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# INCIDENCE OF TRIMETHOPRIM-SULFAMETHOXAZOLE RESISTANT S. MALTOPHILIA INFECTIONS IN A MEXICO CITY HOSPITAL.

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**ABSTRACT** Introduction: Stenotrophomonas maltophilia is a non-fermentative gram-negative bacillus with increasing importance as a multidrug-resistant nosocomial agent. Despite reports of mortality rates between 14 and 69% in patients with bacteremia, the information documented in our environment is minimal. Methods: Descriptive, observational, retrospective and longitudinal study. Outpatients and hospitalized patients were sampled between January 1 and December 31, 2019, from the Centro Médico Nacional siglo XXI. Bacterial growth was evaluated to identify the presence of S. maltophilia. Results: In a total of 7,019 cultures, we observed a frequency of 94 cases of S. maltophilia and in these we identified that 54.5% were resistant to trimethoprim-sulfamethoxazole. Women were the most affected by this entity with a median age of 54.5 years. Fifty percent of the samples came from intensive therapy and the most frequent site of extraction was the trachea. Discussion: We identified a higher resistance to trimethoprim-sulfamethoxazole than that reported in the literature (5%), in an organism capable of developing both nosocomial and community-acquired infections, forcing us to suspect its existence as well as a second treatment option in the face of multidrug resistance.

# **KEYWORDS**: S. maltophilia, trimethoprim-sulfamethoxazole, multidrug resistance, incidence.

## INTRODUCTION

Stenotrophomonas maltophilia is a bacterium of the Gammaproteobacteria class, ubiquitously found in the natural environment (soil, plants, animals, food or aqueous habitats)<sup>1</sup>. In recent years, S. maltophilia has gained attention as an emerging multidrug-resistant opportunistic pathogen worldwide, causing nosocomial and community-acquired infections in immunocompromised patients<sup>2</sup>. S. maltophilia plays important ecosystemic roles in the sulfur and nitrogen cycles, in the degradation of complex compounds and pollutants, and in promoting plant growth and health. However, it is capable of colonizing man-made niches within hospitals and in the community<sup>3</sup>. Another growing concern is related to the complexity of treatment, due to the production of multiple intrinsic and acquired mechanisms of resistance, which render many first-line antimicrobials, particularly  $\beta$ lactams, ineffective<sup>4</sup>. Trimethoprim-sulfamethoxazole (TMP-SMZ) has been considered the medication of choice for S. maltophilia due to its high in vitro susceptibility rate<sup>5</sup>. However, increasing reports of adverse drug effects and resistance, as well as the lack of robust pharmacokineticpharmacodynamics (PK-PD) data to optimize dosing, limit its clinical utility<sup>6</sup>. Few studies report the incidence of infections caused by this agent in our country. Therefore, it is necessary to generate current statistics that allow us to know the magnitude of the nosocomial problem attributed to S. maltophilia as well as the resistance to the drug of first choice (TMP-SMZ). Therefore, the aim of our study was to identify the incidence and factors associated with infection by trimethoprim/sulfamethoxazole-resistant S. maltophilia in a Mexico City hospital.

## MATERIAL AND METHODS

Descriptive, observational, retrospective, longitudinal, retrospective study, conducted at the 3rd level hospital Centro

Médico Nacional siglo XXI, with patient samples collected in a period from January 1 to December 31, 2019. All culture reports were included and sent for analysis for diagnosis of infection at the site from which the sample was taken. For the calculation of incidence, the growth of cultures with *S. maltophilia* over the total number of cultures analyzed in the established period of time were identified. All samples were analyzed using the automated method with Vytek2®. Data analysis was performed with SPSS statistical software SPSS ver 25 in Spanish.

## RESULTS

Among a total of 7019 of cultures analyzed, 66 reported growth of S. maltophilia (0.94%), in a period from January 1th to December 31th, 2019 (Cumulative incidence rate: 94 S. maltophilia-positive cases per 10,000 cultures analyzed). The distribution per month of these 66 cases was more prevalent during the months of October (19.7%) and November (12.1%) (Graph No.1). The age of the study subjects ranged from 35 to 65 years with a median of 54.5 years. The most frequent gender was female (57.6%). Most of the specimens were taken from hospitalized patients (93.9%) and only 6.1% corresponded to outpatients (Table 1). Regarding the requesting services, we observed that 50% of the cases came from the intensive care unit, followed by gastro-surgery (15.2%) and nephrology (10.6%); less frequent were internal medicine, continuous admission, hematology and rheumatology (Graph No.2). The most frequent place where the sample was collected was the trachea (38.8%), followed by the urinary tract (22.7%) (Graph No.3). Regarding the antibiogram results, 54.5% of the samples studied were resistant to TMP/SMZ, followed by 39.4% and 6.1% resistant to ceftazidime and levoflozacin, while 100% sensitivity was observed for chloramphenicol and tigecycline (Table 2). Finally, among the diagnoses associated with the presence of

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a positive culture for S. maltophilia, the most frequent was nosocomial pneumonia (45.5%), followed by urosepsis (21.2%) and bacteremia (16.1%); less frequent were diagnoses of neuroinfection, abscess and appendicitis (**Graph No.4**).



Table No.1 Characteristics Of Patients With Positive S. Maltophilia Cultures N= 66

	median (q25-q75)	
AGE (YEARS)	54.5 (35-65)	
	n (%)	
GENDER		
Female	38 (57.6)	
Male	28 (42.4)	
AREA WHERE THE SAMPLE WAS OBTAINED		
External Consultant	4 (6.1)	
Hospital	62 (93.9)	





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## DISCUSSION

Gram-negative microorganisms have been increasing their importance due to the fact that most of them are capable of developing resistance to  $\beta$ -lactams, among them *S. maltophilia* has been identified as an emerging microorganism. A gram-negative, motile, obligate aerobic bacillus, which in up to 40% of cases can be isolated together with other microorganisms (e.g. *P. aeruginosa, S. aureus, Burkholderia spp and A. baumannii*), belonging to the category of non-lactose-fermenting bacteria<sup>7</sup>. Isolation rates of *S. maltophilia* have been increasing; in a multicenter study by Del Toro et al, in hospitals with more than 500 beds, the incidence of cases ranged from 3.4 to 12.1 per 10,000 admissions, obtaining an estimated overall crude mortality of 44%<sup>8</sup>. We identified an incidence of 0.94%, i.e. *S. maltophilia* was isolated 94 times per 10,000 cultures analyzed.

Although it is generally considered a nosocomial pathogen, in recent years S. maltophilia has been frequently reported in out-of-hospital patients, and is related to the advanced age of the affected individuals and the presence of chronic diseases, especially respiratory pathology<sup>9</sup>. Only 6.1% of the specimens analyzed in our study came from the outpatient clinic; 93.9% were of nosocomial origin. Regarding the increasing presence of cases outside the hospital, Huertas-Franco V et al, describe the case of an 82-year-old woman who was hospitalized. She presented a clinical profile characterized by hyporexia, general malaise, fever and low oxygen saturation, with imaging tests corresponding to bilateral bronchopneumonia. Sputum culture identified the causative agent as Xanthomonas maltophilia, sensitive to TMP/SMZ, and she showed clinical and radiological improvement<sup>10</sup>. Franco et al, studied the patient's home where a water leak under the bedroom floor with the presence of moss and mold was identified as a possible source of the problem. Nicodemus recognizes the complexity of distinguishing between colonization and infection; he mentions that the differential diagnosis should be based on the association of factors such as physical examination, radiographic findings, other clinical or imaging findings, and the results of laboratory tests, including microbiological tests<sup>11</sup>.

Regarding the relationship with advanced age, although the age of our patients ranged from 35 to 65 years, the median age was 54 years, indicating greater susceptibility in older adults. On the other hand, we also observed a higher incidence during the months of October and November. This, in addition to the fact that 50% of the cases came from the intensive care unit (ICU) and the most frequent extraction place was the tracheal. These situations may agree with Carnot et al, regarding its association with respiratory diseases (seasonal predominance)<sup>9</sup>. An important characteristic of *S. maltophilia* is its high and multiple antibiotic resistance due to different mechanisms involving the production of beta-lactamases (L1)

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and L2), the impermeability of the outer membrane and the expression of active efflux pumps<sup>12</sup>. These mechanisms confer high-grade resistance to beta-lactams, including thirdgeneration cephalosporins and carbapenems, aminoglycosides, macrolides and, to a variable extent, quinolones. The presence of an active expulsion system against different antibiotics (SmeC) could play a relevant role in the antimicrobial resistance of clinical specimens<sup>13</sup>. According to Gales A et al, TMP-SMZ in vitro was by far the most potent drug against S. maltophilia, with sensitivity rates generally above 90% in international antibiotic resistance studies<sup>14</sup>. However, given the increasing antibiotic resistance, it was expected in our study that resistance to TMP-SMZ was identified in more than half of the cultures (54.5%), followed by resistance in 39.4% to ceftazidime, which forces us to look for other effective antibiotic therapy options. The main cause of resistance to this antibiotic has resulted from the high communication between integrons and transposons carrying the sull gene from other gram-negative bacteria, due to the increased use of TMP-SMZ. For this reason, in patients with infections that are generating SIRS, the main indication has been the initiation of combination therapy, among the other active compounds with S. maltophilia, including levofloxacin, ceftazidime and tigecycline<sup>12</sup>.

The cultures studied in this research, also put on the table the option of using other antibiotics such as chloramphenicol and tigecycline with a sensitivity of 100%. Nicodemo et al, Friedman et al and other authors have mentioned that chloramphenicol shows some in vitro activity against S. maltophilia strains, although there are considerable differences in susceptibility profiles (11.5-81.4%). Furthermore, clinical experience with this medication in the treatment of S. maltophilia infections is very limited  $^{11,15}$ . On the other hand, regarding the use of tigecycline, its microbiological and pharmacological profiles mean that it can be prescribed for non-conventional indications, especially against infections caused by multi-resistant pathogens against which it shows in vitro activity. Tigecycline was the first glycylcycline approved by the U.S. Food and Drug Administration (FDA) for the treatment of complicated skin and soft tissue infections, complicated intra-abdominal infections and community-acquired pneumonia<sup>16</sup>. A metaanalysis by Zha et al. concluded that, due to its broadspectrum antibacterial activity, particularly against gramnegative bacteria resistant to other antibiotics, it is an excellent choice for use in ventilator-associated pneumonia, hospital-acquired pneumonia and bacteremias caused by multidrug-resistant organisms<sup>17</sup>.

Based on the above findings, we can conclude that *S. maltophilia* is an organism of growing importance as a cause of both nosocomial and community-acquired infections. In addition to presenting multidrug resistance, we detected a resistance to its first choice drug (54.5%) higher than that reported by other authors (5%), so it is necessary to consider treatments that demonstrate *in vitro* sensitivity and whose clinical efficacy has been demonstrated, as is the case of tigecycline.

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