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# Detection of the tst gene and determining the relationship between the presence of the mecA gene and antibiotic resistance of Staphylococcus aureus Isolated from some Hospital in Dhi Qar province

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## ABSTRACT

Methicillin, a β-lactam antibiotic, acts by inhibiting penicillin-binding proteins (PBPs) that are involved in the synthesis of peptidoglycan, an essential mesh-like polymer that surrounds the cell. S. aureus can become resistant to methicillin and other β-lactam antibiotics through the expression of a foreign PBP, PBP2a, that is resistant to the action of methicillin but which can perform the functions of the host PBPs. Methicillin-resistant S. aureus isolates are often resistant to other.

Out of 163 samples, 44 (26.99%) isolates of staphylococcus bacteria were diagnosed. Ten antibiotics were tested, where the bacteria showed the highest resistance of 100% to cefalexin and cefuroxime, and it was sensitive to Erythromycin with a percentage of (52.27%). It was also noted that the percentage of the mecA gene was (41)93.18% in the study samples and the percentage of the tst gene (14) was 31.81%.

**Keywords:** *Staphylococcus aureus , , virulence gene , antibiotic-resistance property*

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## INTRODUCTION

Staphylococcus aureus is considered an opportunistic pathogenic bacterium due to its ability totake advantage of damaged cutaneous layers. It can cause infections ranging from mild skin irritation or a simple rash to severe illness including Toxic Shock Syndrome, abscesses, bone infections, and sepsis. These bacteria are capable of wreaking haoc within the human body, primarily by destroying red blood cells through the production of hemolytic toxins 2 and causing sudden drops in blood pressure that can result in death. S. aureus is the primary cause of lower respiratory tract and surgical site infections and is. the second leading cause of bacteremia, pneumonia, and cardiovascular infections 1.

Methicillin resistant S. aureus (MRSA) has become a major public health problem all over the world. It is correlated with incremented morbidity and mortality, compared to other pathogenic bacteria. The elevated colonization rates lead to the incrimination of infection rates in the community and medical centers which leads to a significant increase in treatment cost 2.

The majority of researches in this field suggested that mecA gene that is present in all MRSA strains and is known to encode penicillin binding protein 2a (PBP2a), which has a low tropism to all $\beta$-lactam antibiotics, is the corner stone responsible for producing MRSA phenomenon 3,4. Beta-lactam resistance is attributed mostly to mutations in the mecA gene, but other genetic elements may also be considered for the explanation of the mechanism of resistance 5. Molecular amplificationof the mecA gene is recognizedas a benchmark to diagnose MRSA in the community as these genes are highly conserved among staphylococcal species 6 .

percentage of strains of MRSA is relatively high in Asia, such as 60% in Taiwan reached, 20% in China, 70% in Hong Kong, 5% in Philippines, and 60%in Singapore. In Indonesia in 2006, MRSA prevalence is 23.5% 7. A study in Dr. Soetomo Hospital, Surabaya showed that of 643 patients there were 52 MRSA (8%) 8 . In contrary, a study in Central Public Hospital Haji Adam Malik Medan showed quite higher prevalence of MRSA, in which in January-June 2015 there were 56 isolates (67%), in July-December 2015 there were 48 isolates (57%), and January-June 2016, 58 isolates (45%) were MRSA. Genotypes examination for MRSA resistance has been conducted to know antibiotics resistance gene such as mecA 9 . The gold standard to determine MRSA genotypes is to detect conserved genes (fixed/ preserved) constantly found in mecA gene, which is within range of a particular chromosome in Staphylococcal Cassette Chromosome (SCCmec) 10 . MRSA resistance is due to the mutant protein of penicillin-binding protein 2a (PBP2a or PBP2 ') encoded by mecA gene. PBP is a group of enzymes in the cell membrane of S. aureus that catalyzes the trans-peptidation for peptidoglycan chain (crosslinkage) formation. The affinity of PBP2a is so low that MRSA stays alive in high concentration of antimicrobial exposure 11. Amplification of mecA can be done by using polymerase chain reaction (PCR), which is the gold standard for the detection of mecA 12 .

Staphylococcus aureus produces a wide variety of exoproteinsthat contribute to its pathogenicity. However, only a small number of its isolates produce additional exoproteins, such as Toxic Shock Syndrome Toxin (TSST), which belongs to pyrogenic toxin superantigens (PTSAgs) 13 . Furthermore TSST is a protein with 22-kD molecular weight, which is encoded by the tst gene 14 . This protein affects cells of the immune system and stimulates release of interleukin-1, interleukin-2, tumor necrosis factor-alpha

(TNF-a) and nonspecific T cell proliferation, which may lead to a severe and potentially fatal disease in humans, known as toxic shock syndrome (TSS) 15,16.

## MATERIALS AND METHODS

### *Culturing and identification*

163 samples were collected from in various hospitals and medical centers at Nasiriyah City, southern Iraq. Clinical samples were collected for the period December 2021 to February 2022 . Staphylococcus grows easily on most routine media at aerobic or micro-aerophilic conditions. It was quickly grows at (37◦C), and the ideal temperature in which the pigment is formed is 20-25◦C S.aureususually forms grey to golden yellow colonies due to carotenoids, Produces _-haemolysis on horse, sheep or human blood agar plates 17,18 The bacterial morphology was observed microscopically as Gram-positive cocci arranged in grape-like irregular clusters 18 All


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S.aureusstrains produce coagulase enzyme. S.aureusare catalase positive and oxidase negative 17 S.aureusexpress a clumping factor (fibrinogen affinity factor) 19 .Staphylococcus can grow in a medium with a high salt concentration, so they can grow easily in MSA. The acidity of the medium changes as the bacteria ferments mannitol and turn phenol red pH-indicator; S.aureuschanges color of MSA from the alkaline (red)to the acidic(yellow), while the rest of the Staphylococcus will grow without changing the color of the medium 18 .

***Antibiotic Susceptibility Testing***

Susceptibility test was done for all the 44 S. aureus isolates against the following antibiotics: Amoxicillin, Cefalexin, Cefazolin, Cefuroxime, Ciprofloxacin, Erythromycin, Gentamycin, Levofloxacin, Vancomycin, and Moxifloxacin E (HiMedia) by modified Kirby-Bauer technique based on NCCLS regulations 20,21. Furthermore, E-test was used to estimate the minimum inhibitory concentrations (MICs) for all MRSA isolates as instructed by the manufacturer.

***DNA isolation***

MRSA was sub-cultured on blood agar and incubated at 37°C for 18-24 hours. The cell was broken by a freeze-thaw method 22 . The freeze-thawed solution was spin at 13.000 rpm for 5 minutes. The supernatant was separated from cell debris, and subjected to DNA purification check.

***Amplification of mecA Gene***

S. aureus strains were subjected to PCR searching for the mecA gene according to Al-Abbas 2012 23. PCR protocol was adopted in 25 $\mu$L volume which contains 1U Taq polymerase and the buffer conditions recommended by the manufacturer (Promega). A PCR program was conducted with initial denaturation at 94∘C for 5min followed by 30 cycles of 94∘C for 60sec, 62∘C for 30 sec, and 72∘C for 35 sec ended with a final extension at 72∘C for 10 min. Then, the PCR product was visualized under UV transilluminator on 2% agarose, and the following primers were used Forward: AAA ATC GAT GGT AAA GGT TGG C and Reverse: AGT TCT GCA GTA CCG GAT TTG C . These produce a PCR amplicon of 532 base pairs.

***PCR for Detection of Virulence Genes tst in Staph. aureus***

For PCR amplification, the reaction mixture (30 µL) contained 1 µL of primer F (10 pmol/µL), 1 µL of primer R (10 pmol/µL), 0.6 µL of deoxynucleoside triphosphate (10 mmol/L) 24 , 3 µL of 10× PCR buffer 25 , 1.8 µL of MgCl2 (25 mmol/ L) 26, 0.1 µL of Taq DNA polymerase (5 U/µL) 27, and 20 µL of distilled water. Finally, 2.5 µL of DNA preparation was added to each 0.2-mL reaction tube. The tubes were subjected to thermal cycling 28. A PCR program was conducted with initial denaturation at 94∘C for 5min followed by 30 cycles (94°C, 2 min; 55°C, 2 min; 72°C, 1 min) ended with a final extension at 72∘C for 5 min. the PCR product was visualized under UV transilluminator on 2% agarose, and the following primers were used Forward: ATG GCA GCA TCA GCT TGA TA and Reverse: TTT CCA ATA ACC ACC CGT TT. These produce a PCR amplicon of 350 base pairs.

## RESULTS

A total of 163 samples were collected from various hospitals and medical centers at Nasiriyah City, for the period December 2021 to February 2022 and examined for detection of S.aureus bacteria. Only 44/163 ( 26.99%) samples have been gave growth for staph aureus, Phenotype test of antimicrobial agents showed that most isolates were resistant . The percentage for antimicrobial sensitivity can be seen in Table below.


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**TABLE 1.** Percentages of antimicrobial resistance of S.aureusagainst 10 types of antimicrobial agents according to CLSI 2014 (n= 44).

| Antibiotic susceptibility | | | |
|---|---|---|---|
| Antimicrobial Agents | Resistant N (%) | Intermediate N ( %) | Sensitive N ( %) |
| Amoxicillin | 43 (97.72) | 0 (0) | 1 (2.27) |
| Cefalexin | 44 (100) | 0 (0) | 0 (0 ) |
| Cefazolin | 42 (95.45) | 1 (2. 27) | 1 ( 2.27) |
| Cefuroxime | 44 (100) | 0 (0 ) | 0 (0) |
| Ciprofloxacin | 43 (97.72 ) | 0 (0 ) | 1 ( 2.27) |
| Erythromycin | 20 (45.45) | 1 ( 2.27) | 23 (52.27) |
| Gentamycin | 38 (86.36) | 1 (2.27 ) | 5 (11.36 ) |
| Levofloxacin | 43 (97.72) | 0 (0 ) | 1 (2.27 ) |
| Moxifloxacin | 41 (93.18 ) | 0 (0 ) | 3 ( 6.81) |
| Vancomycin | 33 ( 75) | 3 (6.81 ) | 8 (18.18) |

***Molecular detection***

The current study, through molecular detection, showed that the mecA gene was found in 93.18% while the tst gene was found in 31.81%, of the samples under study,as shown in the table below.

**TABLE 2.** The percentage of the presence of the gene in the research samples

| Gen ( n = 44 ) | Present % | Absent % | total |
|---|---|---|---|
| mecA | 41 (93.18) | 3 (6.81) % | 44(100%) |
| tst | 14 (31.81)% | 30 ( 68.18) % | 44(100%) |

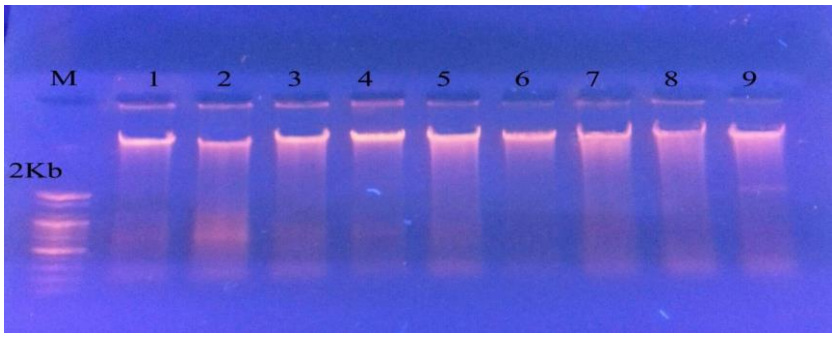


**FIGURE 1.** Electrophoresis of genomic DNA on agarose gel 0.8% . (M) DNA marker (100 bp ladder ). Lane (1- 9) No. of genomic DNA of S.aureus


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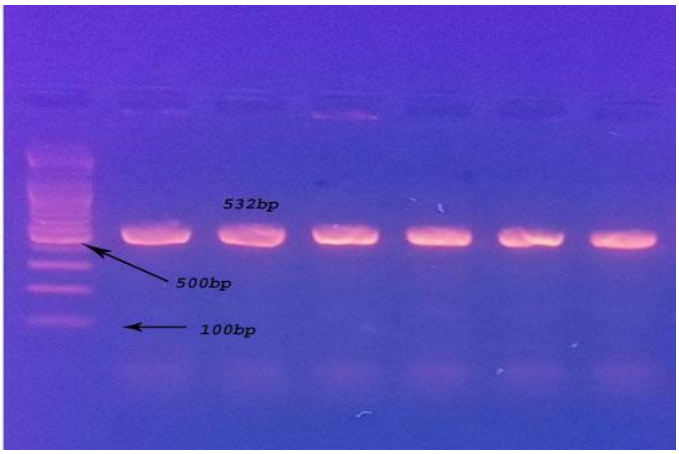


**FIGURE 2.** PCR amplified products of mecA Gene of the Stap. aureus using the designed primers with expected size 532bp. (M) DNA marker (100bp ladder ). Lane (1-12) No. of amplify of mecA gene in isolates of S. aureus

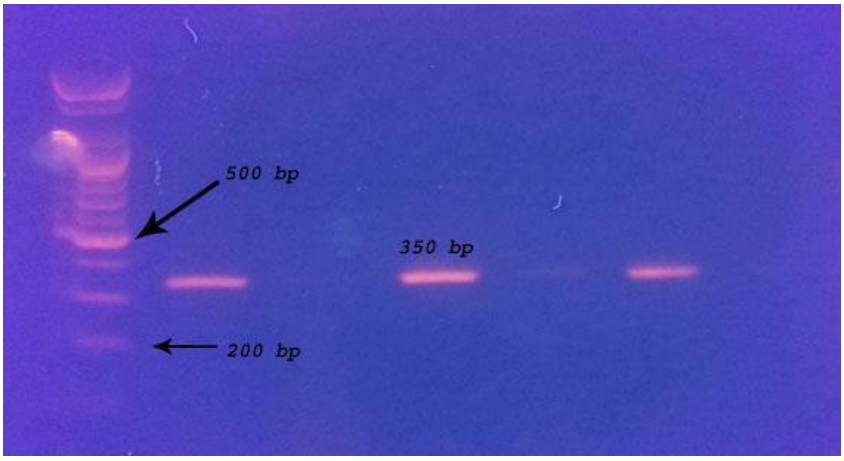


**FIGURE 3.** PCR amplified products of tst Gene of the Stap. aureus using the designed primers with expected size 350bp. (M) DNA marker (100bp ladder ). Lane (2,3,4,5,7) positively amplified mecA and (1,6) tst negative in isolates of S. aureus

## DISCUSSION

The current study, through molecular detection, showed that the mecA gene was found in 93.18%.

Data from Clinical and Laboratory Standards Institute (CLSI) 2015 showed that isolates resisted to cefoxitin were also resistant to 52 other types of antibiotics. Cefoxitin including second generation Cephalosporin is a potent inducer of mecA regulatory system that is used extensively as a marker for the detection of the mecA gene 29.

In this study high resistant was showed to cefalexin and cefuroxime (100 %), amoxicillin , levofloxacin and ciprofloxacin (97.72%),cefazolin (95.45%), moxifloxacin (93.18 %) gentamycin(86.36%).In contrary, the isolates were still sensitive to vancomycin (75%)and erythromycin (52.27%). For antibiotics treatment, these antibiotics may still be used.

Another study in Indonesia showed similar pattern of antibiotic resistant in which S. aureus of clinical samples was resistant not only to penicillin and methicillin, but also resistant to tetracycline (24.55%), oxacillin (2.1%), gentamicin (1.1%), erythromycin (5.11%), chloramphenicol (9.22%), and trimethophrim/sulfamethoxazole (7.11%) 30. However, the percentage of isolates resistant to


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other antibiotics was relatively lower compared to that of this study. Al Ruaily and Khalil (2011) study in Saudi Arabia showed S. aureus isolates were resistance to cephalosporins (95%), gentamycin (95%),ciprofloxacin (87%), vancomycin (100%), and penicillin (100%) 31.

A similar study of Elhassan et al. isolated from different clinical specimens in Shendi City, Sudan showed that all isolates of S. aureus were resistance to methicillin, penicillin, and ampicillin 32. Resistant to gentamycin, ciprofloxacin, and clindamycin were showed in 80% of the isolates, while resistant to trimethoprim/sulfamethoxazole was showed in 74% of the isolates. Sudigdoadi (2010) showed that 89% of his isolates were resistant to gentamycin 33. question may develop the ability to destroy the antibiotic or to grow in its.

Beta-lactam antibiotics kill bacteria by inhibiting cell wall synthesis. MRSA resistance to betalactam group is due to a protein mutant of penicillin-binding protein 2a (PBP2a or PBP 2') encoded in mecA gene. PBP is a group of enzymes in the cell membrane of S. aureus that catalyzes the transpeptidation for the formation of peptidoglycan chain webbing (cross-linkage). Affinity PBP2a antimicrobial beta-lactam group is so low that MRSA remains alive in a high concentration of antimicrobial exposure 34.

It was interesting that the isolates showed resistant to vancomycin. The resistant to vancomycin (VRSA) is associated with changing and resetting bacterial cell wall.

In addition, overproduction of Penicillin Binding Protein-2 (PBP-2) is also considered as an important factor for the expression of resistance to vancomycin. It is known that resistance to vancomycin is mediated by specific gene vanA to glycopeptides 35. Vancomycin resistant isolates is likely due to spontaneous mutations, occur acquisition of resistant factors from elsewhere, or from the surrounding enteric bacterial population 36.

Through molecular detection, showed that the tst gene was found in 31.81%, of the samples under study.

Different numbers of tst-positive S. aureus have been reported in previous studies. Using the PCR method, El- Ghodban et al. recorded that only 3 out of 40 S. aureus isolated from clinical sources possessed the tst gene 37. Mehrotra et al. examined 107 S. aureus isolated fromhealthy carriers to determine tst positive samplesand showed that 24.3% possessed this gene 10. Also many studies have been conducted on the presence of tst gene in S. aureus isolates from Iran. Kord and Amini analyzed 76 S. aureus strains isolated from clinical samples. Their results showed that only 8.95% of isolates were positive for the tst gene 38. In another study, performed on 100 MRSA and 100 MSSA isolates in Hamadan, the prevalence of TSST-1 was 11% 39.

S.aureusproduces a wide variety of exotoxins, among the numerous toxins of including enterotoxins, the enterotoxins super antigens have already been assigned to the pyrogenic toxin super antigen family based on their biological activity and structural similarity, toxic shock toxin-1 (TSST-1) that induces super antigenic activity, and exfoliative toxins (ETs), these toxins are responsible for specific acute clinical syndromes such as toxic shock syndromes (TSS) , food poisoning due to staphylococcus enterotoxins and staphylococcal scarlet fever (a mild form of TSS), all these toxins share in their structural and biological properties, and this indicates that they are derived from a common ancestor. 40. Another class of genetic characteristics of staphylococci is a super-antigen that encoded by tst gene, that carried on mobile genetic elements (MGE) named (SaPIs.), nearly 15 kb genomic regions that significantly denote a number of virulence genes, (SaPIs) linked to specific S.aureusgenetic families, known as lineages 41-46. Toxic shock syndrome-1 (TSS-1) Secondary inflammatory complications include invasive forms of bacterial diseases Such as inflammation of the lungs, lung abscesses, urinary tract infections, food poisoning, osteoarthritis, Endocarditis, meningitis, arthritis, toxic shock syndrome, septicemia, Death 47-50.

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