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Screening for *sul*1 and *Hem*O gene in *Stenotrophomonas maltophilia* Isolated from Urines of Cancer Patients

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Abstract

The opportunistic pathogen *Stenotrophomonas maltophilia* can be isolated in hospitals which is naturally resist to many common antibiotics, such as carbapenems and aminoglycosides. Current study involving 120 urine samples (included prostate cancer patient, bladder cancer patient, renal filer patient in addition to UTI infection patient) collected from Ghazi AL-Hariri Hospital/Medical City Hospital and AL-Amal National Cancer Hospital, Baghdad, Iraq, all urine samples were primary cultured on MacConkey, UTI media and blood agar as well as a selective and differential medium for *S. maltophilia* growth called VIA which contain (vancomycin, imipenem, and amphotericin B). Studying their antibiotic susceptibility pattern using Vitek 2 compact system and screening for presence of virulence genes using polymerase chain reaction technique. The results showed only 87 (72.5%) from total samples were give bacterial growth, involving various bacterial species. *Stenotrophomonas* percentage was 7/87(8%) of total bacteria growth, which show high resistance percentage to sulfonamide antibiotic 85.7%. the ratio of isolates carrying *sul* 1 gene was 7/7 (100%) and *Hem*O gene was 3/7 (42.8%) so looking for new effective antibiotics could be an ideal course of treatment for infections owned to S. *maltophilia*, especially in patients who are critically sick and immunocompromised.

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1. INTRODUCTION

Stenotrophomonas maltophilia is an opportunistic Gram-negative bacterium that is non-fermentable which is resist to many common antibiotics, involving aminoglycosides and carbapenems and naturally [1, 2]. Multidrug-resistant pathogens have emerged in part because of these microorganisms' capacity to trade and acquire resistance to antibiotics [3-7].

The surveillance programs for antimicrobial resistance that keep an eye on these pathogens have identified alarming increases in resistance. Because of these features, in relation of drug resistance, *S. maltophilia* emerged as a vital opportunistic pathogen of hospital infections in the intensive care unit, and causes infections in the bloodstream (developed to be bacteremia), urinary tract infections, eye infections, respiratory infections, endocarditis, nervous system, gastrointestinal tract infections, liver infection, soft tissue and bone infections, and medical implant infections, may become potentially fatal infections [2, 8-32].

S. maltophilia is considered by the World Health Organization (WHO) to be one of the most serious drug-resistant infections in hospitals worldwide. This opportunistic disease is naturally resistant to antibiotics,

included those commonly accustomed to treat the illnesses it causes. *S. maltophilia* isolates have been found to be resistant to beta-lactams, cephalosporins, macrolides, fluoroquinolones, aminoglycosides, and carbapenems [33, 34]. The entire genome of *S. maltophilia* is diverse, exhibiting a broad spectrum of resistance and virulence genes, and Numerous genomic studies have concentrated on the genes linked to virulence and antibiotic resistance; among these, the *sul* 1 gene, which encodes for sulfonamide resistance, may be crucial in the observed high level of SXT resistance. and *Hem*O represent heme oxygenase, which is connected to heme absorption [35-36]. As high resistance antibiotic pattern, the current study aimed to screening the present of some virulence factors gene including resistance gene *sul*1 and hemolysis gene *Hem*O gene in *S. maltophilia* isolated from Iraqi patients.

2. METHOD

Patients demography

One hundred and twenty urine samples were collected from Ghazi AL-Hariri Hospital / Medical City Hospital and AL-Amal National Cancer Hospital, Baghdad Iraq, in the extended timeframe of January 2022 through October 2021. Samples included, 27 urine samples collected from 27 prostate cancer patient, 42 bladder cancer patient, 46 renal filer patient and 5 from urinary tract infection patient. All mid-stream urine samples were primary cultured on, blood agar, MacConkey agar, UTI medium, in addition to as well as a selective and differential medium for *S. maltophilia* growth called VIA (vancomycin, imipenem, and amphotericin B) which contain antibiotics to inhibit the non-favorable bacteria other than *S. maltophilia*, then (incubated at 37 ^{o}C for 24 hours). According to the growth on blood, MacConkey agar, and VIA media, the initial diagnosis of the isolates was determined by examining the colonies morphology, which include colony color, shape, edge and texture. The Vitek 2 compact system (Biomerieux, France) was used on bacteria in accordance with the company's instructions. Unless otherwise specified, results were reported with a high degree of certainty (excellent or very good identification) [37].

Inclusion criteria: Patients with bladder and prostate tumor and patients with kidney dialysis as well as patients with other complications of urinary tract.

Exclusion criteria: Patient treated with chemotherapy, immunotherapy or antibiotics for UTIs for at less than 1 month.

Determination of antibiotic susceptibility

The Vitek 2 compact system identified susceptibility to trimethoprim and trimethoprim /sulfamethoxazole. and the Clinical and Laboratory Standards Institute's break point for each antimicrobial used [38].

Molecular Assay

Bacterial DNA was extracted using XIT Genomic DNA from Gram Negative Bacteria Kit following manufacturer instructions. The extracted DNA samples were as a template for PCR amplification. *S. maltophilia* was subjected to PCR analysis for the detection gene associated with virulence factors. Table 1 describes *S. maltophilia* Sulfonamide resistance gene (*sul* 1), and the hemolysis gene *Hem*O gene, the primer sequence, and the product size.

Table 1. Details of *sul*1 and *Hem*O genes in *S. maltophilia*

Primers	Primer Sequences	Product size	References
*Sul*1	F- TTCGGCATTCTGAATCTCAC R- ATGATCTAACCCTCGGTCTC	800 bp*	[39]
*Hem*O	F-CAGCAATTTCGCCCGTTTC R- GCTTGGCAGCCATCTTGTA	220 bp	[40]

*bp: base pair

The total reaction volume was up to 25µl, which included 12.5µl of FIREPol® Master Mix (5X), 0.5µl of forward and reverse primers (10 pmol), 2µl of DNA concentration, and 9.5l of nuclease-free water. to carry

out the amplification reaction as follows: initial denaturation 5 minutes at 95 ^{o}C, followed by 40 cycles of denaturation at 94 ^{o}C for 1 minute, annealing at 55 ^{o}C and 60 ^{o}C for *sul*1 and *Hem*O gene receptively for 90 secs, and extension at 72 ^{o}C for 3 minutes, followed by a final extension 10 minutes. PCR products were electrophoresed on 1.5 % agarose gel [39, 40].

3. RESULTS AND DISCUSSION (10 PT)

Demography of patients

In the current study, the general demographic parameters shown in figure (1), such as gender, type of cancer, and bacterial infection. The mean patients age ranged from 55.5 ±5 to 86 years. Patient ratios were 76/120 (male to female) and 44/120 (female to male), respectively.

The results of the culture of patient urine samples showed that 87 out of 120 (72.5%) samples tested positive for bacterial growth, encompassing various species. Common culture medium, such as MacConkey agar, blood agar, and UTI media, were used to obtain bacterial growth.

As a selective and differential medium VIA for *Stenotrophomonas* only seven isolates obtained from total 87 bacterial growth with a percentage 7/87(8%). The bacteria grow as a small circular raised colonies on blood agar and pale, non-lactose fermented colonies on MacConkey agar. Then the final diagnosis of bacteria was confirmed by Vitek 2 compact system as relied on 49 biochemical tests to reliably identify the bacteria. Only in cultured urine samples taken from patients with nosocomial infections and compromised immune systems give positive bacterial growth.

Patients with a negative cystoscope report bloody urine, which may be associated with the presence of *S. maltophilia* infections. This is because these bacteria, particularly *S. maltophilia*, require iron as a vital nutrient for survival. The regulation of multiple virulence factors has been found to be significantly influenced by iron [41].

Antibiotic susceptibility

The bacteria showed a resistance to the antibiotic under study (Trimethoprim and Trimethoprim /sulfamethoxazole) in 6/7 (85.7%) and 5/7 (71.4%) respectively, figure1**.**

The results in the current study showed the percentage resistant to Trimethoprim/Sulfamethoxazole 85.7%, the reason of resistance of antibiotic to *Stenotrophomonas maltophilia*, isolated from people with bladder and prostate cancer, renal failure and urinary tract infection, and depend on the results of Vitek 2 results was integrons, Plasmid-mediated resistance, multidrug efflux pumps, insertion sequence common region elements, antibiotic modification enzymes, and decreased outer membrane drug permeability which work together to mediate antibiotic resistance. However, the existence of two intrinsic chromosomal inducible beta-lactamases, L1 and L2, which collectively confer expanded resistance to -lactam and carbapenem treatments and encode an Ambler class B metallo—lactamase and an Ambler class A serine—lactamase, is most important [42, 43]. The current study outcomes were an approach to the results of the study carried out by Abbas and Dhahi in 2022 in Baghdad governorate where the study 6 *Stenotrophomonas maltophilia* isolates had a resistance rate to Trimethoprim /Sulfamethoxazole of 83% [41].

Another study conducted in Turkey by Çıkman and coworker., which involved 118 isolates of *Stenotrophomonas maltophilia* were used in a study that was published in 2016; they discovered that the resistance rate to trimethoprim-sulfamethoxazole was 20.3% [44]. Trimethoprim/sulfamethoxazole (SXT) is advised as the first-line therapy for *S. maltophilia* infection because *S. maltophilia* isolates naturally resist several types of antimicrobial drugs. However, the recent emergence of SXT resistance poses a danger to the management of *S. maltophilia* infections. *S. maltophilia* isolates have been shown in reports from various nations to be resistant to SXT. The *qacE1-sul1 and sul2* genes, which encode the dihydrofolate synthetase enzyme and provide resistance to sulfamethoxazole, have been linked to SXT resistance in *S. maltophilia* [45].

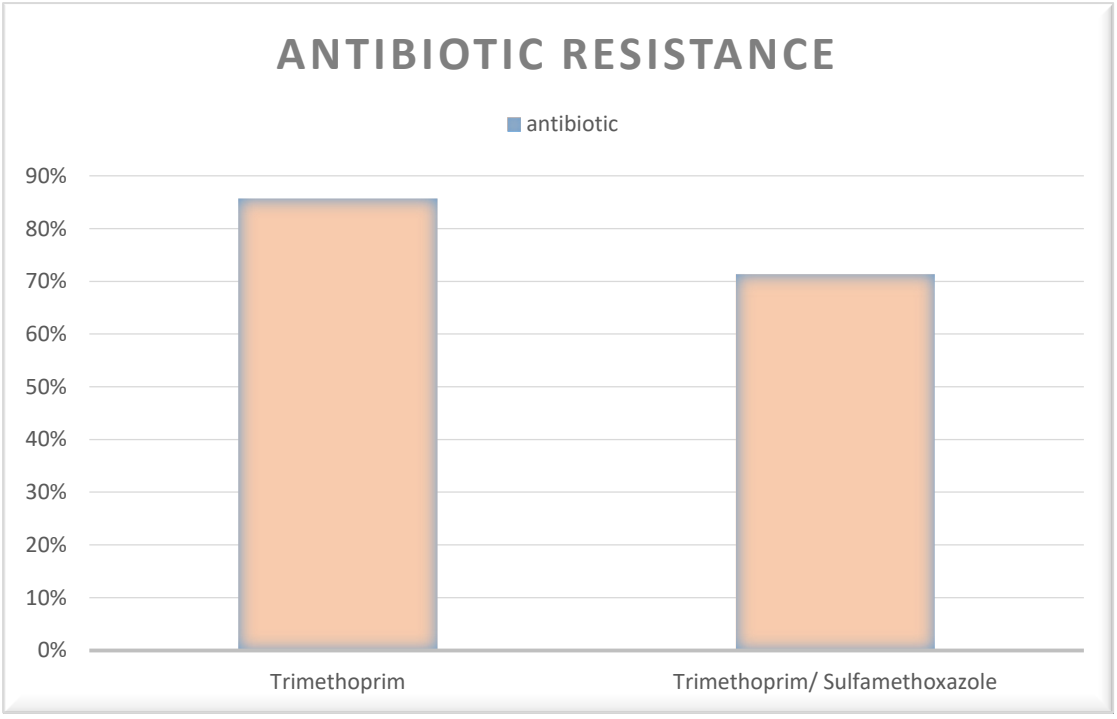

Figure1. Resistant for *Stenotrophomonas maltophilia* to antibiotic

The results of genetic detection in this study shows the presence of the *sul 1* gene at a rate of (80%). This result explains the most common gene has contributed to resistance, was the *sul-1* gene. It is one of the genes responsible for resisting the group of Trimethoprim/ Sulfamethoxazole antibiotics
The investigation into the existence of the *sul* 1 gene shown that the percentage of isolates carrying the gene was 7/7 (100%) and that it was one of the genes in charge of resistance against the sulfonamide group, figure 2. showing the gel electrophoresis of the results of the polymerase chain reaction of this gene.

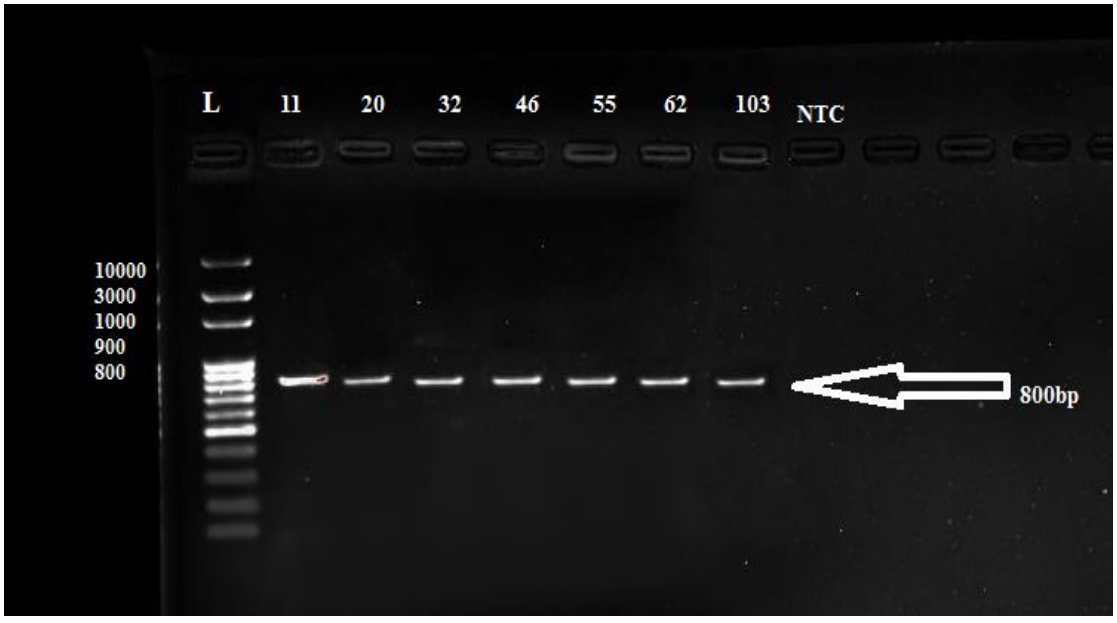

Figure 2. investigation of *sul 1* in *Stenotrophomonas maltophilia*. Lane 11, 20, 32, 46, 55, 62 and 103: isolates positive for *sul 1*. Lane NTC: no template control. Arrow refer to positive. DNA ladder molecular size control (100kbp) in lane L. concentration of agarose was 1.5% with current 100 ampere and Voltage was 45v. Time of electrophoresis was 90 min.

The presence of the *Hem*O gene was investigated and the results showed that the percentage of isolates harboring the gene was 3/7 (42.8%) and was one of the genes responsible for hemolysis of blood, figure 3. showing the gel electrophoresis of the results of the polymerase chain reaction.

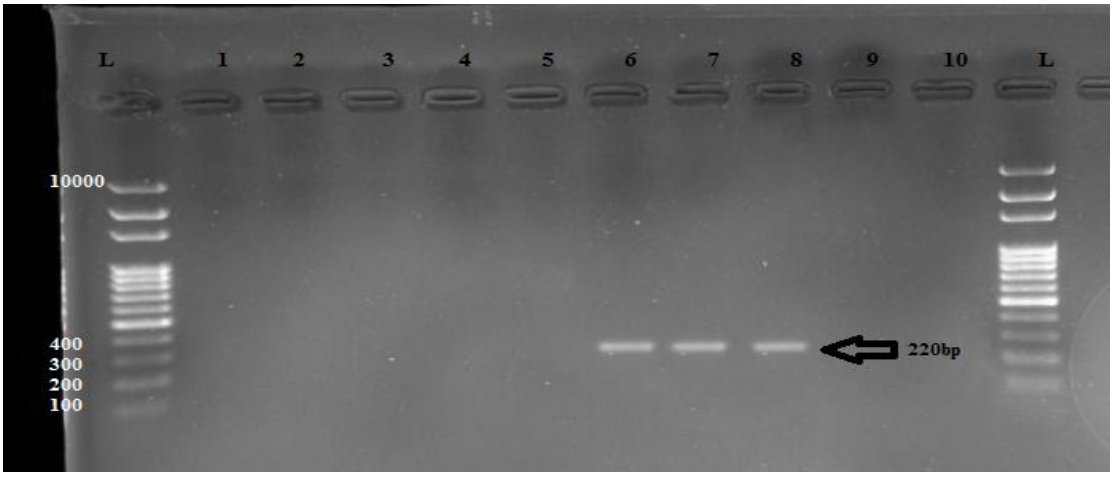

Figure 3. investigation of *HemO* gene in *Stenotrophomonas maltophilia*. Lane 6,7 and 8: isolates positive for *HemO* Lane 2,3, 4, and 5: isolates negative for *HemO*. Lane NTC (1, 9,10): no template control. Arrow refer to positive. DNA ladder molecular size control (100bp) in lane L. concentration of agarose was 1.5% with current 100 ampere and Voltage was 45v. Time of electrophoresis was 90 min.

As a similarity with results conducted in Korea 36 the research aimed to study the spread of resistance genes in 252 isolation from bacteria *S. maltophilia*, results showed that the percentage of isolates harboring the *sul 1* gene was 72%. Another study in Iran [46] included 117 isolates, and they were identified using traditional biochemical techniques from various clinical sources. The research revealed that the percentage of isolators harboring the *sul*1 gene was (55.08 %).

The result of the present study disagrees with many recent studies, Mendes and his colleagues showed that, the *sul 1* gene in 14 of 106 strains (13.2%) [47]. The primary mechanism of SMX resistance in *S. maltophilia* that has been identified to date is the *sul*1 gene. This gene is found in the conserved 3' region of class 1 integrons, which are found in plasmids with sizes varying from 2.1 to 54.2 kB [48]. In addition to the patient age differences, the different ratios result from variations in the number of isolates under investigation.

CONCLUSION

S. maltophilia could be isolated from cancer patients as an opportunistic pathogens or nosocomial infection which has a high level of resistance to sulfonamide antibiotics, so looking for new effective antibiotics for future work may be an optimal therapeutic methods for *sul*-carrying *S. maltophilia* infection, particularly in immunocompromised and critically ill patients.

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