Genotype Study of *L1 Subclass B3* Metallo Beta Lactamase Gene Among Multidrug Resistance *Stenotrophomonas Maltophilia* Isolated from Different Infection in AL- Najaf Province.

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Abstract

Stenotrophomonas maltophilia can be considered a "newly emerging pathogen of concern" that is being isolated more frequently. It is also recognized as one of the underestimated important multi-drug resistant organisms in hospitals by the World Health Organization (WHO). The results were as follows: 42 isolates of *S. maltophilia* and 80 isolates of *P. aeruginosa* out of 230 isolates were Gram-negative bacteria and non-lactose fermenter after growing on MacConkey agar.

The isolates were tested for susceptibility to 11 antibiotics by the Kirby-Bauer disk diffusion method to S. maltophilia. Overall, the resistant rate for β-lactams/ β-lactamase inhibitor combination antibiotic including ticarcillin/clavulanate was (71.4%). The rates of resistance to the ceftazidime (47.7%), cefepime (46.2%), doxycycline (57.1%), minocycline (59.5%), ciprofloxacin (76.1%), levofloxacin (78.5%), norfloxacin (83.3%), moxifloxacin (59.5%), trimethoprim/sulfamethoxazole (28.5 %), chloramphenicol (35.7 %).

As for the molecular study for the detection of L1 subclass B3 Metallo-beta-lactamase genes of *Stenotrophomonas maltophilia* bacteria, it was as follows (80.9%).

1. Introduction

Stenotrophomonas maltophilia is a rapidly spreading opportunistic infection. This inherently multidrug-resistant bacteria has emerged as an infectious agent in hospitals, particularly in intensive care units, due to the use of broad-spectrum antibiotics and an increase in the number of invasive procedures and immunosuppressed patients (ICUs) [1].

Its tolerance to a wide range of antibiotics, including beta-lactams and aminoglycosides, allows it to colonize patients even while antibiotics are being used. *S. maltophilia* can cause a wide range of infections, including pneumonia, bacteremia, endocarditis, urinary tract infection, meningitis, cholangitis, soft tissue infection, and wound infection, despite its low virulence [2].

During the last decade, *S. maltophilia* has been considered as one of the leading multi-drug resistant (MDR) organisms in hospital settings due to exhibiting high levels of intrinsic and acquired resistance to a broad array of antibacterial agents, including fluoroquinolones, aminoglycosides, and the most common of β-lactam antibiotics [3]. Different types of antimicrobial resistance mechanisms, such as expression of antibiotic hydrolyzing or modifying enzymes, membrane permeability alteration and multi-drug efflux system [4].

Stenotrophomonas maltophilia is becoming a major source of human and animal disease around the world. At least two inducible -lactamases (L1 and L2) in S. maltophilia can hydrolyze practically all kinds of -lactams, and these genes are thought to confer carbapenem resistance. This is a major public health concern, especially for hospitalized patients [5].

2. Material and Method

Specimens collection

From November 2020 to November 2021, 850 clinical specimens were collected from patients suffering from different clinical infections from hospitals in Al –Najaf province.

Specimens Culture and biochemical test.

After collecting the specimens using swabs, they were cultured on the commonly used media (MacConkey) which are initially based on isolation and initial diagnosis. And then adopting the biochemical tests from them IMVIC test,catalase test,coagulase and oxidase,In addition to using VITEK-2 Compact System to confirm the diagnosis Identification [6, 7].

Antimicrobial Activity

Antibiotic sensitivity testing is performed by placing a variety of antibiotic discs with known doses on Muller Hinton media, evaluating the results after 24 hours, calculating the diameter of the inhibition zone, and comparing the results to CLSI 2021.

DNA extraction

Genomic DNA was extracted by using a commercial total DNA extraction kits (Favorgen, Taiwan).

Molecular identification

Gel electrophoresis was used for detection of DNA by UV transilluminator. The PCR assay was performed to detect the (*16 s Rrna* and bla-*L1)* genes for *Stenotrophomonas maltophilia.*

3. Results and Discussion

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Isolation and Identification of *Stenotrophomonas maltophilia* Isolates.

Identification of *Stenotrophomonas maltophilia* was first made by the bacteriological methods including colonial morphology (Figure 1), Grams stain, and other biochemical tests (Table 1). Characteristics of *Stenotrophomonas maltophilia* were subjected to biochemical tests for identification and confirmed by Vitek2-automated system. Only 42 isolates belonged to genus *Stenotrophomonas maltophilia*.

Figure (1): Production of colony pigment (yellowish orange) by Stenotrophomonas maltophilia on macConkey agar.

Table (1): Morphological and biochemical tests of *Stenotrophomonas maltophilia* isolates

Test	Result
Gram stain	Negative
Shape	Short rods
Capsule	Positive
Catalase	Positive
Oxidase	Negative
Motility	Positive
Indole test	Negative
Methyl red	Negative
Voges-Proskauer	Negative
Citrate	Variable
Urease	Negative
TSI	K/K
Lactose fermenter	Non fermenter

S. maltophilia is motile due to polar flagella, and grow well on MacConkey agar producing pigmented colonies. *S. maltophilia* is catalase-positive, oxidase-negative (which distinguishes it from most other members of the genus), in addition to the IMVICs tests, they were negative, only the citrate test was variable among the isolates this agree with [8].

All 42 isolates tests gave positive bands in the PCR assay and gave expected size of PCR products. PCR products from isolates collected from different source were obtained with primer pairs in (Figure 2).

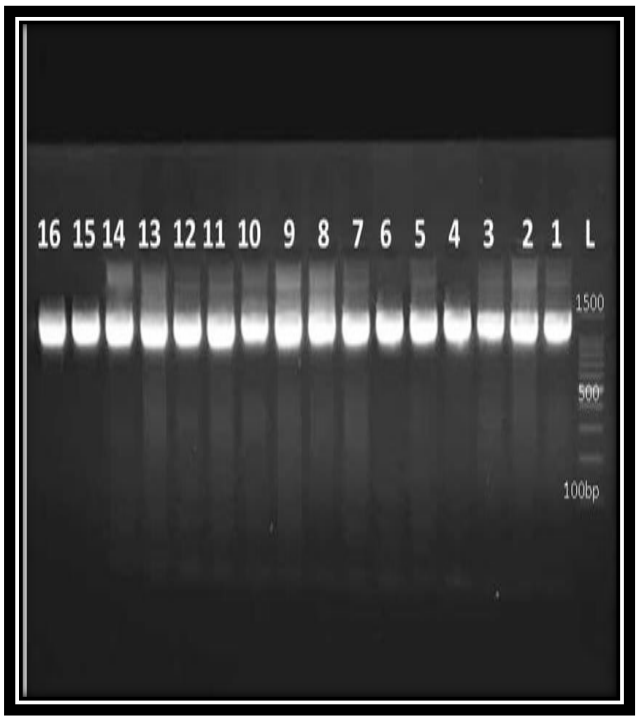
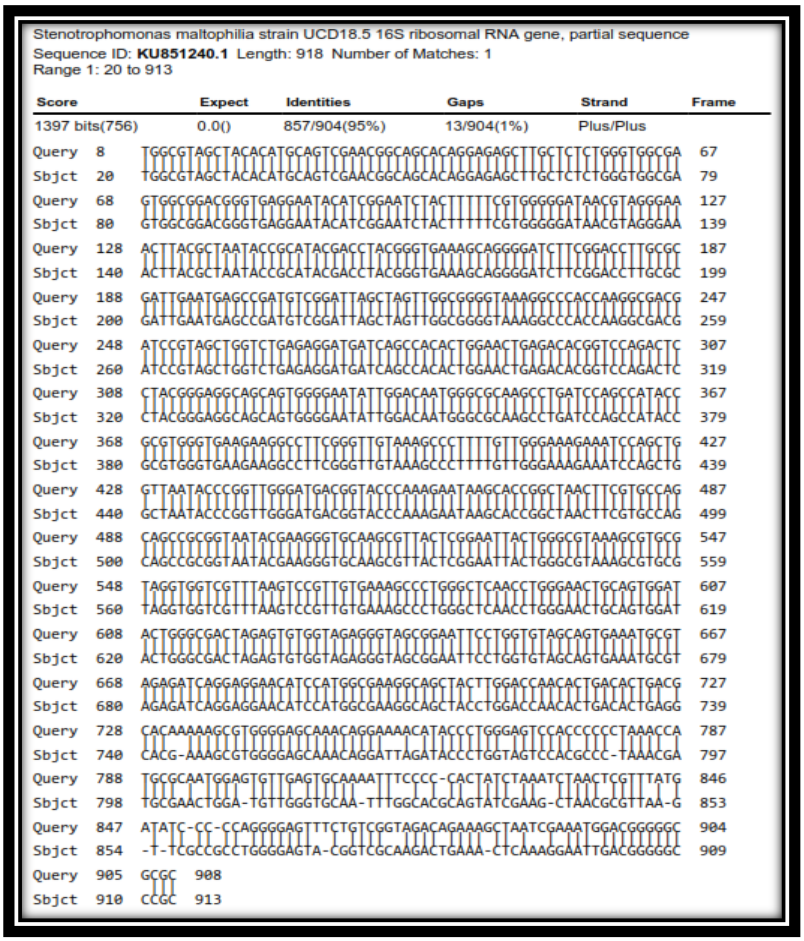


Figure:(2): Ethidium bromide-stained agarose gel electrophoresis of PCR products from extracted total DNA of Stenotrophomonas maltophilia using primer 16s rRNA with product 1475 bp. The electrophoresis was performed at 70 volts for 1- 1.5 hr. (L), DNA molecular size marker (100 bp ladder). (all 42 isolate show positive results with universal 16s rRNA).

16S rRNA Gene Sequencing for *Stenotrophomonas maltophilia*

The 16S rRNA gene was subjected to nucleotide sequencing with an automated DNA sequencing machine at Bio-Service unit. National Science and Technology Development Agency. The 16S rRNA gene sequences determined were aligned along with the sequences of type strains obtained from the GenBank.

Distance phylogeny and pairwise alignment have been investigated for *Stenotrophomonas maltophilia* 16sRNA gene sequences. Online NCBI blast software was used to compare each of the two resulting sequences, to the NCBI data base. One strain was found to be nearest and neighbour to *Stenotrophomonas maltophilia* strain UCD18.5 in Spain, with E -value 0.0 and identity 95%, and with Score 1397 bits (756), Identities (95%), and Gaps (13%) as shown in (Figure 3) to compare with BLAST- NCBI.


Stenotrophomonas maltophilia strain UCD18.5 16S ribosomal RNA gene, partial sequence
Sequence ID: **KU851240.1** Length: 918 Number of Matches: 1
Range 1: 20 to 913

Score	Expect	Identities	Gaps	Strand	Frame
1397 bits(756)	0.0()	857/904(95%)	13/904(1%)	Plus/Plus	

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Query  8    TGGCGTAGCTACACATGCAGTCGAACGGCAGCACAGGAGAGCTTGCTCTCTGGGTGGCGA  67
Sbjct  20   TGGCGTAGCTACACATGCAGTCGAACGGCAGCACAGGAGAGCTTGCTCTCTGGGTGGCGA  79
Query  68   GTGGCGGACGGGTGAGGAATACATCGGAATCTACTTTTTCGTGGGGGATAACGTAGGGAA  127
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Sbjct  200  GATTGAATGAGCCGATGTCGGATTAGCTAGTTGGCGGGGTAAAGGCCCACCAAGGCGACG  259
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Sbjct  260  ATCCGTAGCTGGTCTGAGAGGATGATCAGCCACACTGGAACTGAGACACGGTCCAGACTC  319
Query  308  CTACGGGAGGCAGCAGTGGGGAATATTGGACAATGGGCGCAAGCCTGATCCAGCCATACC  367
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Query  428  GTTAATACCCGGTTGGGATGACGGTACCCAAAGAATAAGCACCGGCTAACTTCGTGCCAG  487
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Query  847  ATATC-CC-CCAGGGGGAGTTTCTGTCGGTAGACAGAAAGCTAATCGAAATGGACGGGGGC  904
Sbjct  854  -T-TCGCCGCCTGGGGAGTA-CGGTCGCAAGACTGAAA-CTCAAAGGAATTGACGGGGGC  909
Query  905  GCGC  908
Sbjct  910  CCGC  913
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Figure (3) Pair-wised alignment of partial nucleotide sequence of 16S ribosomal rRNA gene (Query) to that of Stenotrophomonas maltophilia strain UCD18.5 whose sequence producing highest score (95%) of homology during BLASTn search.

In current study,the highest percentage (42.85%) of *Stenotrophomonas maltophilia* was isolated from urine samples compared to other sites of infections (Figure 4). Other isolates were recovered from burn swabs (35.71%), and for each of the ear swabs, stool, and wound swabs were (7.14%), while no isolate was recovered from blood,throat and CSF samples. Pompilio et al. [9] that reported,*Stenotrophomonas maltophilia* is a Gram-negative, aerobic, nonfermentative bacteria. It is a rare bacterium that is difficult to cure in humans. *S. maltophilia* was formerly classified as *Bacterium bookeri* before being renamed *Pseudomonas maltophilia*. It was also included in the genus *Xanthomonas* before becoming the type species of the genus *Stenotrophomonas* in 1993.

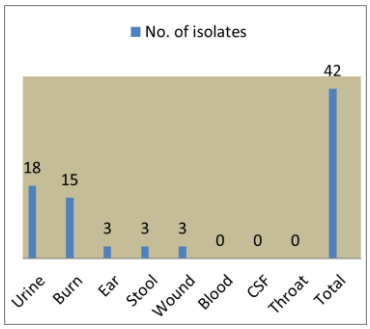


Figure (4): Distribution of Stenotrophomonas maltophilia obtained from different clinical samples according to the sample source.

The findings observed in this study mirror those of the previous studies regarding the presence *Stenotrophomonas maltophilia* is an opportunistic nosocomial pathogen that has caused an increasing number of infections in recent years. It is associated with a number of clinical syndromes, such as endocarditis, urinary infections, and respiratory infections, including pneumonia in patients with cystic fibrosis and the immunocompromised [10].

Similar findings were published by Abbott et al. [11] Chronic respiratory disorders, including cystic fibrosis, hematologic malignancy, chemotherapy-induced neutropenia, organ transplant patients, human immunodeficiency virus (HIV) infection, hemodialysis patients, and neonates are all risk factors for this infection. In addition, hospital settings, long stays in intensive care units, mechanical ventilation, tracheostomies, central venous catheters, severe traumatic injuries, significant burns, mucositis or mucosal barrier damaging factors, and the use of broad-spectrum antibiotic courses have all been linked to an increased risk.

Hu et al. [12] reported that ,*Stenotrophomonas maltophilia*, a non-fermentative Gram-negative bacillus found in the environment, it is a developing opportunistic pathogen that, while not being very virulent, has recently been recognized as one of the main drug-resistant bacteria in hospitals around the world by the World Health Organization. Infection occurs principally in immunocompromised subjects and in patients exposed to

invasive devices and/or broad-spectrum antibiotics. *S. maltophilia* can cause mechanical ventilated pneumonia,catheter-related bacteraemia, septicaemia, haemodialysis, and urinary tract infection. The incidence of *S. maltophilia* hospital-acquired infections is increasing, and is associated with crude mortality rates ranging from 14 to 69 % in patients with bacteraemia. *Stenotrophomonas maltophilia* is a ubiquitous environmental bacterium that has also emerged as an important nosocomial pathogen contributing substantially to morbidity and mortality of immunocompromised patients.

Stenotrophomonas maltophilia for tissue invasion and evasion of host immunity, it uses virulence exoenzymes like as elastase, gelatinase, hyaluronidase, proteases, lipases, DNase, RNase, and mucinase. Lipases, in particular, are thought to cause lipid-rich lung tissue damage, resulting in localized lung necrosis and severe inflammatory responses [13].

Antibiotic susceptibility test of *Stenotrophomonas maltophilia*

In the current study the ability of the 42 *Stenotrophomonas maltophilia* clinical isolates to grow in the presence of antibiotics was tested. Preliminary susceptibility screening of the isolates was performed using the Kirby-Bauer disk diffusion method according to CLSI (2021) guidelines, which included 11 antibiotics from six antimicrobial categories. The results of drug susceptibility testing are shown in Table (2). Overall, the resistant rate for β-lactams/ β-lactamase inhibitor combination antibiotic including ticarcillin/clavulanate was 71.4%. The rates of resistance to the third generation of cephalosporins were as follows: ceftazidime 47.7%. The isolates were resistance to fourth generation cephalosporins (cefepime) 46.2%. According to the susceptibility results for the tetracycline,57.1% of the evaluated isolates exhibited resistance to doxycycline and 59.5% of the isolates showed resistance to minocycline. Resistance to fluorinated quinolones was as follows: ciprofloxacin 76.1%, levofloxacin 78.5%, norfloxacin 83.3% and moxifloxacin 59.5%. Resistance to folate pathway antagonists was as trimethoprim/sulfamethoxazole 28.5 %. Resistance to phenicols class was as chloramphenicol 35.7 %.

In previous studies of bacterial resistance, *S. maltophilia* exhibits resistance to a broad array of antibiotics, including β-lactam antibiotics, macrolides, cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, chloramphenicol, tetracyclines, and polymyxins. The low membrane permeability that contributes to resistance to β-lactams including cefepime, ticarcillin-clavulanate, ceftazidime, and piperacillin-tazobactam. and the presence of chromosomally encoded multidrug resistance efflux pumps, β-lactamases,and antibiotic-modifying enzymes all contribute to the intrinsic antibiotic resistance of *S. maltophilia* [1].

The drug resistance mechanisms are acquired by the horizontal transfer of antibiotic resistance through plasmids, transposons, integrons, integron-like elements, insertion element common region (ISCR) elements [14].

The first-line treatment is trimethoprim-sulfamethoxazole, which has been the recommended empiric single agent against *Stenotrophomonas maltophilia* for many years. It has shown activity against more than 90% of the tested isolates in most studies to date, though as mentioned above, resistance has now been increasingly reported at up to 22-38% in some 21st-century studies [15].

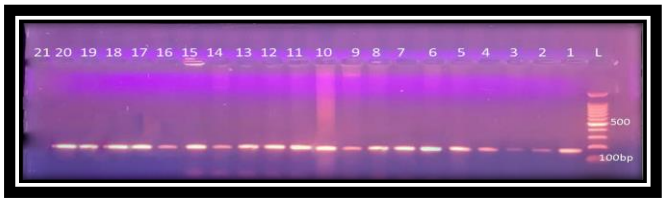
One recent study from Mexico showed an 80% resistance rate to trimethoprim/sulfamethoxazole in a combination of environmental and clinical isolates from Mexico [16]. Zhanel et al. [17] reported that,Another uncommonly used but effective agent is chloramphenicol, with a wide range of susceptibility reports. Cefiderocol is a new injectable siderophore cephalosporin that has shown promising data against carbapenem-resistant gram-negative bacteria, including *Stenotrophomonas maltophilia*.

Table (2): Antimicrobial susceptibility rates among *Stenotrophomonas maltophilia* isolated from clinical samples (n= 42).

Antibiotic	Antibiotic sensitive test result			Resistant(%)
	R	I	S	
Ticarcillin /clavulanate	30	2	10	71.4%
Ceftazidime	20	2	20	47.6%
Cefepime	27	3	12	64.2%
Doxycycline	24	3	13	57.1%
Minocycline	25	2	13	59.5%
Ciprofloxacin	32	1	9	76.1%
Levofloxacin	33	2	7	78.5%
Norfloxacin	35	1	5	83.3%
Moxifloxacin	25	2	13	59.5%
Trimethoprim/sulfamethoxazole	12	0	30	28.5%
Chloramphenicol	15	2	25	35.7%
R=resistant,I=intermediate,S=sensitive				

Molecular screening of MBL producers to *Stenotrophomonas maltophilia*

All 42 *Stenotrophomonas maltophilia* isolates were screened by conventional PCR for potential gene determinants encoding MBL using a specific primer for Ambler class B MBL (blaL1).



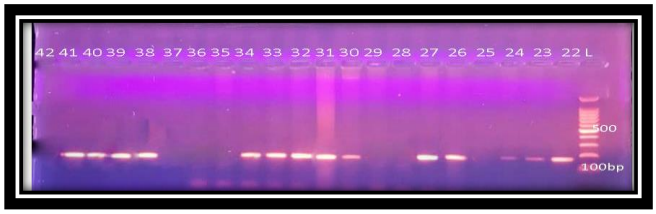


Figure:(5): Ethidium bromide-stained agarose gel electrophoresis of PCR products from extracted total DNA of Stenotrophomonas maltophilia using primer bla L1 with product 178bp. The electrophoresis was performed at 70 volt for 1- 1.5 hr. (L), DNA molecular size marker (100 bp ladder). (1 to 42 except 21, 25, 28, 29, 35,36, 37,42) show positive results with geneL1.

S. maltophilia is Due to the creation of two inducible chromosomal metallo—lactamases, many broad-spectrum antibiotics (including all carbapenems) are naturally resistant (designated L1 and L2). This complicates the treatment of infected people. Because *S. maltophilia* is prevalent in the environment and impossible to eliminate, prevention is equally challenging [8].

Kumwenda et al. [18] in Malawi mentioned,*S. maltophilia* showed resistance to a series of antibiotics, comprising all β-lactams, aminoglycosides,chloramphenicol, minocycline, fosfomycin and fluoroquinolones, but stayed susceptible to colistin and trimethoprim-sulfamethoxazole.

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