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Stenotrophomonas maltophilia infections: Experience from a tertiary care teaching hospital in Eastern India

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Abstract

Stenotrophomonas maltophilia, a gram-negative nonfermenter, is ubiquitous in the environment and has the propensity to colonize devices and even the respiratory tract. The organism shows intrinsic resistance to multiple drugs commonly used in hospitals, like cephalosporins, carbapenems, and aminoglycosides, thus selecting this organism from endogenous patient flora. Here we conducted a retrospective study presented as a case series to share our experience in our setup. We encountered 9 cases during 1 year, most sensitive to levofloxacin and minocycline. All the cases apart from two were discharged successfully following the appropriate regimen. The mean age of patients was 50 years, and most patients had a history of long-standing diabetes. Most of the cases were admitted to ICU and were on ventilators. The organism commonly causes ventilator-associated pneumonia in our series. Our area lacks studies on this organism, which is rising in prevalence. Thus, further large-scale studies are needed to ponder this infection's prevalence and increasing resistance of this organism to TMP/SMX (Cotrimoxazole), the drug of choice in this infection.

Keywords

Stenotrophomonas maltophilia (SM), Ventilator-associated pneumonia, levofloxacin

Cover Page Footnote

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Stenotrophomonas maltophilia infections: Experience from a tertiary care teaching hospital in Eastern India

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Abstract

Stenotrophomonas maltophilia, a gram-negative nonfermenter, is ubiquitous in the environment and has the propensity to colonize devices and even the respiratory tract. The organism shows intrinsic resistance to multiple drugs commonly used in hospitals, like cephalosporins, carbapenems, and aminoglycosides, thus selecting this organism from endogenous patient flora. Here we conducted a retrospective study presented as a case series to share our experience in our setup. We encountered 9 cases during 1 year, most sensitive to levofloxacin and minocycline. All the cases apart from two were discharged successfully following the appropriate regimen. The mean age of patients was 50 years, and most patients had a history of long-standing diabetes. Most of the cases were admitted to ICU and were on ventilators. The organism commonly causes ventilator-associated pneumonia in our series. Our area lacks studies on this organism, which is rising in prevalence. Thus, further large-scale studies are needed to ponder this infection's prevalence and increasing resistance of this organism to TMP/SMX (Cotrimoxazole), the drug of choice in this infection.

Keywords: *Stenotrophomonas maltophilia* (SM), Ventilator-associated pneumonia, levofloxacin.

INTRODUCTION

Stenotrophomonas maltophilia (SM), previously called *Xanthomonas maltophilia*, is a gram-negative non-fermentative aerobic bacillus, ubiquitous in water, plants, and soil.(1) It has a high propensity to form biofilms and thus can easily colonize various devices and even respiratory tract. (2-3) Globally, *S. maltophilia* ranks third amongst the four most common pathogenic non-fermenting Gram-negative bacilli and is the most common Gram-negative carbapenem-resistant pathogen isolated from bloodstream infections acquired both in the community and in the hospital setting in the USA. (4)

As a low-virulence pathogen, SM primarily causes opportunistic infections in patients with cystic fibrosis (CF), malignancies, or any immune-suppressed condition in hospitalized and community-acquired settings. (5-6) Infections caused by SM include endocarditis, bacteremia, skin, and soft tissue infections, VAP (Ventilator-associated pneumonia), and urinary tract infections**.** (7) ICU (intensive care unit) admission, use of central venous catheters and other indwelling devices, meropenems, lengthy hospitalization, and malignancy are a few risk factors for SM infections. (5-6)

SM shows intrinsic resistance to many antibiotics like carbapenems, broad-spectrum penicillin, piperacillin-tazobactam, cefepime, and aminoglycosides. Thus, this organism is selected in a hospital setup where carbapenem and cephalosporins are the common antibiotics administered to patients. Its unique sensitivity profile makes the treatment challenging, thus having a mortality rate of up to 69%.(8) TMP/SMX (Cotrimoxazole) is the drug of choice for treating SM infections; resistance to this antibiotic is also being increasingly reported in the literature.(9-10) Acquired resistance in this strain by integrons, plasmids, and transposons has been noted recently.(11) Other treatment options are tetracyclines, fluoroquinolones, ceftazidime, and ticarcillin/clavulanate. Often the non-fermenting Gram-negative organisms are misidentified or clubbed together as Pseudomonads, which

may prove lethal owing to the vast difference in their sensitivity pattern.

Despite these bottlenecks, there is a paucity of literature from our country showing this organism's epidemiology, risk factors, and sensitivity pattern. The present work looks into a series of patients, over one year, from whom SM was isolated in our tertiary care teaching hospital in Eastern India.

METHODS

This is a retrospective study conducted over 1 year from March 2021 to March 2022 when at our institute, a premier tertiary care 1200-bed teaching hospital catering to a lower and middle economic population in Eastern India. We received 9 cases that grew SM on culture during the above time frame. All the samples were collected aseptically in the respective wards and ICUs by trained nurses as per standard protocol and, on receipt in the lab, were cultured on blood and Macconkey agar plates with a backup broth. All respiratory samples (sputum, tracheal aspirates, bronchoalveolar lavage, etc.) were put for semi-quantitative cultures and reported only when appropriate colony counts were obtained (Tracheal aspirates $\geq 10^5$ colonies forming unit (CFU) /ml, broncho alveolar lavage $\geq 10^4$ colony forming unit(CFU) /ml). (12) Blood culture was done by Bac T Alert, Version B.50, Biomerieux, North Carolina, USA. The colonies thus obtained were further identified by Vitek 2 GN card (version 8.01, BioMérieux, Inc. Durham, USA). Antimicrobial susceptibility testing for minocycline (30µg) was performed by the Kirby-Bauer disc diffusion method, while other antibiotics were tested by Vitek 2 (BioMe'rieux) AST cards. The zone diameter and MIC were interpreted based on the CLSI (clinical and laboratory standards institute) (13) criteria for SM. Using both methods, the sensitivity patterns of the isolates were determined for 3 antibiotics-TMP/SMX, levofloxacin, and minocycline. All the laboratory parameters were collected from bacteriology laboratory records. Patient's clinical data, including sex, age, diagnosis at admission, devices like central venous catheter and ventilator, and the outcome of infection, were recorded from case sheets obtained from the Medical records section. A summary of all the cases is listed in Table 1.

RESULTS

Table (1): Summary of patients with *Stenotrophomonas maltophilia* infections.

Case	Age	Sex	Diagnosis	Underlying illness	Length of stay (in days)	Previous antibiotic history (After admission to the hospital)	Treatment	The outcome of the current admission
1	58	F	Pure motor disease	Diabetes mellitus, Hypothyroidism, hypertension, on steroid and IVIG, Prolonged hospitalization	17	Meropenem	Levofloxacin	Discharged

Case	Age	Sex	Diagnosis	Underlying illness	Length of stay (in days)	Previous antibiotic history (After admission to the hospital)	Treatment	The outcome of the current admission
2	45	M	TB Meningitis	Nil	8	Ceftriaxone, Doxycycline, Vancomycin, Ampicillin	Levofloxacin, Ceftazidime	Left against medical advice
3	52	M	Intra cranial hemorrhage with intraventricular extension	Diabetes mellitus, hypertension	1	Cefoperazone, Metronidazole Piperacillin-tazobactam	Levofloxacin Minocycline	Discharged
4	61	M	Necrotising Fasciitis	Nil	NA	Piperacillin tazobactam Amikacin Metronidazole	Cotrimoxazole	Discharged
5	34	M	Post-open cholecystectomy bile leak	Nil	2	Piperacillin tazobactam Clarithromycin Imipenem cilastatin	Levofloxacin, Ceftazidime	Discharged
6	8	M	Diffuse Axonal Injury	Nil	15	Cefuroxime clavulanate	Levofloxacin	Discharged
7	72	M	Compound Fracture little toe	Diabetes mellitus	1	Ceftriaxone Metronidazole Amikacin	Levofloxacin	Discharge
8	65	M	Subdural hemorrhage	Diabetes mellitus	12	Ceftriaxone, Piperacillin tazobactam Meropenem	Levofloxacin Ceftazidime	Left against medical advice
9	63	M	Pneumothorax, COPD	Diabetes mellitus,	12	Cefoperazone-	Levofloxacin	Discharged

Case	Age	Sex	Diagnosis	Underlying illness	Length of stay (in days)	Previous antibiotic history (After admission to the hospital)	Treatment	The outcome of the current admission
			post COVID	hypertension		Sulbactam Clarithromycin		

Case 1: A 58 yr old female was admitted to our hospital preliminarily needing ICU care. She was diagnosed with pure motor syndrome from her previous hospitalization and was given steroids and IVIG (Intravenous immunoglobulin) for the primary diagnosis. She had a history of Type 2 diabetes mellitus, hypertension, and Hypothyroidism on treatment. During her ICU stay in our hospital, she was catheterized and put on a tracheostomy and central venous catheter. Her ICU stay was uneventful till 18 days, after which she developed a fever spike. There were no other signs suggesting device-related infections. Lab evaluation revealed high CRP (C-reactive protein) with neutrophilic leukocytosis. Blood culture was sent from the peripheral and central lines before administering the meropenem. Both the cultures grew SM with differential time to positivity, suggesting CRBSI (Central line-related bloodstream infection). The patient was put on levofloxacin, and the central line was changed after receiving the culture results, which resulted in an uneventful recovery. The patient was discharged after her primary symptoms improved for future home-based care.

Case 2: A 45 yr old male was admitted to the ward with a fever of low grade, vomiting, and signs of meningeal irritation. The patient was diagnosed with a case of Tubercular meningitis following suggestive CSF examination and was put on anti-tubercular treatment. The consciousness worsened further, and the patient was transferred to ICU, where he was put on ventilator support. On day 4 of the ICU stay, the patient had purulent tracheal secretions, with the return of fever and neutrophilic leukocytosis. The culture of this tracheal aspirate showed SM with a colony count of $> 10^5$ CFU/ml. The patient was put on levofloxacin and ceftazidime, following which he showed clinical improvement. He was discharged against medical advice 6 days after the episode.

Case 3: A 52-year male patient presented to the emergency department from an outside hospital with a diagnosis of intraventricular hemorrhage. On examination, he was unconscious with prior intubation. He was a known case of type 2 diabetes mellitus and hypertension. The tracheal aspirate was sent on Day 1 of ICU admission after noting a purulent discharge and increasing oxygen requirement, which revealed this organism in colony count of $> 10^5$ CFU/ml. His infective episode was reduced with levofloxacin and minocycline. The patient was treated for his primary illness and discharged subsequently.

Case 4: A 61-year male patient was admitted with a complaint of a wound with progressively increasing pain in the left hand for 12 days. On examination, the wound was 10 cm x 6 cm in dimension with minimal erythema around it. There has been a fever for 5 days. There was a history of rat bites at the site, leading to progressive ulceration and pain for which he had been treated in a local hospital. Pus from the lesion was sent for culture, which revealed SM. On receiving the sensitivity report, the patient was started on piperacillin, tazobactam, and amikacin and changed to cotrimoxazole. The patient was discharged 6 days of hospitalization with oral antibiotics.

Case 5: A 34-year-old male was admitted to ICU with a bile leak following an open cholecystectomy at an outside hospital. 4 days prior to this episode. The patient had signs of sepsis with fever, low blood pressure, and severe respiratory distress. Both discharging bile and blood were sent for culture, which

yielded SM. The patient was treated with levofloxacin and ceftazidime. ERCP (Endoscopic retrograde cholangiopancreatography) guided the repair of the leak following the patient's stabilization. The patient was discharged subsequently**.**

Case 6: A 8-year-old child was received in the pediatric outpatient department as a follow-up case for tracheostomy tube removal. He was admitted to our hospital for diffuse axonal injury and was discharged with cefuroxime-clavulanate after a long ICU stay. On examination, there were purulent tracheal secretions and mild fever for one day, and a blood workup showed neutrophilic leukocytosis. The culture of the tracheal secretions showed SM in significant colony count. The patient was started on levofloxacin and subsequently discharged for home-based care.

Case 7: A 72 yr old, known diabetic male patient presented to the emergency with a compound fracture of the proximal phalanx of the right little toe. The wound site was cleaned, and a swab was sent for culture and sensitivity from the base of the ulcer following debridement. The culture revealed SM, which was successfully treated with levofloxacin. The follow-up swab did not grow this organism. The appropriate surgical management of the patient was done for the primary cause.

Case 8: A 65-year-old male patient was admitted to the neurosurgery ICU with nausea, vomiting, and mental confusion. The patient was diagnosed with a subdural hemorrhage after a CT scan and was admitted to ICU for evacuation of it by burr hole and general management. He had a prior history of diabetes mellitus. During the ICU stay, he was intubated and put on a central line and foley catheter. On 12, the day of his stay, he developed fever and leukocytosis with patchy infiltrates on chest X-Ray. The purulent endotracheal aspirate was sent for culture, which revealed this organism. The patient was successfully treated with levofloxacin and ceftazidime**.**

Case 9: A 63-year-old male patient was admitted to the ICU with a history of shortness of breath for 3 days. He had a history of diabetes mellitus, hypertension, and Chronic Obstructive Pulmonary Disease with emphysematous bullae with post-Corona virus disease (COVID-19) status. He was clinically diagnosed with a case of pneumothorax, and the patient was managed with intercostal tube drainage followed by intubation. After 1 day of weaning from the ventilator, the patient developed a cough with expectoration, after which sputum was sent for culture. The culture revealed SM, and the patient was treated with levofloxacin and clinically improved with reduced symptoms. The patient was discharged on 3rd day of starting treatment for home-based care with a piece of advice for bullectomy as soon as possible.

Table (2): Sensitivity pattern of *S.maltophilia* isolated.

Case	Levofloxacin Interpretation (MIC in µg/mL)	Cotrimoxazole Interpretation (MIC in µg/mL)	Minocycline Interpretation (MIC in µg/mL)
1	S (1)	S (≤20)	S
2	S (≤2)	R (160)	S
3	I (4)	R (≥320)	S
4	S (1)	S (≤20)	S
5	S (1)	S (≤20)	S
6	S (≤2)	S (≤20)	S
7	S (≤2)	S (≤20)	S
8	S (1)	S (≤20)	S
9	S (1)	S (≤20)	S

DISCUSSION

In the present series, 8 of 9 (88.9 %) patients were males. The mean age of the patients was 51± 20 yrs, and the median of 58 years. Most patients (6/9; 66.7%) were from ICU, with only 2 from wards and 1 from OPD. The most common sample (5/9; 55.6%) from which this organism was isolated was a respiratory sample (tracheal aspirate) followed by pus and blood. The mean duration of stay in the hospital before isolation of this organism was 5.9 ± 6.5 days. Of the patients 6/9, 66.7% were on central venous catheters, and the same percentage were on ventilators prior to the episode of infection with SM. In most cases (8/9; 88.9 %), the infections were hospital-acquired as these developed as a separate entity from their primary diagnosis after 48 hours of hospital stay. The most common underlying illnesses were type 2 diabetes mellitus (5/9; 55.6%) and hypertension (3/9; 33.3%). No other cause of immunosuppression was noted in our series. The most common prior antibiotics given to the patients during the hospital stay were broad-spectrum cephalosporins (6/9; 66.7%) and piperacillin-tazobactam (4/9; 44.4%). Apart from two cases that were left against medical advice, other patients (77.8%) were discharged after successful infection treatment.

SM is an organism with low virulence generally associated with nosocomial disease. This infection is generally seen among patients in the intensive care unit (82.4%).(14) In our series, also similar finding was observed. Pneumonia, followed by bacteremia, is the common infection caused by SM.SM-VAP is generally considered in patients with immunosuppression or those undergoing invasive procedures and long-term hospitalization.(2-3,15) In our case, pneumonia in an artificial ventilated setting was the most common infection. As *Stenotrophomonas* colonizes the respiratory tract, diagnosis of VAP requires clinical and bacteriological approaches.(15) In our series, cases had clinical signs of infection, thus, were probably true pathogens rather than colonizers.

Besides bacteremia and pneumonia, SM infects the biliary tract, endocardium, urinary tract, meninges, eye, and bones, as documented in many case reports.(5) In our study, we also had two cases with SM from pus and one isolated from bile. Severe community-acquired skin infections due to *S. maltophilia* have also been reported in both immunocompetent and immunocompromised patients.(16) One of our cases had a history of rat bite, which led to necrotizing fasciitis like the clinical picture caused by this organism. This is a rare clinical picture that is not nosocomially acquired. There are reports of SM from various pet animals, birds, marine animals, and insects, both as commensal flora and pathogen.(5,17) of new But it has never been recovered from animal bites which is a point for further research.

Unlike other studies, bacteremia was rare in our series. *Stenotrophomonas* bacteremia is generally polymicrobial, as seen in other studies.(18) A single case of bacteremia encountered in our series was monomicrobial.

Aged patients of ≥60 and male sex were more susceptible to SM infection as per previous studies.(19) In the present case series, the age of the patients was relatively less, with a mean age of 50 years, while we had a male predominance (88.9%). A study from south India (14) also had a similar mean age of patients (48.6 years). In addition, the literature has reported prolonged ICU stay, immunosuppression, mechanical ventilation, neutropenia, and malignancy as important risk factors in SM infections.(20-22) In our series ICU stay, mechanical ventilation, and diabetes mellitus were the major associated factors that may have contributed to immunosuppression. We did not find any other factors like organ transplants, malignancy, steroid use, etc., in our study.

SM-VAP (Ventilator-associated pneumonia by *Stenotrophomonas maltophilia*) is associated with long exposure to broad-spectrum antibiotics like piperacillin-tazobactam and ciprofloxacin within the week before diagnosis.(2) Similarly, we had a high incidence of piperacillin-tazobactam and cephalosporins administration. Carbapenem administration in our series was much lower (2/9; 22.2%) than in other studies (14), where carbapenem exposure within the previous month was as high as 66%. As this organism is resistant to cephalosporin and carbapenem, their use helps select SM as the dominant flora. SM infection is

believed to be of endogenous origin and rarely spreads interpersonally in a ward.(5)

While performing susceptibility patterns there, are few points should be kept in mind: a) Common antibiotics which are empirically given are ineffective against SM b) Susceptibility testing of SM isolates is susceptible to changes in incubation temperature, culture media, and technique c) Automated systems like Vitek 2 provide sensitivity to a very few antibiotics often needing manual sensitivity testing in places where resistance is an issue. In our series, susceptibility to minocycline is high, as in other studies.(6) As per a recent study from south India,(14) *Stenotrophomonas* isolates were more susceptible to levofloxacin and minocycline, 96.4% and 97.2% of cases, respectively, while cotrimoxazole was sensitive in 93% cases only. Our patients also had similar findings. Many chromosomal and plasmid-mediated genes like sul1, sul2, and dfrA, which contribute to resistance to TMP/SMX, are observed. These genes are often associated with resistance to other antibiotics like aminoglycosides and chloramphenicol.(23-24) Multidrug resistance to minocycline, trimethoprim/ sulfamethoxazole, and ceftazidime will gradually reduce the drugs available in the armamentarium.(25)

This infection generally carries a high mortality rate (46.2%).(14) Risk factors for mortality in SM infections are ICU stay, mechanical ventilation, malignancy, central venous catheter use, failure to remove a central line, lack of effective antibiotic treatment, hypotension, thrombocytopenia, neutropenia, and infection along with enterococci. (20,6,23-24) Mortality risk factors reported for S. maltophilia ventilator-associated pneumonia include age and chronic heart failure (25), favorable factors in our series amounting to lower mortality. In our study, most patients were administered levofloxacin rather than TMP/SMX, probably contributing to reduced mortality. Fluoroquinolone treatment in SM pneumonia is associated with higher survival rates than TMP/SMX treatment, as per a study by Ko *et al*.(26) Quinolone resistance is also a risk factor for higher mortality. TMP/SMX resistance in SM is also being increasingly reported.(9-10) A cystic fibrosis patient was treated successfully for SM by continuous infusions of both ceftazidime/avibactam and aztreonam in a study by Cowart *et al*.(27) However decrease in the susceptibility of SM to ceftazidime has been demonstrated.(28) Minocycline, doxycycline, and tigecycline have shown good potency against SM, but clinical data, particularly from our country, is lacking.(29).

CONCLUSION

SM commonly causes nosocomial infection, particularly causing VAP in intensive care patients, as shown in our work. The mean duration of hospitalization and carbapenem exposure was much less in the present study than in previous ones. Levofloxacin, rather than TMP/ SMZ, can improve the outcome of patients with these infections. There is a need for further work to establish this antibiotic's efficacy in clinical cases and use a combination regimen in case of resistance to available drugs.

Ethics approval and consent to participate: Implied consent from all the patients was present for diagnosis and treatment. Due to the retrospective nature of the work, no different sample was collected from patients. Patient confidentiality was not breached at any point.

Consent for publication: Present from all authors

Availability of data and materials: Present with corresponding authors

Author's contribution: Swati Mishra: conceptualization, writing-original draft, data curation, manuscript preparation, editing, and review. **Priyadashini Bhoi:** data curation, formal analysis, funding acquisition, investigation, methodology. **Diptimayee Rout:** Investigation, methodology, writing review, Original draft preparation. **Nabanita Chakraborti:** data curation, formal analysis, Original draft preparation, investigation, methodology. **Kundan Kumar Sahu:** Supervision, validation, Literature search & editing. **Sarita Otta**: Design, Definition of intellectual contents, project administration, resources, software, supervision, validation, visualization, and writing review & editing. Ms. Diptimayee Rout- Ph.D. student, and Dr. Nabanita Chakraborti, MD student in Dept of

Microbiology, IMS, and SUM Hospital, were involved in the study and have been given the authorship for it.

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