sul-1* strains. This finding suggests that the presence of the gene alone does not necessarily define resistance.

The *sul2* gene, which is present in transposase-like (ISCR) elements located in plasmids or within the bacterial chromosome, is also associated with resistance to SMX/ TMP[6]. The authors suggest that *Sul*2 may reduce the sensitivity of *S. maltophilia* to SMX/TMP. In this study, *Sul*2 was detected in only one of the 106 samples tested (0.9%), demonstrating that it is not a relevant mechanism in our population of patients.

*Int*1 genes were found in 21 samples (19.8%), and when associated with detection of the *sul*1 gene, they apparently resulted in strains with higher MICs.

Another mechanism of resistance recently described in *S. maltophilia* is the presence of trimethoprim- resistant (TMP) enzyme dehydrofolate reductase (*dfrA*), *dfrA12*, *dfrA13*, *dfr17* genes located in class 1 integrons and carried by plasmids[2]. In this study, although 21 samples (19.8%) had the *int1* gene, *drfA* was detectable only in one strain, which was sensitive to SMX/TMP (0.9%).

In our analysis, the polyclonal profile and previous use of SMX/TMP suggested that the resistance was related mainly to the antibiotic use. Moreover, some authors have described *S. maltophilia* as polyconal, highlighting the diversity of this microorganism[10,17].

The main limitation of this study is the lack of information on the clinical outcome of the patients in whom the samples were isolated, even though the main objective of the study was to evaluate the characteristics of the strains. *S. maltophilia* has a wide variety of resistance mechanisms. Most isolates resistant to SMX/TMP did not have the mechanism defined in this study. Intrinsic mechanisms such as inducible efflux pumps have not been evaluated[18,19].

CONCLUSION

In conclusion, this study showed that *S. maltophilia* infection was observed mostly in severe immunocompromised patients. The most frequent SMX/TMP resistance mechanism was the *sul1* gene associated with previous use of this antibiotic. These findings warn on the potential spread of the resistance to SMX/TMP in hospital settings.

REFERENCES

1. Samonis G, Karageorgopoulos DE, Maraki S, Levis P, Dimopoulou D, Spernovasilis NA, et al. Stenotrophomonas maltophilia infections in a general hospital: patient characteristics, antimicrobial susceptibility, and treatment outcome. PLoS One. 2012;7:e37375.
2. Hu LF, Chang X, Ye Y, Wang ZX, Shao YB, Shi W, et al. Stenotrophomonas maltophilia resistance to trimethoprim/sulfamethoxazole mediated by acquisition of sul and dfrA genes in a plasmid-mediated class 1 integron. Int J Antimicrob Agents. 2011; 37:230-4.
3. Chang YT, Lin CY, Chen YH, Hsueh PR. Update on infections caused by Stenotrophomonas maltophilia with particular attention to resistance mechanisms and therapeutic options. Front Microbiol. 2015;6:893.
4. Barbolla R, Catalano M, Orman BE, Famiglietti A, Vay C, Smayevsky J, et al. Class 1 integrons increase trimethoprim-sulfamethoxazole MICs against epidemiologically unrelated Stenotrophomonas maltophilia isolates. Antimicrob Agents Chemother. 2004;48:666-9.
5. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008;36:309-32.
6. Clinical and Laboratory Standard Institute. Performance standard for antimicrobial susceptibility testing: M100. 30th ed. Wayne: CLSI; 2020.
7. National Center for Biotechnology Information. Basic Local Alignment Search Tool (BLAST). [cited 2020 Nov 13]. Available from: https://blast.ncbi.nlm.nih.gov/Blast.cgi
8. Crossman LC, Gould VC, Dow JM, Vernikos GS, Okazaki A, Sebaihia M, et al. The complete genome, comparative and functional analysis of Stenotrophomonas maltophilia reveals an organism heavily shielded by drug resistance determinants. Genome Biol. 2008;9:R74.
9. Wood GC, Underwood EL, Croce MA, Swanson JM, Fabian TC. Treatment of recurrent Stenotrophomonas maltophilia ventilator-associated pneumonia with doxycycline and aerosolized colistin. Ann Pharmacother. 2010;44:1665-8.
10. Looney WJ, Narita M, Mühlemann K. Stenotrophomonas maltophilia: an emerging opportunist human pathogen. Lancet Infect Dis. 2009;9:312-23.
11. Safdar A, Rolston KV. Stenotrophomonas maltophilia: changing spectrum of a serious bacterial pathogen in patients with cancer. Clin Infect Dis. 2007;45:1602-9.
12. Gales AC, Jones RN, Forward KR, Linares J, Sader HS, Verhoef J. Emerging importance of multidrug-resistant Acinetobacter species and Stenotrophomonas maltophilia as pathogens in seriously ill patients: geographic patterns, epidemiological features, and trends in the SENTRY Antimicrobial Surveillance Program (1997–1999). Clin Infect Dis. 2001;32 Suppl 2:S104-13.
13. Farrell DJ, Sader HS, Jones RN. Antimicrobial susceptibilities of a worldwide collection of Stenotrophomonas maltophilia isolates tested against tigecycline and agents commonly used for S. maltophilia infections. Antimicrob Agents Chemother. 2010;54:2735-7.
14. An SQ, Berg G. Stenotrophomonas maltophilia. Trends Microbiol. 2018;26:637-8.
15. Ansari SR, Hanna H, Hachem R, Juang Y, Rolston K, Raad I. Risk factors for infection with multidrug-resistant Stenotrophomonas maltophilia in patients with cancer. Cancer. 2007;109:2615-22.
16. Toleman MA, Bennett PM, Bennett DM, Jones RN, Walsh TR. Global emergence of trimethoprim/sulfamethoxazole resistance in Stenotrophomonas maltophilia mediated by acquisition of sul genes. Emerg Infect Dis. 2007;13:559-65.
17. Almeida MT, Rubio FG, Garcia DO, Pavarino-Bertelli EC, Rossit AR, Bando SY, et al. Genetic relatedness among clinical strains of Stenotrophomonas maltophilia in tertiary care hospital settings in Sao Paulo State, Brazil. Braz J Microbiol. 2007;38:278-84.
18. Sánchez MB, Martínez JL. The efflux pump SmeDEF contributes to trimethoprim-sulfamethoxazole resistance in Stenotrophomonas maltophilia. Antimicrob Agents Chemother. 2015;59:4347-8.
19. Gil-Gil T, Martínez JL, Blanco P. Mechanisms of antimicrobial resistance in Stenotrophomonas maltophilia: a review of current knowledge. Expert Rev Anti Infect Ther. 2020;18:335-47.