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Original Article

Microbiology Section

Insight into *Stenotrophomonas maltophilia* Infections in a Tertiary Care Teaching Hospital in Western India and Review of Literature: A Retrospective Observational Study

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ABSTRACT

Introduction: *Stenotrophomonas maltophilia (S. maltophilia)* is a ubiquitous and opportunistic pathogen of growing importance. This gram-negative, non fermenter is widely distributed in moist hospital environments. It is intrinsically resistant to a number of antibiotics, making it a challenge both for the clinician and the microbiologist. Very sparse data is available from Western India regarding this emerging pathogen.

Aim: To determine the prevalence and spectrum of infections caused by *S. maltophilia* and to provide an overview of associated co-morbidities, antibiotic susceptibility pattern of these isolates, and clinical outcomes.

Materials and Methods: This retrospective observational study was carried out in a tertiary care private hospital (Mahatma Gandhi Hospital) in Jaipur, Rajasthan, India over a period of one year (July 2021-June 2022). A total of 11,170 samples were received in the microbiology laboratory for bacterial culture and susceptibility testing during the study period and processed as per standard protocols. Only one isolate per patient was included for the purpose of the study. Culture identification and antibiotic susceptibility testing was done using the VITEK-2 automated system. Data regarding patients' demographic profile, epidemiological profile, baseline characteristics, co-morbidities, laboratory findings, and clinical outcome were tabulated in an Excel worksheet and analysed. All statistical analysis was done using the Software Statistical Package for the Social Sciences (SPSS) version 20.0.

Results: Fourteen patients were found to have *S. maltophilia* infection during the study period. The majority of patients had respiratory tract infection and bacteraemia. All isolates were from inpatients, more than two-thirds being from the Intensive Care Unit (ICU). A high level of susceptibility was seen to routinely recommended drugs, with 100%, 93% and 79% being susceptible to minocycline, levofloxacin and co-trimoxazole, respectively. All patients (except one) were successfully managed and discharged.

Conclusion: *S. maltophilia* is an emerging opportunistic pathogen and is associated with a plethora of clinical conditions. Early and accurate diagnosis by embracing automation in microbiology laboratories is essential to identify this pathogen. *S. maltophilia* infections have a favourable outcome when diagnosed and treated timely.

Keywords: Bacteraemia, Co-trimoxazole, Non fermenter, Opportunistic pathogen

INTRODUCTION

Stenotrophomonas maltophilia is a ubiquitous and opportunistic pathogen closely related to the genus *Pseudomonas*. It was initially isolated in 1943 and given the name *Bacterium bookeri*. Since then, it has undergone several taxonomic changes and was finally assigned to its own genus in 1993 [1]. This gram-negative, non fermenting bacterium is widely distributed in moist hospital environments [2]. It can also be found on medical devices (such as dialysis machines, blood pressure monitors), faucets, disinfectants, bronchoscopes, and ventilators, thereby serving as a focus of infection [2].

The spectrum of diseases caused by this organism includes bacteraemia, respiratory tract infections, eye infections, endocarditis, meningitis, infections of bone and joint, urinary tract, mucocutaneous and soft-tissue infections [3]. Patients with co-morbidities such as diabetes, organ transplantation, malignancies, previous antibiotic administration, and the presence of invasive devices are more prone to acquire the infection [4]. There are several reports of *S. maltophilia* being increasingly associated with opportunistic infections. It was reported as the third most common non fermentative gram-negative bacilli causing nosocomial infections in a survey conducted in China [5].

S. maltophilia is known to possess a variety of resistance mechanisms like the production of hydrolytic enzymes, the presence of qnr genes, and efflux pumps. Thus, therapy of *S. maltophilia* infections represents a significant challenge for both the clinician and the microbiologist [3,4]. Very sparse data is available from our set-up regarding this emerging pathogen. With these issues in mind, the current study was conducted to determine the prevalence and spectrum of infections caused by *S. maltophilia*. The study also provides an overview of associated co-morbidities, antibiotic susceptibility pattern of these isolates, and clinical outcomes.

MATERIALS AND METHODS

The retrospective observational single-centre study was conducted in the Department of Microbiology of a tertiary care teaching hospital (Mahatma Gandhi Hospital) in Jaipur, Rajasthan, Western India, over a period of one year (July 2021-June 2022). The study was duly approved by the Institutional Ethics Committee under number MGMC&H/IEC/JPR/2022/816.

This was a time-bound study and only those samples available in the study duration were considered. A total of 11,170 samples were received in the microbiology laboratory for aerobic bacterial culture and susceptibility testing and processed according to standard

protocols. Primary sample inoculation was performed on blood agar and MacConkey agar (Hi-Media Laboratories, Mumbai, India), and incubated for 18 to 24 hours at 37°C. Culture identification and antibiotic susceptibility testing were conducted using the VITEK 2 automated system (BioMerieux, France).

Inclusion criteria: Only one isolate of *S. maltophilia* per patient was included for the study.

Exclusion criteria: Samples other than *S. maltophilia* isolates were excluded from the study.

The electronic patient records were reviewed, and data regarding patients' demographic profile, epidemiological profile, baseline characteristics, co-morbidities, laboratory findings, and clinical outcomes were tabulated in an Excel worksheet and analysed.

STATISTICAL ANALYSIS

The data pertaining to socio-demographic and other clinical variables were entered in the form of a data matrix in Microsoft Excel and analysed using the SPSS version 20.0. The descriptive statistics for categorical variables were represented in the form of frequencies and percentages, and for continuous variables, they were represented as means and standard deviations.

RESULTS

During the study period, a total of 11,170 samples were submitted to the microbiology laboratory for aerobic bacterial culture and susceptibility testing. Out of these, 14 patients were found to have *S. maltophilia* infection. The details of the clinical features of the patients infected with *S. maltophilia* are elaborated in [Table/Fig-1].

Twelve out of the 14 patients were critically ill and were admitted to the ICU, as depicted in [Table/Fig-1]. The median length of stay in the hospital for all patients was 11 days (IQR: 3-84 days). The majority of patients presented with respiratory tract infections and bacteraemia. Among these patients, males were predominant: 11 (78.57%) were male and 3 (21.43%) were female. The patients' ages ranged between 26 and 69 years {Interquartile Range (IQR): 51.5 years}.

[Table/Fig-2] depicts the distribution of *S. maltophilia* isolates from various clinical samples.

Clinical samples	No. of patients (%) from which *Stenotrophomonas maltophilia* isolated
Blood	6 (42.8)
Endotracheal (ET) aspirate	3 (21.4)
Pleural fluid	2 (14.2)
Sputum	2 (14.2)
Cerebro Spinal Fluid (CSF)	1 (7.14)

[Table/Fig-2]: Distribution of *Stenotrophomonas maltophilia* isolates from various clinical samples (n=14).

The antimicrobial susceptibility pattern of *S. maltophilia* isolates is presented in [Table/Fig-3]. All isolates were sensitive to minocycline. A high level of sensitivity was also seen with routinely recommended drugs, with 13 (93%) and 11 (79%) being susceptible to levofloxacin and cotrimoxazole, respectively. Most of the isolates, 6 (43%), were resistant to ceftazidime.

Antibiotics	Sensitivity (%)	Resistance (%)
Minocycline	14 (100)	0
Levofloxacin	13 (93)	1 (7)
Cotrimoxazole	11 (79)	3 (21)
Ticarcillin-clavulanic acid	10 (71)	4 (29)
Ceftazidime	8 (57)	6 (43)

[Table/Fig-3]: Antimicrobial susceptibility profile of 14 clinical isolates of Stenotrophomonas maltophilia.

DISCUSSION

The present study aimed to investigate the epidemiology of *S. maltophilia* infections, including the clinical presentation and antibiotic susceptibility pattern. *S. maltophilia* species are increasingly isolated and reported as an emerging pathogen from various parts of the world, including India. There is a high likelihood that this increased recognition is due to the adoption of automated methods in several laboratories. The Clinical and Laboratory Standards Institute (CLSI) also provides an annual update on the breakpoints to be used while conducting antibiotic susceptibility testing [6].

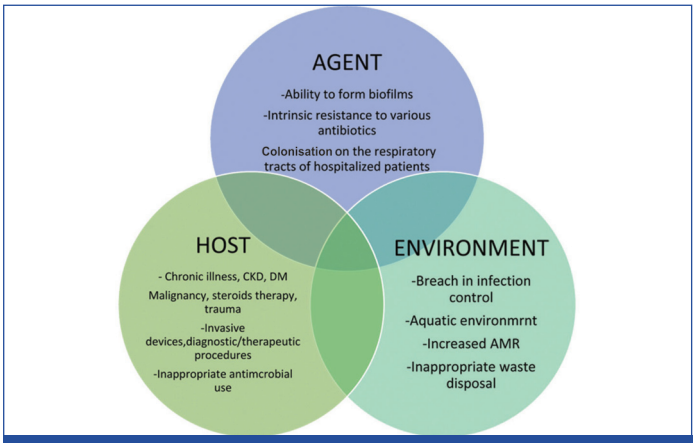
Although not a particularly aggressive organism, it has a few virulence factors, such as the capacity to form biofilm, enabling it to colonise or infect vulnerable populations, especially those

Case no.	Age/ Sex	Co-morbidities	Clinical presentation	Sample for culture	Duration of hospital stay	Ward of admission	Antibiotic susceptibility pattern					Outcome
							TCC	CAZ	MINO	LEVO	COT	
1	53/F	DM	Decompensated CLD jaundice	Blood	86 days	Liver T ICU	S	S	S	S	S	Survived
2	58/M	DM, HTN	Post COVID pneumonia, Rhinocerebral Mucormycosis	ET	11 days	MICU	S	S	S	S	S	Survived
3	50/M	NA	AKI, UTI, Renal calculi	Blood	4 days	MICU	S	S	S	S	S	Survived
4	54/F	DM,HTN, CKD	Subdural haematoma craniotomy	ET	15 days	MICU	R	R	S	S	S	Survived
5	48/M	NA	Details NA	ET	3 days	ICU	S	S	S	S	S	Survived
6	44/F	DM	Altered mental status	Blood	21 days	MICU	R	R	S	S	S	Survived
7	56/M	NA	TB	CSF	19 days	PICU	S	S	S	S	S	Survived
8	26/M	NA	NA	Pleural fluid	11 days	HDU	S	R	S	S	S	Survived
9	69/M	NA	NA	Pleural fluid	4 days	HDU	S	R	S	S	S	Survived
10	42/M	CLD	Portal hypertension, decompensated CLD	Blood	57 days	MICU	R	R	S	S	S	Survived
11	53/M	COPD	NA	Sputum	58 days	MICU 3	S	S	S	S	S	Survived
12	48/M	Acute kidney disease	ANCA vasculitis sepsis bed wound	Blood	21 days	MICU	S	S	S	R	R	LAMA
13	50/M	CKD	Hydronephrosis	Blood	19 days	SICU	R	R	S	S	R	Survived
14	65/M	TB	Ileocecal TB, Pulm Koch's, intestinal perforation	Sputum	6 days	SICU	S	S	S	S	R	Death

[Table/Fig-1]: Clinical features of the patients with *S. maltophilia* (Sm) infection.
AKI: Acute kidney injury; ANCA: Antineutrophilic cytoplasmic antibody; CAZ: Ceftazidime; CKD: Chronic kidney disease; CLD: Chronic lung disease; COPD: Chronic obstructive pulmonary disease; COT: Cotrimoxazole; CSF: Cerebro spinal fluid; DM: Diabetes mellitus; ET: Endotracheal aspirate; HDU: High dependency unit; HTN: Hypertension; ICU: Intensive care unit; LAMA: Left against medical advice; LEVO: Levofloxacin; MICU: Medicine ICU; MINO: Minocycline; NA: Not applicable; PICU: Paediatric ICU; R: Resistance; SICU: Surgical ICU; S: Sensitive; TICU: Transplant ICU; TB: Tuberculosis; TCC: Ticarcillin/clavulanic acid; UTI: Urinary tract infection

with malignancies and underlying lung diseases [7]. An important consideration when handling such infections is differentiating them from colonisation. Instituting unnecessary therapy for colonisation would not only foster growing Antimicrobial Resistance (AMR) but also cause collateral damage to the patient. In the current study, ample clinical evidence was generated while documenting each such infection as a true one. This included repeat isolation from a fresh sample, correlation with gram stain findings, and the use of haematological and inflammatory biomarkers. Clinicians also need to keep in mind the possibility of finding it as a co-pathogen in polymicrobial infections, thereby having a negative impact on clinical outcomes.

Several studies have elucidated the risk factors for *S. maltophilia* infection. These include neutropenia, a history of antibiotic treatment with broad-spectrum antibiotics, presence of a central venous catheter, and prolonged hospitalisation [8,9]. [Table/Fig-4] elucidates the epidemiological triad as evidenced in *S. maltophilia* infections.



[Table/Fig-4]: Epidemiological triad of *Stenotrophomonas maltophilia* infections.
AMR: Antimicrobial resistance; CKD: Chronic kidney disease; DM: Diabetes mellitus

Most of the patients had one or more underlying co-morbid diseases. Diabetes Mellitus, hypertension, chronic obstructive pulmonary diseases, and kidney diseases have been found to be the most frequent co-morbidities in this study. These disorders impair the innate and adaptive immune systems, making the patients more vulnerable to infection by *S. maltophilia* [10].

[Table/Fig-5] provides a brief summary of contemporary studies on blood stream infections caused by *S. maltophilia* [5,10-21].

There is a rise in the rate of morbidity and mortality due to the innate resistance and extensive antibiotic treatment of this organism, especially in bacteraemia cases [22]. There is ample literature suggesting high mortality and morbidity rates associated with ICU-acquired *S. maltophilia* [12,23].

Bacteraemia (Blood samples) was the most common (42.8%) clinical presentation observed, which is discordant with a study conducted in Iran where bacteraemia was observed in only 16.3% of cases [10]. This discordance may be due to a different selection of cases. A 71.4% of patients had co-morbid conditions, and the rest of them were previously healthy. By far, the vast majority (82.4%) of cases of *S. maltophilia* infections are seen in persons who were severely ill and admitted to the ICU [12]. Isolates of *S. maltophilia* are primarily seen among patients admitted to the ICUs for a long period of time, and most of them had a poor outcome with a high mortality rate. However, it was observed in South India and France that there is a strong association between targeted antibiotics and a reduced mortality rate, suggesting that the pathogenic role of *S. maltophilia* should not be underestimated [12,23]. A review of the SENTRY antimicrobial surveillance program revealed *S. maltophilia* representing 0.6% to 0.9% of all isolates collected during the three-year study period [24]. In that study, the respiratory tract was the most frequently reported site of infection.

S. no.	Author name and publication year	Study design	No. of patients	Site of infection	Immune status	Antimicrobial susceptibility profile	Treatment given	Outcome
1.	Umar Z et al., 2022 [11]	Systematic review and meta-analysis	6 published articles	NM	NM	S- TMP/ SMX	TMP/ SMX	NM
2.	Jacob A et al., 2022 [12]	Original research article	119	Lungs, blood	Immunocompromised	S- LEVO, MINO R- NM R- NM	MERO	NM
3.	Alsuhaibani M et al., 2021 [13]	Original article	72	NM	Immunocompromised	S- TMP/ SMX, LEVO	TMP/SMX as monotherapy and combination with other antibiotics (FQ, CAZ, AG)	Mortality (33.8%)
4.	Bostanghadiri N et al., 2021 [14]	Original article	85	NM	NM	S- LEVO, MINO, TMP-SMX R- IMI, DORI, MERO	NA	NM
5.	Kanderi T et al., 2020 [15]	Case report	1	Lungs	Immunocompromised (adenocarcinoma)	S- TMP-SMX, LEVO R- CAZ	VAN, CPM, MET	Expired
6.	Duan Z et al., 2020 [5]	Original article	93	Lungs, blood and multiple fractures	Immunocompromised	S- MINO R- TMP-SMX, LEVO	-	NM
7.	Biswas S et al., 2020 [10]	Original research article	80	NM	Immunocompetent	S- TMP-SMX, LEVO	MERO, beta lactam-beta lactamase inhibitor combinations	NM
8.	Liu B and Tong S, 2019 [16]	Original article	25	Lungs	NM	S- MINO, LEVO R- CAZ, IMI	NM	NM
9.	Guerci P et al., 2019 [17]	Original article	282	Lungs	Immunocompromised	S- TMP-SMX, TCC R- CAZ, CIPRO	PTZ, 3rd gen ceph	Mortality (49.7%)
10.	Mishra M, 2018 [18]	Case report	1	Lungs	Immunocompetent	S- TMP-SMX R- NM	VAN, PTZ, AZI. Change treatment- TMP-SMX	Improved
11.	Cho SY et al., 2015 [19]	Original article	31	Blood	Immunocompromised (hematological malignancies)	S- CAZ, LEVO, TMP-SMX R- CIP	FQ, anti-Pseudomonal, CEPH, AG, Carba	NM

12.	Behnia M et al., 2014 [20]	Original article	43	NM	Immunodefiency	S-TCC, LEVO 50% cases are Resistant to CAZ	TMP-SMX, TGC	Mortality (37%)
13.	Harthan AA and Heger ML, 2013 [21]	Case report	1	Lungs	Immunodeficiency	S- NM R- TCC	Cefdinir, TMP-SMX, FQ	NM
14.	Present study, 2024	Original article	14	Lungs, blood	Immunocompromised	S- MINO, LEVO, TMP-SMX R- 43% cases are Resistant to CAZ	MINO, LEVO, TMP-SMX or monotherapy and combination with other antibiotics	Only 1 patient expired out of 14 patients

[Table/Fig-5]: Overview of recent reports on *Stenotrophomonas maltophilia* infection cases.
AG: Aminoglycosides; AZI: Azithromycin; Carba- carbapenem; CAZ: Ceftazidime; C: Chloramphenicol; CEPH: Cephalosporin; CIPRO: Ciprofloxacin; Col: Colistin; CPM: Cefepime; CTZ: Ceftezole; DORI: Doripenem; FQ: Fluoroquinolone; GENTA: Gentamicin; IMI: Imipenem; LEVO: Levofloxacin; MERO: Meropenem; MET: Metronidazole; MINO: Minocycline; MOXI: Moxifloxacin; NM: Not mentioned; PTZ: Piperacillin/tazobactam; R: Resistance; S: Sensitive; TCC: Ticarcillin/clavulanic acid; TGC: Tigecycline; TMP-SMX: Trimethoprim-sulfamethoxazole; VAN: Vancomycin

Most drugs used routinely are rendered ineffective in *S. maltophilia* infections because of intrinsic resistance (aminoglycosides), production of a variety of beta-lactamases (beta-lactams), and upgradation of efflux pumps (fluoroquinolones). Recently, the Infectious Diseases Society of America (IDSA) generated a guidance document for the treatment of *S. maltophilia* infections. For mild infections, TMP-SMX, minocycline, tigecycline, levofloxacin, or cefiderocol monotherapy are the suggested treatment options, with minocycline and TMP-SMX being the preferred drugs. For moderate to severe infections, a combination regimen is suggested, including the above-mentioned drugs. IDSA suggests that a "combination of ceftazidime-avibactam and aztreonam may be used as an alternative when inactivity or intolerance is experienced to the primary panel of drugs suggested" [25].

This study has demonstrated a generally low frequency of antibiotic resistance among the *S. maltophilia* isolates, with 7% (1/14) and 21%(3/14) of isolates being resistant to levofloxacin and cotrimoxazole, respectively. All the isolates were sensitive to minocycline [Table/Fig-3]. Biswas S et al., observed that cotrimoxazole (93.8%) was the most sensitive antibiotic, followed by ciprofloxacin (88.8%) and piperacillin-tazobactam (32.5%) in the case of *S. maltophilia* infections [10]. Likewise, Duan Z et al., have also revealed 96% and 100% susceptibility to levofloxacin and minocycline, respectively [5]. Colgan R et al., also found a mere 5% resistance to the most effective antimicrobial agent used to treat *S. maltophilia* infections, i.e., SMX/TMP [26]. Very favourable susceptibility rates to the tune of 95% have been found in several studies conducted in Europe, North America, and Latin America [14].

Based on the antimicrobial profile, the treatment of the patients was modified, and mortality was observed in only one patient. Of the primary drugs available, cotrimoxazole is recommended as the drug of choice. There is ample clinical data available providing evidence of its use and effectiveness. Cefiderocol has issues like availability and affordability, and levofloxacin may be rendered ineffective because of the presence of efflux pumps and modifications in qnr genes. Ceftazidime is again not suggested because of the expression of several beta-lactamases. Tetracycline derivatives like minocycline and tigecycline may be considered as good therapeutic options because of ease of availability, being inexpensive, and having a good safety profile. The flip side, however, is that they achieve rapid tissue distribution, making them largely ineffective for urine and bloodstream infections [27].

AMR is a highly dynamic phenomenon. The bacteria keep evolving because of natural selection as well as the constant selection pressure of antibiotics, especially in critical care settings. While encountering these infections, it is important for healthcare personnel from all specialties to work as a team and formulate customised antimicrobial prescriptions for the patients. This mandates astute monitoring of such emerging infections for their better management. This study shall serve as an important baseline while developing policy guidelines for this lesser understood pathogen.

There are some strengths and limitations of present study that merit discussion. Jaipur, the Pink City, is the capital and largest city of the Indian state of Rajasthan. It is fast becoming the abode for medical tourism and well-being. In such a scenario, it is essential to understand the emerging infection profile as seen in hospitals. To the best of our knowledge, this was the first work providing insight into the *Stenotrophomonas* infections experienced in this area. The strength of the study lies in the fact that it provides a comprehensive summary of all microbiological as well as clinical details associated with these infections. This data shall help in formulating treatment guidelines for use in the future.

Limitation(s)

The limitations of this study include its retrospective nature. The effect of confounding variables cannot be entirely ruled out. Secondly, no molecular typing was performed on *S. maltophilia* isolates. As a result, the transmission dynamics are difficult to elucidate, and the possibility of cross-transmission cannot be entirely ruled out.

CONCLUSION(S)

S. maltophilia has emerged as an important opportunistic pathogen. Its management is often difficult because of its ability to persist in biofilms and its inherent resistance to several commonly used antibiotics. The current study provides robust clinical and microbiological data pertaining to the *S. maltophilia* infections encountered in our set-up. Early diagnosis, by embracing automation in microbiology laboratories, is essential to identify these novel bugs in time to avoid therapeutic failures. The principles of antimicrobial stewardship and infection control need to be followed wholeheartedly to prevent this problem from becoming insurmountable.

Author's contribution: DB: Literature search, data acquisition, and manuscript writing; ER: Concept, design, literature search, data acquisition, manuscript editing, review; SK: Manuscript editing and review; CS: Literature search, and data acquisition; RS: Manuscript review and editing; VKG: Data acquisition, manuscript review and editing.

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- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

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