ORIGINAL ARTICLE

Clinical outcomes and risk factors associated with *Stenotrophomonas maltophilia* infections: A comprehensive study

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Abstract

Background: Stenotrophomonas maltophilia is an environmental organism which is intrinsically multidrug resistant and causes infection in immunocompromised patients. *Aim and Objectives:* To evaluate the rate of isolation of *S. maltophilia*, antibiotic resistance profile, risk factors, and clinical outcome. *Material and Methods:* It was a retrospective study wherein clinical and laboratory data related to various clinical samples which yielded *S. maltophilia* in 2½ year period were included. Risk factors and clinical outcomes were analysed. *Results:* Maximum isolation rate of *S. maltophilia* was from respiratory samples 52/80 (65%), 78 (97.5%) were sensitive to ofloxacin; 76 (95%) levofloxacin; 75 (93.8%) chloramphenicol; 73 (91.2%) tigecycline; 61(76.2%) ticarcillin clavulanic acid and 60 (75%) were sensitive to trimethoprim-sulfamethoxazole (TMP/SMX). Of the 45 patients whose clinical history could be obtained, 13 (28.9%) patients expired. Of these 3 (23%) were cancer patients, 1 (7.6%) was a kidney transplant patient, 3 (23%) had chronic kidney disease, 3 (23%) had brain damage due to an accident, 2 (15.3%) had septic shock and one was COVID 19 patient. Conclusions: Mortality of the patients was associated with longer period of stay in the hospital. Of the 80 *S. maltophilia* isolates approximately 96% were sensitive to fluoroquinolones and 75% were sensitive to TMP/SMX. Further studies with larger sample sizes or prospective designs are needed for stronger evidence.

Keywords: Antibiotic Resistance, Clinical Outcome, Immunocompromised Host, Risk Factors, *Stenotrophomonas maltophilia*

Introduction

Stenotrophomonas maltophilia is a facultative anaerobe which is non-fermenting,oxidase-negative, gram-negative bacillus [1-2]. It was initially named under the genera Xanthomonas, and Pseudomonas and later under the genus Stenotrophomonas in 1993 [1-2].

It is an environment organism and has been isolated from vegetation. In the hospital environment, it may colonize irrigation fluids, catheters, disinfectants, haemodialysis solutions, hand wash solutions, and endoscopes. So may cause nosocomial outbreaks, especially in Intensive Care Units (ICUs).

It may cause nosocomial pneumonia associated with mechanical ventilation [1-8]. It can cause catheter-associated bloodstream infection, skin and soft tissue infection, endocarditis, meningitis, endophthalmitis, catheter-associated septicaemia, and urinary tract infection [1-8]. Some of the most common predisposing factors can be central venous catheters, urinary catheters, prolonged hospitalization, recent surgery, mechanical ventilation, neutropenia, admission in the ICUs, malignancies, and use of broad-spectrum antibiotics for empirical therapy [1-8].

S. maltophilia is considered as a low-virulence, environmental organism that is intrinsically multi-drug-resistant and causes infection in immuno-compromised patients [4-12]. But it possesses various virulence factors like ability to form bio-films, flagella, fimbriae/pili, adhesins, outer membrane lipopolysaccharide, siderophore production [4-6]. Biofilm allows the bacteria to adhere firmly to both animate and inanimate surfaces and can also cause antibiotic tolerance [4-6]. Like other bacteria, *S. maltophilia* depends on Quorum Sensing (QS) for intercellular communication and virulence. Further it bears diffusible signal factor dependent QS for regulation of virulence factors [6]. It also produces a series of enzymes which help in virulence like nucleic acid degrading enzymes, hyaluronidase, protease, lipases to name a few. Phenotyping switching is also seen. It switches to small colony variant under antibiotic pressure and hence survives in adverse conditions [4-6].

Considering the number of virulence factors it possesses, it also causes disease in immunocompetent individuals like non healing ulcers, cellulitis, pyomyositis and otitis externa [4-13]. Drug resistance in *S. maltophilia* may be due to decreased permeability, presence of efflux pumps and the production of enzymes which act of common drugs used in the treatment [10-15]. The frequency of isolating *S. maltophilia* from various samples, its antibiotic resistance profile, risk factors, and clinical outcome were studied in the present study.

Material and Methods

It was a retrospective study wherein all consecutive clinically significant samples received for a period of 30 months between Jan 2021 to June 2023 which yielded *S. Maltophilia* were included. Institutional ethical clearance (IEC KMC MLR 07-2023/332) was received for the present study. Clinical samples such as blood and sterile body fluids, urine, pus and exudates, tissue, and respiratory samples received in the laboratory attached to our hospital were included. Identification was done with the VITEK2 system and antibiotic sensitivity done by conventional disc diffusion method using the discs containing cotrimoxazole (TMP/SMX) (1.25/23.75 μg), ofloxacin (5 μg), levofloxacin (5 μg), tigecycline (15 μg), ticarcillin clavulanic acid (75/10 μg) and chloramphenicol (30 μg). Samples which yielded bacteria other than *S. maltophilia* were excluded from the study. Demographic details along with clinical history of patients were collected from the medical records department. The antibiogram of *S. maltophilia* was collected from laboratory reports generated in the laboratory. To assess different risk factors for fatal outcome of *S. maltophilia* infected patients, logistic regression was applied using Jamovi, a free and open-source statistical software, version 2.6.

Results

There were 80 clinical samples yielding *S. maltophilia* during the study period. These 80 patients included 27 (33.8%) female and 53 (66.2%) male patients; 45 (56.2%) were ≥ 55 y, 33 (41.2%) were aged between 20 years and 54 years, 2 (2.5%) were up to 10 years, mean age of the study population being 54.8 ± 17.3. Only 45 out of the 80 patients had complete clinical data as given in Table 1. Of these 45 patients, 40 (88.9%) had been admitted in ICU and of these 13 (32.5%) patients expired. Other than diabetes mellitus and hypertension, 12 patients had respiratory illness, of which 8 were COVID 19 positive. The mortality rate was associated with longer period of stay in the hospital ($p = 0.047$) (Table 1). The details of the 13 patients who expired are provided in Table 2. Most of the 13 patients who expired belonged to age group 50-80

years. It was observed that *Stenotrophomonas* spp. was isolated from respiratory samples in case of these 13 patients, except for the 3-year-old malignancy patient whose blood yielded the organism under study. These 13 patients included three COVID 19 pneumonia cases, two accidental trauma cases, three malignancy cases, two cases of septic shock, two cases of chronic kidney disease and one case of coronary infarction. The different patient samples which yielded *S. maltophilia* are shown in Figure 1. The maximum yield of the bacteria under study was from respiratory samples like sputum, bronchoalveolar lavage and Endotracheal Tube (ET) followed by blood. Out of 80 isolates of *S. maltophilia,* only two isolates (2.5%) were highly resistant to almost all antibiotics tested. Among these two, one was isolated from a dialysis patient's blood sample and the other was from an ET tip. Out of 80 isolates of *S. maltophilia,* 78 (97.5%) were sensitive to ofloxacin; 76 (95%) levofloxacin; 75 (93.8%) chloramphenicol; 73 (91.2%) tigecycline; 61(76.2%) ticarcillin clavulanic acid and 60 (75%) were sensitive to TMP/SMX (Figure 2).

Table 1: Logistic regression analysis performed on clinical history of 45 patients using the software jamovi-2.6.44.0-win-x64.exe to assess the risk factors associated with fatal outcome

Clinical condition	N (%)	Expired N (%)	Discharged alive N (%)	p	Odds ratio
Duration (hospital days) Mean ± SD	-	13 (31%) 23.3 ± 16.9	32 (76.1) 14.3 ± 10.3	0.047	0.95
Surgery	5 (11)	1 (20)	4 (80)	0.65	1.71
Carcinoma	7 (15.6)	3 (42.9)	4 (57.1)	0.38	0.48
Chronic liver disease	2 (4.4)	0 (0)	2 (100)	0.99	6.78e +6
Chronic kidney disease	9 (20)	3 (33.3)	6 (66.7)	0.74	0.77
Respiratory illness	12 (26.6)	3 (25)	9 (75)	0.73	1.30
COVID 19	8 (17.7)	3 (37.5)	5 (62.5)	0.56	0.617
Heart disease	9 (20)	2 (22.2)	7 (77.8)	0.62	1.54
Brain damage	6 (13.3)	3 (50)	3 (50)	0.23	0.35
Hypertension	17 (37.7)	5 (29.4)	12 (70.6)	0.95	0.96
Diabetes mellitus	15 (33.3)	5 (33.3)	10 (66.7)	0.64	0.73
Connective tissue disorder	1 (2.2)	0 (0)	1 (100)	0.995	6.56e+6
Sepsis	9 (20)	4 (44.4)	5 (55.6)	0.26	0.42
Burns	1 (2.2)	0 (0)	1 (100)	0.99	6.56e+6
Trauma	6 (13.3)	3 (50)	3 (50)	0.22	0.35
Hemiparesis	2 (4.4)	0 (0)	2 (100)	0.99	6.78e+6
ICU patients	40 (88.9)	13 (32.5)	27 (67.5)	0.99	4.88e-8

ICU – Intensive care unit

Table 2: Clinical history of the 13 patients who had a fatal outcome and their samples yielded *S. maltophilia*

Age	Sex M/F	Stay in ICU Yes/No	Number of hospital days	Clinical features	Sample from which *S. maltophilia* was isolated	Sensitive to how many out of 6 antibiotics tested
35	M	Yes	5	Covid 19 pneumonia, kidney transplant	ET aspirate	5
70	M	Yes	15	Covid 19 pneumonia	Sputum	4
60	M	Yes	51	Brain stem dysfunction, accident	Tracheostomy tip	5
39	F	Yes	55	Septic shock, PRES, chronic interstitial nephritis, hypertension	ET aspirate	3
52	M	Yes	15	Heart attack, coronary artery disease	Sputum	5
80	M	Yes	23	Chronic kidney disease	ET suction tip	6
68	M	Yes	18	Polytrauma sustained in road accident	ET suction tip	6
77	M	Yes	35	Chronic kidney disease aspiration pneumonia	ET suction tip	5
3	M	Yes	21	Hydrocephalus, intracerebral bleed, medulloblastoma	Blood	6
42	M	Yes	16	Brainstem dysfunction, cerebrovascular accident	ET suction tip	6
56	M	Yes	4	Severe metabolic acidosis, septic shock with multi-organ failure	ET suction tip	5
53	M	Yes	5	Right buccal carcinoma, hypertension, septic shock, drug-induced neutropenia	Sputum	6
64	F	Yes	40	Malignant pleural effusion, COVID-19 pneumonia, bronchogenic carcinoma	Sputum	6

PRES - Posterior reversible encephalopathy syndrome; ET – endotracheal tube.

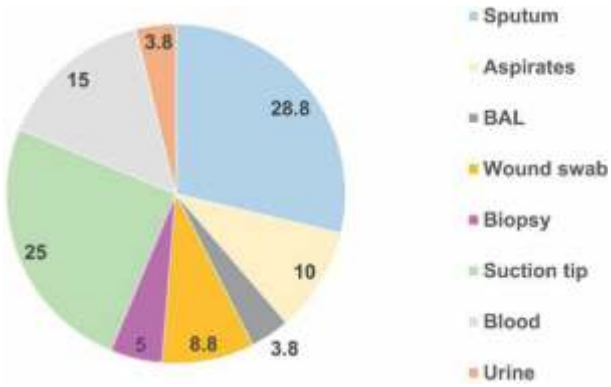

Figure 1: Eighty patient samples that yielded *S. maltophilia*

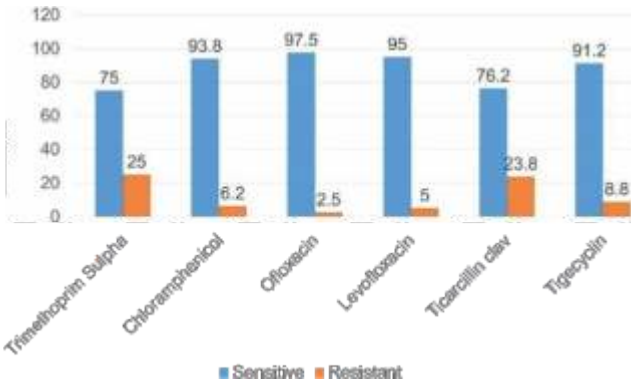

Figure 2: Antibiotic sensitivity pattern of the 80 clinical isolates of *S. maltophilia*

Discussion

With emerging hospital acquired infections by non-fermenting drug-resistant bacteria, studying the antibiotic sensitivity patterns and risk factors associated with such infections time and again helps to decide the empirical treatment options and preventive measures [16-18]. *S. maltophilia* is emerging as a multi drug resistant nosocomial pathogen in recent years [1].

In a recent retrospective study conducted in Hungary, on 579 cases of *S. Maltophilia* cases of respiratory tract infection, it was found that drug resistance to Trimethoprim Sulfamethoxazole (TMP/SMX) and levofloxacin was increasing over a period, from 2008 to 2017. Totally *S. maltophilia* showed a resistant rate of 8.99% against levofloxacin and 12.1% against TMP/SMX. Most of the patients (78.46%) were of extremes of age i.e. < 5 years to > 50 years of age [10]. The patients had a clinical history of underlying conditions like malignancy, cystic fibrosis, respiratory distress syndrome, recent trauma, surgery, and congenital disorders [10].

In a study, Multilocus Sequence Typing analysis was conducted on 93 isolates, and it showed 61 different sequence types (ST), of which 45 were novel STs. Maximum isolation rate was from sputum samples 87% (81/93) and from male patients 66.7% (62/93). The resistance to TMP/SMX was 9.7%, levofloxacin 4.3% and minocycline 0%. [11].

A past study, performed to determine the antibiogram of 118 *S. maltophilia* strains isolated from various clinical specimens like tracheal aspirates, blood, sputum, and wound samples over 6 years from 2006 to 2012, found that the maximum isolation rate was from respiratory samples 65.3% (77/118) followed by blood (14.4%). Resistance rate to levofloxacin was very low 7.6%, followed by chloramphenicol (18.2%), TMP-SMX (20.3%) and with maximum resistance to ceftazidime at 72% [12].

In an Indian study, 50 patients with *S. maltophilia* infections over the years 2019-2021 were included. Maximum samples which yielded *S. maltophilia* were blood (44%) followed by respiratory samples (32%), and wound infection (24%). Out of 50 strains, 3 (6%) and 8 (16%) were resistant to levofloxacin and TMP-SMX respectively. Mortality rate was 6%. Risk factors for colonisation were mechanical ventilation (34%) chronic kidney

disease (14%), malignancy (8%), and catheter-related blood stream infection (2%) [13].

In a study including 106 cases of *S. maltophilia* infection, isolation rate was maximum in blood stream infection (44.2%), followed by respiratory samples (34.9%). 21.7% (23/106) of the isolates were resistant to TMP/SNX and 13.3% were resistant to levofloxacin [14].

In a retrospective study involving 100 cases of *S. Maltophilia* infections, most were respiratory infections (53%) followed by blood stream infection (25%), 46% had a median APACHE II score of 18. Mortality was associated with prolonged hospital stay, mechanical ventilation and immunosuppressive therapy. The isolates were 100% sensitive to minocycline, 94% sensitive to levofloxacin and 91% sensitive to TMP/SMX [15].

Like past studies, in the present study also maximum isolation rate was from respiratory samples, followed by blood. [10-15]. But the resistance rate was 25% against TMP-SMX which is much higher than the past studies. But like other studies, in the present study also there was more resistance shown against TMP/SMX when compared to levofloxacin. We had not included ceftazidime in our laboratory standard operating procedure for the genus Stenotrophomonas. The organism possesses L1 and L2 β-lactamase which make β-lactams and aztreonam ineffective against *S. maltophilia* [19, 20].

There are many risk factors in studies related to bloodstream infection caused by *S. Maltophilia* [21-27]. A study carried out by Yibing Chen *et al.*, for a period of 9 years 2010-2018 with 76 cases of *S. Maltophilia* bacteraemia, found that minocycline and TMP/SMX are the antibiotics that can be optimally chosen for the treatment of *S. maltophilia*. Among these patients, the mortality rate was higher among haemodialysis, patients on mechanical ventilation, and central venous catheters. It was also noted that over 9 years, there were 76 cases of bacteraemia making an average of 8 per year [21].

A retrospective study from 2010 to 2017, showed that the mortality rate had increased after 2014 and was associated with ICU admission and ventilator use. Out of 36 patients in the study period 2010 to 2013, 7 had expired (19.4%) whereas out of 34 patients, during the study period 2014-2017, 17 (50%) had expired showing an increase in the mortality rate, whereas present study showed mortality associated with sepsis to be 44.4% [22].

A study conducted in Beijing showed a mortality rate of 37.3% and it was noted that APACHE II score significantly predicted *S. maltophilia* bacteraemia. The other risk factors were pulmonary disease, chronic kidney disease, use of Foley's catheter, and anti-fungal drug therapy [23].

A study was conducted in South Korea in which out of 126 *S. maltophilia* bacteraemia patients, the mortality rate was 65.1%. Mortality was associated with quinolone-resistance, hypoalbuminemia, and haematological malignancy. It was found that the Charlson co-morbidity score and the in dwelling of a central venous catheter were predictors of quinolone-resistance in *S. maltophilia* isolated from bacteraemia patients [24].

In a study conducted between December 2005 to December 2014 in a total of 142 bacteraemia patients enrolled, the most frequently encountered underlying condition was solid tumour (55.6%), diabetes (16.2%), and haematological malignancy (23.2%). The source of bacteraemia was most commonly respiratory tract and central venous catheter (CVC); 21 patients were treated with TMP-SMX (14.8%) and 40 patients (28.2%) were treated with levofloxacin. The study concluded that

removing CVC may help as a factor in reducing the mortality caused by *S. Maltophilia* bacteraemia [25].In a study conducted in Thailand where 117 *S. Maltophilia* bacteraemia patients were analysed, TMP-SMX showed a high susceptibility of 93% and fluoroquinolone showed a susceptibility of 88% respectively. Appropriate empirical therapy significantly reduced duration of hospital stays and mortality [26].

A study conducted in Chicago, USA, out of 54 patients with *S. maltophilia* blood stream infection, 3 deaths occurred in patients on fluoroquinolone versus 10 deaths in patients treated with TMP-SMX [27]. In another study conducted in Tamil Nadu, India, vasopressor use, autoimmune disease, thrombocytopenia, and lower P/F ratios were associated with mortality [28]. A study done in anarmy hospital, *S. maltophilia* isolates had high susceptibility to TMP-SMX and minocycline and *S. maltophilia* infected patients with traumatic or early surgical amputations, longer hospital stays had higher overall mortality [29]. In a study conducted in Mexico, all the environmental isolates of *S. maltophilia* were resistant to TMP-SMX [30].

Conclusion

All patients in the present study were immunocompromised individuals as they had many underlying conditions like ICU admission, mechanical ventilation, carcinoma, chronic kidney disease, chronic liver disease, hemiparesis, and sepsis. Mortality of the patients was associated with longer period of stay in the hospital. But a larger sample size is required to get statistically relevant correlation between risk factors and outcome of the infection. Resistant rates were approximately 4% against fluoroquinolones and 25% against TMP/SMX. There is a regional variation in resistance rates.

Limitations

All data had been collected from a single hospital and only 45 out of the 80 patients had complete clinical data.

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